Endocrine therapy for hormone receptor-positive, HER2-negative metastatic breast cancer: extending endocrine sensitivity

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Abstract

Targeted agents have significantly prolonged survival and improved response rates in first- and second-line settings of HR-positive/HER2-negative metastatic breast cancer (MBC). Optimal sequencing of the available options may prolong endocrine sensitivity, slow disease progression, and delay the need for chemotherapy. However, the optimal treatment sequence remains unclear and therapeutic decisions are complex. We review the latest recommendations and supporting evidence for endocrine therapy in women with HR-positive/HER2-negative MBC and discuss strategies for the optimal sequential therapy in scenarios of response to endocrine therapy. Although more data are needed to define the best sequence of endocrine treatments, more personalized sequential strategies, which take into account response to previous treatments as well as disease symptoms and safety issues, will be increasingly feasible.

Keywords: CDK4/6 inhibitor, endocrine therapy, metastatic breast cancer, palbociclib, ribociclib, abemaciclib, fulvestrant

Introduction

Recurrence rates in breast cancer have significantly declined thanks to the development of a multidisciplinary team approach, newer surgical techniques, and advances in systemic and targeted therapies. About 20% to 30% of cases diagnosed as early-stage non-metastatic cancer will experience a recurrence with distant metastatic disease, while only 6% to 10% of new breast cancer cases present at an advanced stage, as *de novo* metastatic breast cancer (MBC) [1]. Although MBC is generally incurable, substantial improvements in survival of patients with advanced disease have been achieved in recent years [2-4]. Of note, most MBC patients are postmenopausal women, who constitute the prevailing population in clinical trials.

Up to 75% of breast cancers express the estrogen and progesterone receptors and are referred to as hormone receptor (HR)-positive [2-4]. Owing to the role of the estrogen receptor in breast cancer biology, the modulation of estrogen signaling through endocrine therapy has long been an essential component in the treatment of HR-positive breast cancer at all stages [5]. Different types of endocrine therapy are available for MBC: selective estrogen receptor modulators (SERMs), including tamoxifen and

toremifene; aromatase inhibitors (AIs) including non-steroidal AIs (anastrozole, letrozole) and steroidal AIs (exemestane); selective estrogen receptor degraders (fulvestrant); progestins; anabolic steroids; and estrogens [1]. Over the past few years, the introduction of new agents including everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), and the inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6) palbociclib, ribociclib, and abemaciclib, which are all used in combination with endocrine therapy, has further increased the number of options for treatment of HR-positive, HER2-negative MBC in postmenopausal women. The addition of targeted agents that inhibit intracellular pathways important for cell proliferation has been suggested to enhance the efficacy of currently available endocrine therapies [6].

In MBC, even if the results of more recent trials indicate the combination of hormone therapy plus CDK4/6 inhibitors as the more effective treatment option (with the exclusion of patients with visceral crisis) for ER+/HER2- BC, both in hormone-sensitive and in hormone-resistant disease, several aspects deserve further considerations. The type of hormone to be combined with CDK4/6 inhibitors, the role of the combination in aggressive visceral and in indolent disease, the room for hormonal drug alone, the impact of disease free interval from previous hormones on the treatment choice, the efficacy and safety differences among the three available CDK4/6 inhibitors are all aspects that deserve further investigations. Further issues relate to the fallout on the oncology services organization, and the costs of therapies. Finally, the optimal sequence of different available treatments is largely unknown, mainly sacrificed to the dogma of “the more active drug first”, even if no clear evidences support the fact that a stronger upfront approach could prolong the survival and delay the use of chemotherapy in a better way than a sequential use of the available drugs [7]. Current guidelines provide only general indications about the use of the different treatment options, and on possible sequences [2,7,8], based on a largely arbitrary definition of hormone resistance. On the other hand, several putative predictive biomarkers failed to the expectation for a personalized treatment of ER+/HER- MBC patients [9].

In the present review, we will discuss the clinical problems that have to be addressed in daily treatment of ER+/HER2- MBC, moving from the latest recommendations for endocrine therapy and navigating the evidences behind them to extrapolate data useful in the management of specific in patient’s subgroups.

Current recommendations

The main treatment endpoint in MBC is palliation, aimed at maintaining or improving quality of life and possibly prolonging survival. Guidelines generally suggest to choose therapy in ER+/HER2- MBC taking into consideration clinical parameters for choosing therapy in ER+/HER2- MBC (like disease-free interval

from previous endocrine therapy, previous therapy and response, tumor burden, need for rapid disease/symptom control) and patient-related factors (like patient preferences, biological age, comorbidities and performance status, socio-economic and psychological factors) [2].

There is full agreement among guidelines (NCCN, ASCO, ESMO, AIOM) [2,3,7,8] that endocrine therapy should be the preferred option for HR-positive disease, and that hormone-based treatment should be continued until a clear evidence of resistance occurs. Chemotherapy is considered a more appropriate treatment only in case visceral crisis, defined as a clinical condition in which there is a high risk of rapid disease progression leading to death, or in tumors in which, with high probability, a subsequent treatment after failing hormone-based therapy would not be feasible. Despite this, real-life data [10-12] show that a significant proportion of patients with HR+/HER2- MBC still receive chemotherapy as their first treatment in clinical practice.

Based on the previous exposure to endocrine treatment, metastatic patients can be divided in hormone-naïve (patients with de-novo MBC, or, rarely, patients who did not receive adjuvant hormonal therapy) and endocrine pretreated (an heterogeneous group comprising patient already treated with hormonal therapy in the metastatic setting and patients with relapse of disease during adjuvant hormonal therapy or after stopping it, early or late).

The interval between the previous exposure to endocrine therapy and the occurrence of disease progression or relapse has been used as a surrogate of the tumor endocrine-resistance (i.e. the probability that patient does not benefit from a subsequent endocrine-based therapy), that is accepted to progressively increase as the patient had no, past, recent or current exposure to hormonal therapy [2]. In these cases, the failure to respond to HT is considered as a primary (intrinsic) resistance (the growth of neoplastic cells (even if ER+) is already independent from the endocrine stimulation, mainly due to intrinsic subtype, low estrogen receptors, constitutive activating mutations of downstream estrogen dependent pathway [13,14] or as a secondary (acquired) resistance (tumor cells become resistant after a previous phase of sensitivity, mainly due to estrogen receptor mutations or overcoming crosstalk mechanisms [15,16]).

The occurrence of resistance is unfortunately a common problem during HT, and several drugs have been developed to prevent or to overcome hormone-resistance, either aimed to degrade the Estrogen Receptor (like fulvestrant or new SERD [17]), or to target some key-mediators of intracellular pathways (like PIK3CA/AKT/mTOR inhibitors, or CDK4/6 inhibitors).

