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Management of ER positive metastatic breast cancer

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ABSTRACT

There are over 2 million cases a year of breast cancer, leading to over 600,000 deaths globally [1]. Despite these large numbers, increasingly more women are being cured with early stage disease and women with advanced disease are living longer [2]. The appreciation for molecular subtypes of the disease has led to significant therapeutic advances and estrogen receptor positive (ER+) breast cancer represents the largest of these subgroups. An appreciation for the importance of estrogen signaling in ER+ dates back to 1896 when Dr. George Thomas Beatson observed impressive disease responses after performing bilateral oophorectomy in 3 women at Glasgow Cancer Hospital [3]. The evolution of treatment for advanced disease from progestins, to the selective estrogen receptor modulator tamoxifen, and subsequently the aromatase inhibitors and the selective estrogen receptor degrader fulvestrant, has been accompanied by improved efficacy and decreased side effects. While the use of these drugs has changed the natural history of both early and advanced disease, it has been long recognized that many patients will develop resistance to this approach. After many years of trying to improve on single-agent endocrine treatment, since 2012 there has been an explosion of new drugs that have shown improved efficacy in combination with endocrine approaches. The first of these to receive FDA approval was the mTOR inhibitor everolimus (2012) [4], followed by the approval of 3 cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors [palbociclib (2015) [5], ribociclib (2018) [6], and abemaciclib (2018) [7]], and more recently the PI3-kinase inhibitor alpelisib (2019) [8]. In addition, chemotherapy is still used frequently when endocrine manipulations have been exhausted. Like other incurable malignancies, the goal in advanced ER+ breast cancer is to prolong survival and maintain quality of life. Currently, we have more tools available to achieve this than ever before and we will review the efficacy and side effect data with these agents that are driving physician choices for individual patients.

Introduction

Breast cancer is the most common malignancy in women and remarkable progress has been made in the management of women with advanced breast cancer [1,2]. There are an unprecedented number of new agents available, with increased attention to the molecular diversity of the disease and its impact on treatment selection. ER+ breast cancer has led the way in drug development given the early appreciation for its dependence on estrogen signaling [3]. This drove the development of several effective agents including the selective estrogen receptor modulators (SERMs), the aromatase inhibitors (AIs), and selective estrogen receptor degraders (SERDs). However, it has also been appreciated for many years that the majority of women with advanced ER+ breast cancer will progress on these treatments; some with de novo resistance and other will acquire resistance over the course of their disease eventually requiring the use of cytotoxic chemotherapy, which while active, is associated with more significant side effects than those drugs targeting the ER-pathway. A tremendous scientific effort, both laboratory and clinical, has been dedicated to understanding these mechanisms of resistance and evaluating agents that are aimed at disrupting them [4]. One area that has received a significant amount of attention has been alternative growth factor signaling to steroid hormones. Numerous studies have focused on targeting various receptor tyrosine kinases, and except for HER2, none have been successful [5]. The significant clinical advances have come over the past decade with the successful development of drugs targeting intracellular mechanisms, including mTOR, CDK4/6, and PI3-kinase [6–10]. In fact, the rapid progress made only in the past 5 years has disrupted traditional treatment paradigms on the role of chemotherapy, how best to sequence agents, and the efficacy of older drugs in the context of new data.

While still early, we are now seeing significant improvements in overall survival (OS) with the integration of these new drugs into

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a patient's treatment course. Advanced ER+ breast cancer remains incurable and our goals for patients remain the same (Box 1).

Box 1. Therapeutic goals of advanced ER+ breast cancer treatment.

- Improve overall survival
- Minimize side effects from treatment
- Improve and maintain quality of life
- Delay disease progression
- Delay time to start chemotherapy
- Provide psychosocial support

We will describe the available data with endocrine agents, molecular targeted agents, and chemotherapy, focusing on ER+/HER2-negative disease, that are providing helping patients achieve these goals. Importantly, when considering treatment options for any individual patient, there are several baseline clinical and pathological features that must be considered (Box 2).

Box 2. Baseline clinical and pathological features to consider when deciding treatment for advanced ER+ breast cancer.

- Menopausal status
- HER2 status
- PI3-kinase mutation status
- Medical co-morbidities
- Performance status
- Patients preferences
- Prior (neo-)adjuvant treatment
- Disease-free interval from adjuvant treatment
- Prior treatments for advanced disease
- Durability of response from prior therapies
- Side effects from prior treatments
- Sites of disease and overall tumor burden

Single-agent endocrine treatment

Endocrine-based treatment remains the backbone for patients with advanced ER+ breast cancer and should be the first choice for the majority of women at presentation. Guidelines have recommended chemotherapy for patients with "visceral crisis" though this is an inexact group of patients, often defined by a high tumor burden causing significant symptoms and organ dysfunction [11-13]. The basis for this recommendation is the desire for a rapid response to avoid imminent death, though there is not randomized data to support this concept. A number of endocrine agents have been studied and refined over the past several decades, establishing endocrine therapy in HR+ breast cancer as one of the first "targeted therapies" with multiple lines of treatment available (Table 1).

SERMs

Tamoxifen was the first endocrine agent approved for metastatic breast cancer in 1977 [14]. Tamoxifen is a SERM that has differential, tissue-specific effects on the estrogen receptor, resulting anti-proliferative effects in breast tissue, but in partial agonistic effects in uterine, bone, and heart muscle tissues [15]. In 1971, Cole et al. reported response to tamoxifen (known as ICI46474 at that time) in 10 out of 46 patients with advanced breast cancer, with an acceptable side effect profile [16]. In the 1980s, studies compared tamoxifen against oophorectomy, which showed comparable objective response rate (ORR) and favorable toxicity of tamoxifen [17,18]. While still used broadly, the AIs demonstrated superior efficacy as compared to tamoxifen.

Aromatase inhibitors

AIs were initially introduced in the 1980s, and work by blocking conversion of androgens to estrogens by the enzyme aromatase, thereby depriving tumor cells of the growth effects of estrogen [19]. There are currently 3 third-generation inhibitors used clinically: anastrozole, letrozole (both nonsteroidal AIs), and exemestane (a steroidal AI). In premenopausal women, AIs alone are insufficient to achieve a total blockade of estrogen synthesis, as AIs do not block ovarian production of estrogens. Therefore, they are coupled with ovarian suppression medications such at leuprolide or goserelin to achieve combined ovarian and peripheral estrogen synthesis blockade.

Anastrozole, letrozole, and exemestane have all been studied in a series of randomized phase III trials in patients with advanced breast cancer who had progressed on prior antiestrogen therapy [20-24]. Different doses of anastrozole (1 mg *v*10 mg) and letrozole (0.5 mg *v* 2.5 mg), as well as exemestane 25 mg, were compared against megestrol 160 mg total daily dose [20-22,24]. Anastrozole 1 mg was shown to be comparable to the 10 mg dose, as well as to megestrol in terms of time to progression and other clinical endpoints, but a more convenient dosing schedule and side effect profile (especially with regards to weight gain) [20,21]. Letrozole 2.5 mg compared to letrozole 0.5 mg or megestrol did exhibit a significantly better ORR, duration of response, and time to treatment failure, but not time to progression. Letrozole was also associated with a better side effect profile and a lower discontinuation rate [22]. Exemestane 25 mg compared to megestrol showed improved ORR, time to treatment failure, and time to progression [24]. Letrozole (0.5 mg and 2.5 mg) was also compared against the first generation AI aminoglutethimide 250 mg twice daily, with letrozole 2.5 mg showing superior disease control than letrozole 0.5 mg or aminoglutethimide, as well as improved treatment-related adverse effects in the letrozole arms [23].