According to current ESMO guidelines [2], first line treatment should be performed with CDK4/6 inhibitor in addition to hormonal agent (AI if HT naïve or late recurrent; fulvestrant if recurrent during or early after (<12 month) completing adjuvant HT). Other first-line options however might include HT alone (as monotherapy - fulvestrant, AIs or tamoxifen) or, for patients without any exposure to endocrine therapy, as a combination of AI plus fulvestrant [18]. The optimal sequence after a first-line endocrine therapy for metastatic disease depends on the type of therapy previously used: if AIs, the recommend options are CDK4/6 inhibitor plus fulvestrant, or everolimus plus examestane; if CDK4/6 inhibitor plus HT the options might be (without clear supporting evidence) everolimus plus examestane, or fulvestrant (if prior AIs), or other hormones (ike AIs, tamoxifen and megestrol acetate). The same considerations could be made for a hypothetical third line

For premenopausal and perimenopausal women, the same recommendations can be applied, provided the patient undergoes to ovarian suppression, pharmacologically with gonadotropin-releasing hormone analogs or, in selected cases, through surgical oophorectomy [2]

Navigating the evidences that support current recommendations

Over the past decades, tamoxifen and AIs (plus LH-RH analogues in premenopausal women) has been considered the best endocrine therapies in HR-positive MBC. According to some studies in postmenopausal women, AIs have shown superior efficacy compared with tamoxifen, but differences are modest [19,20]. A survival benefit favoring AIs over other endocrine therapies, although small, also emerged from a Cochrane analysis [19]. However, a randomized phase III trial comparing tamoxifen with exemestane (a steroidal AI) as first-line endocrine therapy in postmenopausal women with MBC did not report significant differences in progression-free survival (PFS) or overall survival (OS) between the two treatments [20]. Despite these controversial results, AIs are generally considered as one of the main first-line options for MBC patients not previously treated with adjuvant therapy, or presenting with "de novo" stage IV disease [8].

In the last years however, a large body of evidence have been published, supporting the profound change in guidelines recommendations.

Recent key trials with HT (AIs and fulvestrant) alone and in combination with CDK4/6 inhibitors or everolimus in ER+/HER2- MBC are summarized in **Table 1.** Trials are classified either as first line (patients untreated with HT o with late recurrence, *mainly HT sensitive)*, or as second line (patients pretreated

with HT as adjuvant or in first line metastatic, *mainly HT resistant)*, as already done by Slamon in the analysis of the Monaleesa-3 trial [21]).

Main results and differences of phase III trials of endocrine therapy plus targeted agents

The Paloma 2 (PL2) [22], Monaleesa 2 (ML2) [23,24] and Monarch 3 (MC3) [25,26] were all designed to compare an AI (letrozole in the first 2, any AI in the other) with the same HT plus respectively palbociclib, ribociclib or abemaciclib. The target population included postmenopausal women with ER+/HER2- MBC, untreated with hormones or relapsed at least 12 months after the end of adjuvant HT.

The Monaleesa 3 (ML3) [21] partially included a similar patient population (49.2% of the enrolled received treatment as first line, and 50.8% for relapse after previous HT), but in this case fulvestrant was used as hormonal partner

Some differences among the trials exist, mainly related to the enrolled patient population and to the timing of response evaluation: % of de novo vs recurrent patients (30% PL2, 34% ML2, 41% MC3); long DFI: (60% ML2 (>24m); 40% PL2 (>12m); 62% MC3 (>36m), % of visceral disease (59% ML2; 48% PL2; 52% MC3), % of bone only disease (20% ML2; 23% PL2; 21%MC3), % of previous chemotherapy (34% ML2; 48% PL2; 38% MC3), % of hormone naïve (44% PL2; 48% ML2; 54% MC3); time of response evaluation (q12w PL2 (bone scan q24w); q8w-q12w ML2; q8w MC3 (bone scan q24w).

All the trials reported a significant improvement in PFS (primary endpoint of the studies), with a HR of 0.58, 0.56 and 0.54 respectively, and of 0.57 for the ET-naïve population of Monaleesa-3 (21). However, Monarch3 population could be considered more HT-sensitive, due to a higher number of de novo or very late recurrent patients, to a lower % of patients treated with adjuvant chemotherapy (38%) and higher % of patients never exposed to hormones (54%). Also timing of evaluation is somewhat different (longer in Paloma2), and different for visceral vs bone evaluation, with some difficulties in comparing the trial results.

The improvement in PFS was present in all the patient's subgroups, even if at a different degree, potentially due to the size of the subgroups.

The PFS results were similar also in Monaleesa 3, in which ribociclib was combined with fulvestant, with a median PFS (in the whole population, including patients pretreated for metastatic disease) of 20.5 months (vs 12.8 of fulvestrant alone). Median PFS was 24.8 in Paloma2 and 28.2 in Monaleesa 2.

The response rate in these trials was also remarkable (42% in PL2, 40.7% in ML2, 59% in MC3, in patients with measurable disease), similar if not higher than the response rate expected with chemotherapy regimens in ER+/HER2- MBC.

A numerical difference in deaths favoring the first line CDK4/6 inhibitor has been recorded at the time of PFS analysis [24], and mature OS data are awaited for PL2 and ML2. In ML3 a survival benefit has been recently reported [27]. At a median follow-up of 39.4 mo, ribociclib plus fulvestrant showed a significant OS prolongation (median OS not reached vs 40.0 mo; HR, 0.724). OS resulted significantly increased also in the subgroup of patients treated as first line (median not reached vs 45.1 mo; HR, 0.700).

Monaleesa 7 (ML7) [28,29] was the only trial specifically designed to compare HT (LH-Rh analog in combination with Letrozole or Tamoxifen) with or without ribociclib in pre- and perimenopausal women untreated with hormones for metastatic disease (40% de novo and 60% recurrent, with DFI >12 month in the majority of the cases). Young women represent about 20% of invasive breast cancer in the USA, and the optimal treatment of ER+/HER2- metastatic cases is a matter of debate, due to the frequently perceived more aggressive behavior. In ML7 patients, visceral metastases were present in 56% of cases. The combination of ribociclib + HT showed a significant improvement in PFS (from 13 to 23 months, HR 0.53), both using tamoxifen (22.1 vs 11 months) and letrozole (27.5 vs 13.8 months). More importantly, ML7 demonstrated a significant OS advantage [29], (Median not reached with ribociclib vs 40.9 months with HT only, HR 0.71), more evident in patients treated with letrozole (median not reached with ribociclib vs 40.7 months with HT only, HR 0.69). The combined treatment was beneficial in all subgroups of patients, and delayed the need for first subsequent chemotherapy by 40%, with 16% less of women treated with chemotherapy after 42 months. Finally, a possible “carry-over” effect (i.e. a PFS benefit that extends to the next line of treatment) has been observed, with 31% reduction in the risk of progression to therapy administered after CDK4/6 inhibitor plus HT (PFS-2).