Given the success in the second-line setting, these drugs were compared against tamoxifen in the first-line setting in a number of clinical trials. Letrozole and anastrozole both have shown improved time to progression and clinical benefit compared to tamoxifen in large, randomized phase III trials [25,26]. A third trial of anastrozole versus tamoxifen in the first-line setting did not demonstrate superiority [27]. Exemestane was also shown to be superior to tamoxifen in the first-line metastatic setting, with improved time to progression and ORR [28]. With efficacy and tolerability results in the first- and second-line setting, AIs became the standard choice for postmenopausal women in the first-line metastatic setting.

SERDs

Fulvestrant is a SERD, has a favorable side effect profile compared to other antiestrogens, but requires intramuscular (IM) injection due to poor oral availability [29]. Fulvestrant was originally approved in the second-line setting at a dose of 250 mg IM every 28 days based on noninferiority against anastrozole [30]. However, subsequently, the CONFIRM study established that high-dose (HD) fulvestrant (500 mg every 28 days) was superior to the 250 mg dose in both progression-free survival (PFS) and OS [31]. The FIRST and FALCON trials both investigated first-line fulvestrant HD versus anastrozole in postmenopausal patients with advanced breast cancer, and showed that fulvestrant HD was associated with an 2.8-month improvement in PFS (8.5 months improvement in patients without visceral disease), but similar clinical benefit rate and OS [32,33]. Based on the phase III FALCON results, fulvestrant HD was also approved in the first-line setting in 2017 [34].

Table 1
Select trial of single-agent endocrine therapy in advanced breast cancer.

Trial	Regimens	Prior lines	N	Outcomes	Notes
Ingle et al [17]	T *v* Oop	FLT	54 (26 *v* 27)	Response rate 27% *v* 37% ($P = .45$); TTP 160 *v* 144 days ($P = .74$)	Premenopausal patients; similar toxicity in both arms
Buchanan et al [18]	T *v* Oop	NR	117 (59 *v* 58)	ORR: 24% *v* 21% (NS); mOS: 15 *v* 25 months ($P = .18$)	Premenopausal patients; 2 patients in T arm with prior line category "Other"; greater toxicity in Oop arm
Jonat et al [21]	A1 *v* A10 *v* M	T	378 (135 *v* 118 *v* 125)	Response rate 34.1% *v* 33.9% *v* 32.8% (NS); mPFS 132 *v* 156 *v* 120 days (NS)	Worse weight gain with M, worse GI effects on A
Buzdar et al [20]	A1 *v* A10 *v* M	T	386 (128 *v* 130 *v* 128)	ORR 27% *v* 24% *v* 30% (NR); mPFS 170 *v* 143 *v* 151 (NR)	Worse weight gain with M, worse GI effects on A
Dombernowsky et al [22]	L2.5 *v* L0.5 *v* M	AEst	551 (174 *v* 188 *v* 189)	ORR 24% *v* 13% ($P = .004$) *v* 16% ($P = .04$); DoR NYR *v* 18.2 *v* 17.9 months ($P = .02$)	L had fewer SAEs, lower discontinuation rate, and less weight gain compared to M
Gershanovich et al [23]	L2.5 *v* L0.5 *v* Ag	AEst	555 (185 *v* 192 *v* 178)	ORR 19.5% *v* 16.7% *v* 12.4% (NS); mOS 28 *v* 21 *v* 20 months ($P = .002$)	Trend towards significant ORR favoring L2.5 *v* Ag; improved TTP for L2.5 over Ag
Kaufmann et al [24]	E *v* M	T	769 (366 *v* 403)	ORR 15% *v* 12.4% (NS); mOS NYR *v* 123.4 weeks ($P = .039$)	Weight gain more common with M; improved TTP with E
Mouridsen et al [25]	L *v* T	FLT	977 (453 *v* 454)	ORR 30% *v* 20%; $P < .001$; TTP 41 *v* 26 weeks ($P < .001$)	No significant differences in toxicity
Nabholtz et al [26]	A *v* T	FLT	353 (171 *v* 182)	ORR 21% *v* 17% (NS); CBR 59% *v* 46% ($P = .0098$)	A associated with increased TTP; more VTE and vaginal bleeding with T
Bonneterre et al [27]	A *v* T	FLT	668 (340 *v* 328)	ORR 32.9% *v* 32.6% ($P = .79$); mTTP 8.2 *v* 8.3 months ($P = .94$)	More VTE and vaginal bleeding with T
Paridaens et al [28]	E *v* T	FLT	371 (182 *v* 189)	ORR 46% v 31% ($P = .005$); mPFS 9.9 *v* 5.8 months (0.028)	No difference in long term PFS or OS
CONFIRM [31]	Fhd *v* Fsd	T or AI	736 (362 *v* 374)	mOS 26.4 *v* 22.3 months ($P = .02$)	No differences in SAEs
FIRST [33]	Fhd *v* A	FLT	205 (102 *v* 103)	CBR 72.5% *v* 67% ($P = .386$); ORR 36% *v* 35.5% ($P = .947$)	TTP significantly better with Fhd, similar toxicity profile
FALCON [32]	Fhd *v* A	FLT	462 (230 *v* 232)	mPFS 16.6 *v* 13.8 months (0.0486); DoR 20 *v* 13.2 months	Similar toxicities and discontinuation rates in both arms