In patients developing recurrence during adjuvant HT or shortly after, or during 1st line HT for metastatic disease, the combination of CDK4/6 inhibitor with fulvestrant as second line yelded a significant prolongation of PFS compared with fulvestrant alone, consistently in Paloma 3 (PL3) [30,31], Monaleesa 3 (ML3) [21] and Monarch 2 (MC2) [32] (HR 0.46, 0.56 and 0.55 respectively). However, as expected, the median PFS were clearly smaller than those observed in first line, ranging from 9.5 to 16.4, mainly depending on the characteristics of patients enrolled in the trials regarding the previous exposure to HT. In the Paloma 2, a meaningful difference in median OS has been also reported, from 28 to 34.9 months (HR 0.81, statistically not significant) [31]. In Monarch 2 a significant improvement in OS has been reported [33], from 37.3 months for fulvestrant alone versus 46.7 months for abemaciclib plus fulvestrant ([HR 0.757). Interestingly, the improvement appeared greater in patients with visceral

disease (HR, 0.675) and with primary resistance to prior ET (HR, 0.686), clearly challenging the role of chemotherapy in these patient's groups.

These studies also enrolled also a small number of premenopausal patients, who, at subgroup analysis, obtained the same degree of benefit than post-menopausal women.

In the Bolero-2, patients progressing on AI were treated with the combination of everolimus, an mTOR inhibitor, with exemestane versus exemestane alone. The combination treatment resulted in a significant improvement in median PFS as compared to exemestane alone (from 3.2 to 7.8 months, HR 0.45) in the Bolero-2 trial [34], even if associated with higher toxicity. A numerically increase in median OS has been also reported with Everolimus plus exemestane (HR 0.81, not significant) [35].
Taken together, the evidences strongly support the use of CDK4/6 combination with HT both in patients untreated or pretreated with HT, reserving the combination of everolimus plus exemestane to patients failing CDK4/6i + HT. However, several aspects have not been fully elucidated by the trials, particularly as to which should be the optimal sequence to apply in different clinical situations. In fact, even if on average all patient's subgroups seem to have similar benefit, many of these are underpowered to derive solid evidences.
Moreover, because the delay in starting chemotherapy has been claimed as a meaningful clinical endpoint, strategies to extend the duration of treatment with HT, alone or combined with other targeted drugs, is a reasonable goal to be pursued through an optimal use of all the available options.

Questions deserving further considerations

Question 1: in patients with bone only disease, hormone naïve or (very) late recurrent, could HT alone be an option?

All the trials mentioned above reported a benefit with CDK4/6 inhibitors plus HT in patients with bone only disease. About 20% of patients enrolled in the trials had disease limited to the bone. In these patients, the risk of progression was reduced by 64% in PL2 (HR 0.36) [22], by 31% in ML2 (HR 0.69) [23] and by 42% in MC3 (HR 0.58) [25]. However, longer time intervals in evaluating the effect on the bone has been reported in in PL2 and MC3 than in ML2, potentially influencing the degree of the benefit reported in the trials (as a longer exposure to the drug before the assessment of response could have improved the control of disease). However, in the Falcon study [36] patients without visceral disease, comprising patients with bone only disease, showed a remarkable PFS of 22.3 months, suggesting that ET alone could be a good alternative in patients HT naïve. On the other hand, in ML3 [21] the

combination of ribociclib with fulvestrant reduced the risk of progression by 62% in case of bone only disease (HR 0,379) in respect with fulvestrant (about 50% of patients were treated as first HT line). However, the degree of OS benefit, in the subgroup analysis, resulted lower than that observed in visceral disease. Finally, the administration of fulvestrant as first option raises the question of which subsequent treatment could be used at the time of progression, as we have very limited evidence about the effect of CDK4/6 inhibitor plus AI in such patients.

The DFI has been reported as a surrogate of hormone sensitivity. In a combined analysis of MC3 and MC2 [37], a DFI of 36 months or longer was associated with a lack of effect for CDK4/6 inhibitors. On the contrary, no difference of effect has been observed in PL2 [38] and ML2 [24], after a longer follow-up.

Question 2: in patients with high burden, aggressive disease, should HT plus CDK4/6 inhibitor be recommended?

In patients with visceral disease (mainly liver), or with high burden of disease (reported in several trials as 3 or more sites of metastases) the use of chemotherapy has been considered for long time the preferable option by many oncologists. Current guidelines recommend instead HT as a first line of treatment (unless there is an overt visceral crisis – i.e. a condition in which patient suffers for an organ failure with high risk of death). In all the trials, CDK4/6 inhibitors combined with HT improved significantly the PFS even in patients with high burden of disease in patients untreated with HT for metastatic disease: PFS HR was 0.63 in PL2 [22,39] 0.56 in ML2 [24], 0.64 in ML3 [21], 0.50 in ML7 [28] and 0.61 in MC3 [26]. The effect seems greater when CDK4/6 inhibitor is combined with fulvestrant: the median PFS was 24.9 and 22.8 in ML2 and ML7 respectively, but has not been reached in ML3 [21] at 24 months. CDK4/6 inhibitor combination with fulvestrant resulted also in a significantly improved OS in ML3 [27], reinforcing the alternative role of this combination to chemotherapy as first line.

Similar or greater effect has also been observed also in patients already exposed to HT for metastatic disease: the PFS HR was 0.47 in PL3 [39], 0.64 IN ML3 [40] and 0.48 in MC2 [37]. A high rate of objective response has also been obtained in patients with liver metastases, ranging from 41.3% in PL2, to 53% in ML2 and 54.1% in MC3. Moreover, a tumor shrinkage has been observed as early as 8 weeks [after starting treatment [41]. In MC2, patients with ET resistance and visceral disease obtained the greater degree of benefit in respect with second line ET alone, (HR 0.675) [33]. As a whole, despite the lack of direct comparisons, these results are probably better than those achievable with chemotherapy.

Question 3: is there any difference among the different CDK4/6 inhibitors that could guide the choice of a specific compound?

The pharmacodynamic effects of the 3 different CDK4/6 inhibitors are quite different [42]: the effect on CDK6 (that plays a critical role in hematopoietic stem cell differentiation) is higher for palbociclib than for abemaciclib and ribociclib, whereas the effect on CDK4 (important for breast tumorigenesis) is greater for abemaciclib. Moreover, abemaciclib inhibits also CDK 9 (and at a lesser extent CDK 2), which are probable responsible for the gastrointestinal side effects. Due to pharmacokinetic parameters abemaciclib needs for a continuous schedule of administration, whereas both palbocilib and ribociclib are used with an intermittent schedule (3 weeks on, 1 week off). The bioavailability of palbociclib is influenced by foods, whereas both ribociclib and abemaciclib can be taken independently from foods. Finally, abemaciclib seems to better penetrate the brain barrier, with a potential effect on brain metastases.

The adding of a CDK4/6 inhibitor to HT increases the incidence of side effects [22,23,25,30,32]. Some difference exists among the three CDK4/6 inhibitors, mainly due to the different selectivity for different CDKs. Drugs with higher selectivity on CDK4 and 6 (palbocilib and ribociclib) show high frequency of hematologic side effects, like neutropenia and, at a less extend, of anemia. Abemaciclib, inhibiting also CDK9, has more effects on the gastrointestinal tract, mainly diarrhea and nausea [43]. All the three drugs where associated with fatigue, and ribociclib can also induce a QTc prolongation. This latter has not yelded clinically important arrhythmias in the Monaleesa trials; however, it could rise concern in case of other QTc modifying concomitant drugs or in case of electrolyte disturbance (mainly ipokaliemia) due to other drug side effects or disease complication [44]. Both ribociclib and abemaciclib can induce ALT and/or AST increase, and abemaciclib has been associated with a higher incidence of thromboembolic events. During treatment with abemaciclib an increase in creatinine level has been reported: this seems related to an on-target effect of the drug as a competitive inhibitor of the efflux transporter (MATE1 and MATE2-K) in the proximal tubule of the kidney and should not reflect a renal dysfunction [45].

These effects should be taken into consideration when prescribing CDK4/6 inhibitor, particularly in case of patients with concomitant hematological, liver or cardiovascular disease, along with a careful evaluation of potential interactions with concomitant drugs. The need for frequent monitoring of patients (during the first 2 courses) should also to be considered, mainly in patients with difficulties in

accessing hospital, like elderly patients, living in the countryside and/or without caregivers (even if age per se is not a criterion to treatment exclusion).

These differences, along with the different safety profile, might be considered at the time of treatment choice, particularly in case of concomitant gastrointestinal disease.

Question 4: in patients with early recurrence after AI, should a CDK4/6 inhibitor with fulvestrant be preferred to everolimus plus exemestane?

No data from a direct comparison between these regimens are available. However, at a cross-trial comparison, the results of Bolero-2 (BL2) [34] can be matched with those of PL3 [30,31], MC2 [32] and ML3 [21]. Patients in BL2 had received a higher number of previous lines of therapy (≥ 3 lines: 53% in BL2, 14% in PL3, which can partially explain (along with the different HT companion) the different results (both for the control arm and the experimental arm of the trials). Median PFS was 7.8 months in BL2 (HR 0.45), 9.5 in PL3 (HR 0.46), 16.4 in MC2 (HR 0.55) and 14.9 in ML3 (HR 0.56). A not significant increase in median OS, from 26.6 to 31 months (HR 0.89), has been reported in BL2 [35], whereas a meaningful increase, from 28 to 34.9 months in PL3 (HR 0.81) [31], and from 37.3 to 46.7 months in MC2 [32] has been reported. Moreover, the different safety profile and patient's tolerability of everolimus versus CDK 4/6 inhibitors has to be considered: stomatitis, hyperglycemia, anemia, fatigue, dyspnea and pneumonitis, observed with everolimus [34], while neutropenia, leukopenia, fatigue, nausea, diarrhea (mainly for abemaciclib), and liver enzyme increase are commonly observed with CDK 4/6 inhibitors (with some differences among them) [21,22,23,25,30,32].

FInally, the data obtained with CDK4/6 inhibitors plus fulvestrant can be better translated to the current clinical scenario, in which patients have received HT just as adjuvant or as first line metastatic therapy. However, if we consider these patients as potentially hormone-resistant, a reasonable alternative could be chemotherapy. No data from randomized trials about this comparison are available to date.

Question 5: should any biomarker be recommended to guide the choice between HT and HT plus CDK4/6 inhibitor or HT plus everolimus?

All the trials with CDK4/6 inhibitors or with everolimus had an extensive biomarker program. In many cases the biomarker data derive from analyses of primary tumor, and on a limited extent from metastatic tissue. In many cases blood samples obtained before starting treatment have been used for the analysis of ctDNA. In patients potentially endocrine-sensitive (unexposed to HT or with late recurrences), the results of these analyses did not detect any biomarker clearly associated with response or resistance to CDK4/6 inhibitors in PL1 [46], PL2 [47] and ML2 [23]. PFS improvements were obtained

irrespective to Rb, p16, Ki76, CCND2A, CCND1, ERS1 and PIK3CA status. In patients with acquired resistance (i.e. recurrence during HT) in PL3 trial, ctDNA ESR1 mutations, promoting an estrogen independent tumor growth, were detected in 25-30 % of patients [47]. However, no evidence of a differential effect of HT plus palbociclib was observed, probably depending on the retained activity of fulvestrant also against the mutated receptor. Indeed, the same positive effect of palbociclib plus fulvestrant was observed in the mutated or WT cohorts (HR 0.48 and 0.45 respectively). Interestingly, the "dynamic" of ctDNA biomarkers seem to provide predictive information, as patients with a reduction both of ESR1mut ations and PIK3CAmutations at day 15 showed a PFS significantly better than patients with persistently high level of ctDNA mutations [48]. The circulating DNA ratio at day 15 (CDR15) of PIK3CA mutation was also predictive of the effect of palbocilib plus fulvestrant, but not of fulvestrant alone [49].

In the Bolero 2, in patients failing treatment with NSAI, an extensive biomarkers analysis was performed [50]. PIK3CA was the most frequent genetic alteration, and was associated with worst outcome, but not with a differential benefit of the everolimus and exemestane combination over exemestane alone. The combination was also associated with better PFS both in case of ESR1 D538G mutation and in ESR1wt, whereas no difference in the ESR1 Y537S mutation has been observed.

A recently published post-hoc analysis of Bolero2 showed that about 60% only tumors had a genetic profile belonging to the luminal subclasses (46.7% luminal A and 15.7% luminal B) with PAM50 [51]. Both luminal and non-HER2 enriched showed a significant PFS benefit with everolimus versus non-luminal and HER2-enriched, respectively. However, this could not be true for CDK4/6i, due their ability to inhibit the growth of HER2-positive cell lines in preclinical model and to reduce cell proliferation in neoadjuvant setting when combined with fulvestrant and anti-HER2 agents, without chemotherapy [52]. Taken together, the currently studied biomarkers seem to be robustly prognostic (i.e associated with early progression and worst prognosis), but fail to demonstrate a predictive value.

Question 6: Which is the optimal therapeutic strategy after first line therapy with CDK4/6 inhibitors?

Three main types of resistance to CDK4/6 inhibitors have been identified [47, 53], related to 1) hyperactivation of the target (like CDK6 increase due to FAT1 & HIPPO pathway activation), 2) to the loss of target (like Rb loss) or 3) to activation of bypass mechanisms (like cyclin E increase). Moreover, FGFR1 gain and p53 mutation have been supposed as inductors of early progression.

Several rational therapeutic approaches are in development to address these situations. At the moment, current options in case of progression after CDK4/6 inhibitors are represented by chemotherapy, mTOR inhibitors plus exemestane, or HT alone.

The use of CDK4/6 inhibitors beyond progression have been explored through different strategies, mainly represented by: a) changing the CDK4/6 inhibitor: abemaciclib after palbocilib failure has been administered in 58 pts, alone or combined with antiestrogen, with about 35% patient remaining on therapy for more than 6 months [54,55]; b) continuing the same CDK4/6i plus hormone, and adding everolimus. In the TRINITI-1 trial [56] 95 pts (66% with liver metastases) were treated with ribociclib plus exemestane plus everolimus after progression on a previous ribociclib-based treatment. A 24 week-clinical benefit (the primary endpoint of the study) was observed in 41% of cases, with 8% ORR. Median PFS was 5.7 months, with 1-year PFS of 33.4%. Notably, detection of ESR1 mutation in the ctDNA was associated with worse outcome (median PFS 3.5 vs 6.9 in patients with and without ESR1 mutation, respectively). Numerically shorted PFS was also observed in PIK3Ca mutated tumors. Some other prospective trials are exploring the triplet combination (MAINTAIN, NCT02632045; PACE, NCT 03147287; PALMIRA, NCT 3809988); c) in the PIK3Ca mutated tumor, after the first signal of activity with PIK3CA selective inhibitor alpelisib in the SOLAR-1 (10.9 mos median PFS in endocrine resistant tumors, few exposed to CDK4/6i) [57], trials enrolling only PIK3Ca mutated and CDK4/6 failing tumors are ongoing, like the confirmatory BYLive trial (NCT03056755) . Capivasertib (a selective AKT inhibitor) has been also combined with fulvestrant in the phase 1-2 FAKTION trial [58] in 140 menopausal women failing AIs, also doubling the response rate. An interesting increase in PFS from 6.3 to 10.3 months has been reported., more evident in the subgroup showing an activation of the PIK3/AKT/PTEN pathway. The final results of these and future trials would allow for a more tailored approach to these tumors.

Question 7: Are the results achieved with the CDK4/6 inhibitors in post-menopausal women transferables to premenopausal patients?

In the PL3, ML3 and MC2 trials a limited number of premenopausal women were enrolled, provided that their ovarian function was inhibited with LH-RH agonist (ovarian function suppression, OFS). The subgroup analysis of these trials did not show any differential effect in PFS. A substantial proportion of hormone-receptor positive, metastatic breast cancer patients are pre-menopausal. ML7 [28, 29] was the first trial specifically addressing the role of a CDK4/6 inhibitor (ribociclib) in premenopausal women. A total of 672 patients treated with goserelin were randomized to receive NSAI or TAM + ribociclib vs placebo. After a median FU of 34.6 months significant benefits in PFS, and more important, in OS were reported. Ribociclib reduced the risk of progression by 31%, and the risk of death by 29%, with median OS not reached vs 40.9 months. At 42-month landmark analysis, 70% of patients treated with ribociclib were alive, vs 46 with placebo. Patients receiving NSAI seemed to derive a greater benefit with respect

to those treated with tamoxifen. Ribociclib significantly delayed the time to first chemotherapy, and seemed also to favorably impact on the efficacy of the next line of therapy (carry-over effect).

These results established the combination of ribociclib plus ET and OFS as the new standard for premenopausal ER+/HER2- metastatic breast cancer as first line.

In premenopausal women the combination of OFS plus exemestane plus palbociclib was compared with chemotherapy (capecitabine at standard dose) in the Young-PEARL trial [59]. Among the 178 tamoxifen-pretreated patients enrolled, 51% were treatment naïve for advanced disease, about 20% had been exposed to chemotherapy in the metastatic setting, and about 50% had visceral disease. Median PFS was significantly better with the palbociclib-based treatment (20.1 vs 14.4 months, HR 0.659, p=0.046), with a response rate was also numerically higher in the palbociclib-ET combination arm (50.8% vs 44.8%). This study further supports the role of CDK4/6 inhibitors combined with ET in first line advanced breast cancer.

Strategies to prolong response to endocrine therapy

Several options are now available to treat ER+/HER2- metastatic breast cancer, which can be used rationally based on tumor biology, clinical course of disease and patient's characteristics. The ultimate goal is to maintain the inhibition of the hormone-related cell control machinery as long as possible, through a fine tuning of the different mechanisms operating in the tumor, without either over or under treatment. Eventually, all patients develop hormone resistance and need chemotherapy; however, delaying the time to definitively abandon hormone drugs and to start chemotherapy is a significant endpoint, in order to preserve quality of life. Indeed, the response to chemotherapy is frequently suboptimal in ER+/HER2- BC, the duration of response is limited and toxicity often substantial. CDK4/6 inhibitors combined with hormones represent a new important option, and the impulse to use them in every case is very high. No patient subgroup was identified that seemed to derive no benefit from the addition of a CDK4/6in to ET, independently of age, tumor location, tumor burden and DFI, but considering the different degree of benefit in subgroups of patients could reasonable. Therefore, the combination of a CDK4/6 inhibitor + ET should always be considered, unless in presence of clear contraindications to CDK4/6i due to comorbidities or to visceral crisis. On the other hand, no trials included a predefined crossover from ET to ET+CDK4/6 inhibitor at time of progression, not allowing a clear understanding as to whether an upfront CDK4/6 inhibitor use is superior to a sequential use. The supporters of early use of CDK4/6i emphasize the length and degree of response, and the risk that a rapidly progressing tumor could preclude their subsequent use. On the opposite, the number and

duration of side effects, the need for closer patient's monitoring, the increased service workload for treating institutions, and the costs of treatments could suggest to carefully select patient for early or delayed combination therapy.

Based on reported evidence from clinical trials and ABC and ESMO guidelines, attempts to refine current recommendations for treatment of HR+/HER2- MBC by suggesting possible treatment sequences in three scenarios of response to endocrine therapy can be proposed **(Figure 1).** The scenarios include primary and secondary resistance, as defined by the ESMO guidelines [2], and a situation of prolonged endocrine sensitivity defined by late or very late relapse after adjuvant endocrine therapy. In patients with primary resistance, the OS survival benefit observed with the addition of CDK4/6 inhibitors to endocrine therapy clearly justify their role as first option in respect to chemotherapy, unless signs of severe organ dysfunction are present (i.e. overt visceral crisis). Everolimus combined with exemestane appears to have a lower efficacy and tolerability than CDK4/6 inhibitor-based combinations and may, therefore, be more suitable for subsequent lines of treatment, as an alternative to chemotherapy depending on disease burden and symptoms. Of note, the evidence supporting an additional line of treatment with another regimen containing a targeted agent is currently limited.

Treatment sequences for patients with secondary resistance are similar to those for patients with primary resistance **(Figure 1)**, with even less room for chemotherapy.

In patients exhibiting long endocrine sensitivity, asymptomatic disease, bone-only disease, and no visceral disease, the best choice may be endocrine therapy with fulvestrant or AIs, coupled with close monitoring of disease progression **(Figure 1)**. Postponing the addition of CDK4/6 inhibitors to endocrine therapy in these patients may be worth considering since robust evidence supports the efficacy of CDK4/6 addition not only in the first- but also the second-line setting.

Finally, in symptomatic patients exhibiting endocrine sensitivity and presenting with visceral disease – even if with high burden of disease – it may be advisable to use the combination CDK4/6 inhibitor plus AI (letrozole) or fulvestrant, based on the elevated response rates reported in the clinical trials.

Future Perspective

The CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib have substantially changed the treatment options for HR+/HER2- MBC and, used in combination with endocrine therapy, prolong survival and improve response rates in both first- and second-line settings. However, while appropriate sequencing

of the currently available options has the potential to prolong endocrine sensitivity, slowing disease progression and postponing the need for chemotherapy as long as possible, considerable researches continue in the attempt to define the optimal treatment sequence. Strategies for the optimal sequential use of the available options in various settings of response to endocrine therapy are being refined through ongoing clinical trials paralleled by advances in clinical practice.

Efforts to overcome intrinsic and acquired resistance ant to identify predictive biomarkers remain challenging. Progress in this area is urgently required to guide therapy and improve the ability of the multidisciplinary team to determine optimal treatment regimens taking into consideration response to previous treatments alongside with disease symptoms and tolerability, leading to more personalized sequential strategies and improved outcomes for patients with MBC. The evaluation of PIK3CA mutation (both on tissue and plasma) seems to be particularly important, due to the availability of PIK3CA selective inhibitors. PIK3CA mutations occurs in about 40% of breast cancer patients, resulting in possible impairment of ET-sensitivity. Mutations occur early in the disease evolution, and the knowledge of PKI3CA status might be important in defining treatment strategy. SOLAR-1 [57] demonstrated that alpelisb (a selective PIK3CA inhibitor) combined with fulvestrant improves PFS 5.7 to 11 months from (HR 0.65) in patients failing ET (70% of whom with secondary resistance). These results could suggest to assess as soon as possible the PIK3ca status, and to consider alpelis for mutated breast cancer with secondary resistance to ET (the evidence for primary resistance are weaker due to the limited number of patients enrolled in SOLAR-1). However, no data comparing ET plus alpelis or CDK4/6 inhibitors are available. In case of primary resistance, CDK4/6 inhibitors plus ET, due to OS improvement, should be clearly considered as first option. In case of secondary resistance or in patients ET-naïve, a differential strategy for PIK3ca wild-type or mutated tumors might be discussed.

As new evidence accumulate, progressive changes in guideline recommendations are expected in the next future.

Multiple relationships have been reported also among ER, CDK pathway and BRCA mutations [60]. In clinical trials, ER+/BRCA mutated metastatic breast cancer PARP inhibitors (olaparib and talazoparib) [61,62] showed to be more effective than standard therapy, even if better effects were observed in triple negative subgroup. The potential role for combining a PARP inhibitor with CDK4/6 inhibitor is currently under investigation.

Finally, the role of CDK4/6 inhibitors in the adjuvant setting is also being addressed by large ongoing studies, like PALLAS, MONARCH-E and NataLEE, whose results could further modify the scenario of their clinical use, either for early and advanced breast cancer settings.

Executive Summary

Hormone receptor (HR)-positive/HER2-negative metastatic breast cancer

- Targeted agents that inhibit intracellular pathways important for cell proliferation –CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib, everolimus, PIK3CA selective inhibitors – have expanded the treatment options for hormone receptor (HR)-positive/HER2-negative metastatic breast cancer (MBC).
- In combination with endocrine therapy, targeted agents prolong the time to progression and improve response rates in both first- and second-line settings.
- Improvement in overall survival recently reported reinforced the main role of CDK4/6 inhibitors plus ET in treatment strategy
- Optimal sequencing of the available options may prolong endocrine sensitivity, slow disease progression, and delay the need for chemotherapy.

Extending disease control

- Endocrine therapy can ensure extended disease control in HR-positive MBC.
- CDK4/6 inhibitors, everolimus, PIK3CA inhibitors target key mechanisms of the estrogen receptor pathway.
- Targeted agents prolong endocrine sensitivity and delay the need for chemotherapy.
- Optimal sequencing of endocrine therapy combined with targeted agents is crucial.

Personalized therapy

- More data are needed to define the best sequence of endocrine treatments, and there is a lack of predictive markers.
- More personalized sequential strategies, which take into account response to previous treatments as well as disease status and symptoms and safety issues, will be increasingly feasible in patients with MBC.

Figure legends

Figure 1. Sequence of treatments in three scenarios of response to endocrine therapy in postmenopausal patients.

a. If previous endocrine therapy was tamoxifen.

b. If previous endocrine therapy was an aromatase inhibitor.

c. If not previously exposed to fulvestrant.

d. Close monitoring of disease progression required.

AI: aromatase inhibitor; CDK4/6i: inhibitor of cyclin-dependent kinases 4 and 6; ET: endocrine therapy.

Table legends

Table 1. Key phase III trials investigating endocrine therapies for the treatment of HR-positive, HER2-negative metastatic breast cancer

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Table 1. Key phase III trials investigating endocrine therapies for the treatment of HR-positive, HER2-negative metastatic breast cancer

STUDY	PATIENT POPULATION (N)	TREATMENTS	PRIMARY ENDPOINT	SECONDARY ENDPOINTS	RESULTS (Arm 1 vs. Arm 2)
STUDIES WITH FULVESTRANT					
CONFIRM Di Leo et al, 2014 [63]	• Postmenopausal women with metastatic or locally advanced breast cancer (736) • Relapsed on adjuvant therapy or within 12 months from completion • Relapsed after >12 months from adjuvant therapy or with *de novo* advanced disease, and already treated with ET or AI	• Arm 1: fulvestrant 500 mg IM/month + 500 mg on day 14 of month 1 • Arm 2: fulvestrant 250 mg IM/month + 500 mg on day 14 of month 1	PFS	ORR, CBR, DoCB, DoR, OS, tolerability, QoL	• PFS significantly longer with fulvestrant 500 vs. 250 mg (HR 0.80; 95% CI 0.68-0.94; p = 0.006) • Median OS: 26.4 vs. 22.3 months (HR 0.81; 95% CI 0.69-0.96; p = 0.02) • Fulvestrant 500 mg well tolerated with no dose-dependent AEs
FALCON Robertson et al, 2016 [36]	ET-naïve postmenopausal women with locally advanced or metastatic breast cancer (462)	• Arm 1: fulvestrant 500 mg IM/month + 500 mg on day 14 of month 1 • Arm 2: anastrozole, 1mg/d orally	PFS	ORR, CBR, DoCB, DoR, OS, QoL, safety and tolerability	Median PFS: 16.6 vs. 13.8 months (HR 0.797; 95% CI 0.637-0.999; p = 0.0486)
FACT Bergh et al, 2012 [64]	• Post- and premenopausal women at first relapse after primary treatment (514) • One-third ET-naïve	• Arm 1: fulvestrant 500 mg IM on day 1 and 250 mg on days 15 and 29 and then every 4 weeks + anastrozole 1 mg/d orally • Arm 2: anastrozole 1 mg/d orally	TPP	ORR, TTF, DoR, CBR, OS	• TPP: 10.8 vs. 10.2 months (HR 0.99; 95% CI 0.81-1.20; p = 0.91) • Median OS: 37.8 vs. 38.2 months (HR 1.0; 95% CI 0.76-1.32; p = 1.00)
SWOG 0226 Metha et al, 2019, 2012 [18,65]	• Postmenopausal women with MBC • No prior treatment for metastatic disease • Adjuvant tamoxifen, or adjuvant AI completed >12 months before enrollment (707) • 39% with *de novo* MBC	• Arm 1: anastrozole 1 mg/d orally • Arm 2: anastrozole 1 mg/d orally + fulvestrant 250 mg IM on day 14 and 28 of first cycle, then every 28 days	PFS	OS, CBR, ORR	• Median PFS: 13.5 vs. 15.0 months (HR 0.80; 95% CI 0.68-0.94; p = 0.007) • Median PFS in women with no prior tamoxifen: 12.6 vs. 17.0 months (HR 0.74; 95% CI 0.59-0.92; p = 0.006) • Median OS: 41.3 vs. 47.4 months (HR 0.81; 95% CI 0.65-1.00; p = 0.05)

SoFEA Johnston et al, 2013 [66]	• Postmenopausal women with locally advanced or metastatic breast cancer who had relapsed or progressed on a NSAI (723) given as adjuvant for ≥12 months or as first-line for ≥6 months • 81% had previously received an NSAI in the advanced or metastatic setting	• Arm 1: fulvestrant (500 mg IM on day 1, followed by 250 mg on days 15 and 29, and then every 28 days) plus anastrozole (1 mg/d, orally) • Arm 2: fulvestrant plus anastrozole-matched placebo • Arm 3: exemestane (25 mg/d, orally)	PFS	OS, ORR, CBR, DoR, DoCB, tolerability and safety	Median PFS: 4.4, 4.8, 3.4 months in arms 1, 2, and 3, respectively; Arm 1 vs. Arm 2 and Arm 2 vs. Arm 3 not significantly different
STUDIES WITH EVEROLIMUS					
BOLERO-2 Baselga et al, 2012; Piccart et al, 2014 [34,35]	• Postmenopausal women with advanced breast cancer refractory to NSAIs in the adjuvant or advanced setting, or both (724) • Refractory disease defined as recurrence during or within 12 months after adjuvant treatment, or progression during or within 1 month after the end of treatment for advanced disease • 20% received study treatment as first-line	• Arm 1: exemestane (25 mg/d, orally) + everolimus (10 mg/d, orally) • Arm 2: exemestane (25 mg/d, orally)	PFS	OS, ORR, CBR, time to deterioration of ECOG performance status, safety, QoL	• Median PFS (final): 7.8 vs. 3.2 months (HR 0.45; 95% CI 0.38-0.54; $p < 0.0001$) • Median PFS (final, central assessment): 11.0 vs. 4.1 months (HR 0.38; 95% CI 0.31-0.48; $p < 0.0001$) • ORR (final): 12.6% vs. 1.7%, $p < 0.0001$ • ORR (final, central assessment): 12.6% vs. 2.1%, $p < 0.001$ • No difference in OS • Manageable AEs in both arms
STUDIES WITH CDK4/6 INHIBITORS					
PALOMA-2 Finn et al, 2016 [22]	• Postmenopausal women with advanced breast cancer and no prior systemic therapy for advanced disease (666) • About 30% in both arm with *de novo* disease • About 56% in both arms had received ET in the adjuvant setting	• Arm 1: letrozole (2.5 mg/d, orally) + palbociclib (125 mg/d, orally) for 3 weeks followed by 1 week off in 28-day cycles • Arm 2: letrozole (2.5 mg/d, orally)	PFS	OS, ORR, CBR, PRO, PK effects, safety	• Median PFS: 24.8 vs. 14.5 months (HR 0.58; 95% CI 0.46-0.72; $p < 0.001$) • ORR: 42.1% vs. 34.7% (OR 1.40; 95% CI 0.98-2.01) • CBR: 84.9% vs. 70.3% (OR 2.39; 95% CI 1.58-3.59) • OS data immature • Higher rate of myelotoxic effects with combination therapy

PALOMA-3 Cristofanilli et al, 2016 Turner et al, 2018; [30,31]	• Premenopausal, perimenopausal and postmenopausal women with advanced breast cancer that had relapsed or progressed during prior ET (521) • 79.3% postmenopausal • 23.4% with *de novo* MBC	• Arm 1: palbociclib (125 mg/d orally for 3 weeks, followed by 1 week off) + fulvestrant (500 mg IM every 14 days for the first 3 injections and then every 28 days) • Arm 2: fulvestrant (500 mg IM every 14 days for the first 3 injections and then every 28 days)	PFS	OS, ORR, CBR, PRO, safety	• Median PFS (final analysis): 9.5 vs. 4.6 months (HR 0.46; 95% CI 0.36-0.59; p < 0.0001) • ORR (final): 19% vs. 9% (OR 2.47; 95% CI 1.36-4.91; p = 0.0019) • CBR: 67% vs. 40% (OR 3.05; 95% CI 2.07-4.61; p < 0.0001) • OS 34.9 vs 28.0 months (HR 0.81 ; 95% CI 0.64-1.03 ; p= 0.09) • Hematologic AEs more frequent with combination therapy
MONALEESA-2 Hortobagyi et al, 2016; Hortobagyi et al, 2018 [23,24]	• Postmenopausal women with MBC not previously treated with systemic therapy for advanced disease (668) • Previous neoadjuvant or adjuvant NSAI not allowed, unless disease-free interval >12 months • 34% had *de novo* MBC	• Arm 1: ribociclib (600 mg/d on a 3-week-on, 1-week-off schedule, orally) plus letrozole (2.5 mg/d, orally) • Arm 2: letrozole (2.5 mg/d, orally)	PFS	OS, ORR, CBR, safety, QoL	• Median PFS (second interim analysis): 25.3 vs. 16.0 months (HR 0.568; 95% CI 0.457-0.704; p = $9.63x10^{-8}$) • Longer PFS also in pts with *de novo* MBC (HR 0.45; 95% CI 0.27-0.75) • ORR: 42.5% vs. 28.7%, p = $9.8x10^{-5}$ (54.5% vs. 38.8% in pts with measurable disease, p = $2.54x10^{-4}$) • OS data immature • Higher rates of myelosuppression with combination therapy
MONALEESA-7 Tripathy et al, 2017; Im et al, 2019 [28,29]	Premenopausal and perimenopausal women with advanced breast cancer (672)	• Arm 1: ribociclib (600 mg/d on a 3-week-on, 1-week-off schedule, orally) plus either tamoxifen or NSAI, and goserelin • Arm 2: either tamoxifen or NSAI, and goserelin	PFS	ORR, OS	• Median PFS: 23.8 vs. 13.0 months • Media OS: not reached vs 40.9 months (HR 071; 95% CI 0.535-0.948) • ORR: 51% vs. 36% • More AEs with combination therapy, though manageable • Low (<5%) and similar rates of AEs leading to permanent discontinuation
MONALEESA-3 Slamon et al, 2018, 2019 [21,27]	• Postmenopausal women with advanced breast cancer (726) • 49.2% receiving study treatment as first-line ET	• Arm 1: ribociclib (600 mg/d on a 3-week-on, 1-week-off schedule, orally) plus fulvestrant (500 mg IM every 14 days for the first 3 injections and then	PFS	Overall RR, OS, safety and tolerability	• Median PFS: 20.5 vs. 12.8 months (HR 0.593; 95% CI 0.480-0.732; p < 0.001); HR in ET-naïve patients 0.577 (95% CI 0.415-0.802) • Median OS : NR vs 40.0 months (HR 0.724 ; 95% CI 0.568-0.924 ; p=

		every 28 days) • Arm 2: fulvestrant (500 mg IM every 14 days for the first 3 injections and then every 28 days)			0.0045) ; HR in first line 0.70 (95% CI 0.479-1.021) • Overall RR: 32.4% vs. 21.5%, p < 0.001; in the population with measurable disease: 40.9% vs. 28.7%, p = 0.003 Grade 3-4 AEs with a frequency >5%: neutropenia (53.4% vs. 0) and leukopenia (14.1% vs. 0)
MONARCH-3 Goetz et al, 2017; Johnston et al, 2019 [25,26]	Postmenopausal women with advanced breast cancer and no prior systemic therapy for advanced disease (493)	• Arm 1: abemaciclib (150 mg twice daily, orally) plus anastrozole (1 mg/d, orally) or letrozole (2.5/d, orally) • Arm 2: anastrozole (1 mg/d, orally) or letrozole (2.5/d, orally)	PFS	ORR, safety	• Median PFS 28.18 vs 14.76 (HR 0.54; 95%CI 0.41-0.69) • ORR: 59% vs. 44% (p = 0.004) • Acceptable safety profile
MONARCH-2 Sledge et al, 2017, 2019 [31,33]	• Women of any menopausal status, with advanced breast cancer who had progressed on neoadjuvant or adjuvant ET, ≤12 months after adjuvant ET, or while receiving first-line ET for advanced breast cancer (669) • 91.2% had progressed during first-line ET	• Arm 1: abemaciclib (150 mg twice daily, orally) plus fulvestrant (500 mg, as per label) • Arm 2: fulvestrant (500 mg, as per label)	PFS	OS, ORR, DoR, CBR, QoL, safety	• Median PFS: 16.4 vs. 9.3 months (HR 0.553; 95% CI 0.449-0.681; p < 0.001) • Median OS: 46.7 vs 37.3 months (HR 0.757; 95% CI 0.606-0.945; p=0.01) • ORR: 48.1% vs. 21.3% • Acceptable safety profile • Discontinuation rate due to AE: 15.9% vs. 3.1%

AE: adverse event; AI: aromatase inhibitor; CBR: clinical benefit rate; CI: confidence interval; CT: chemotherapy; d: day; DoCB: duration of clinical benefit; DoR: duration of response; ET: endocrine therapy; HR: hazard ratio; IM: intramuscular; MBC: metastatic breast cancer; NSAI: non-steroidal aromatase inhibitor; OR: odd ratio; ORR: objective response rate; OS: overall survival; PFS: progression free survival; PRO: patient reported outcome; pts: patients; QoL: quality of life; RR: response rate; TTP: time to progression.

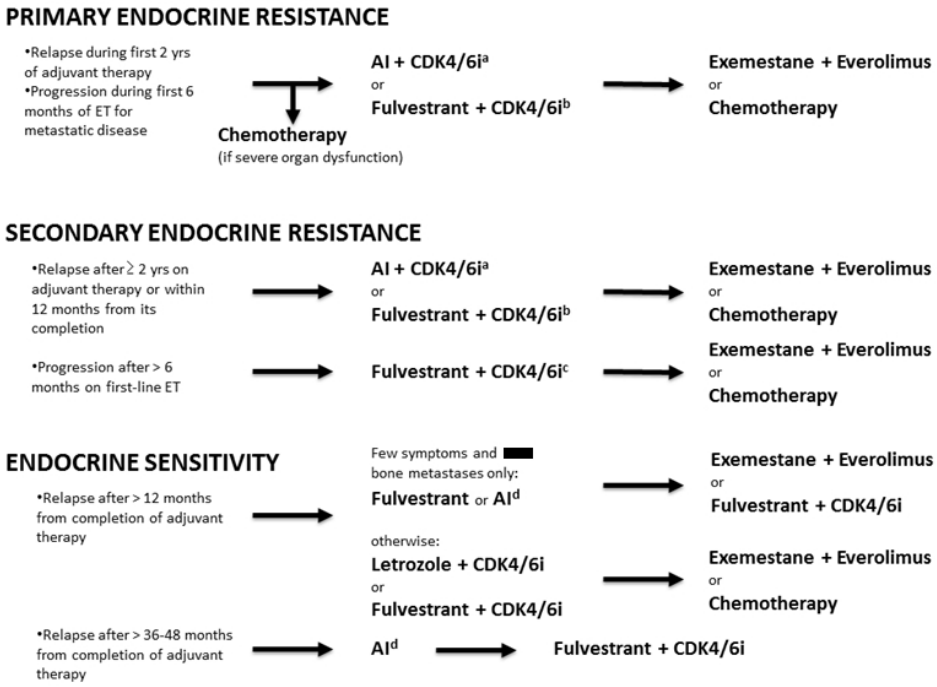

Figure 1

215x162mm (96 x 96 DPI)