A = anastrozole; AEst = antiestrogen; Ag = aminoglutethimide; CBR = clinical benefit rate; DoR = duration of response; E = exemestane; Fhd = fulvestrant high dose; FLT = first-line therapy; Fsd = fulvestrant standard dose; L = letrozole; M = megestrol; NR = not reported; NS = not significant; NYR = not yet reached; Oop = oophorectomy; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; T = tamoxifen; TTP = time to progression; VTE = venous thromboembolism.

Endocrine-based doublets

The approach to overcome endocrine resistance has taken 2 broad approaches: (1) to develop better ways of blocking estrogen signaling with endocrine-based approaches as discussed in section 2 above, and (2) to target alternative signaling pathways that may play a role in resistance. While the use of sequential single-agent endocrine manipulations can be of benefit, including even supplemental estradiol [35], the clinical benefit diminishes with each subsequent line of therapy, eventually leaving chemotherapy as the next option. Only in the past several years, has the approach to develop drugs in combination with endocrine treatments proven to be effective. These include the mTOR inhibitor everolimus, the CDK 4/6 inhibitors, and more recently the PI3-kinase inhibitor alpelisib.

Combination endocrine therapy

Before the addition of novel agents, combination studies of endocrine treatments were evaluated. Two phase 3 studies were conducted with conflicting results. The FACT study randomized over 500 patients to fulvestrant (250 mg dosing) plus anastrozole or anastrozole [36]. Approximately two-thirds had received adjuvant antiestrogens. Median time-to-progression was 10.8 and 10.2 months in the experimental versus standard arm, median OS was 37.8 and 38.2 months, respectively. On the other hand, the SWOG S0226 study randomized over 700 women to the same combination or anastrozole alone but demonstrated an improvement in median PFS from 13.5 months with anastrozole to 15.0 months with the combination (hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.68-0.94; $P = .007$) [37]. OS was also longer with combination therapy, 41.3 months versus 47.7 months (HR, 0.81; 95% CI, 0.65-1.00; $P = .05$) with similar side effects between the 2 groups. A recent update on the OS data revealed that this benefit was maintained with median OS of 49.8 months with the combination versus 42.0 months in the anastrozole-alone group (HR 0.82; 95% CI, 0.69-0.98; $P = .03$) [38]. In a subgroup analysis based on prior tamoxifen exposure in the adjuvant setting, OS among women who had not received tamoxifen previously was longer with the combination therapy than with anastrozole alone (median, 52.2 months and 40.3 months, respectively; HR, 0.73; 95% CI, 0.58-0.92) as compared to women who had received tamoxifen previously where there was no difference (median, 48.2 months and 43.5 months, respectively; HR, 0.97; 95% CI, 0.74-1.27). It is felt that the difference in adjuvant endocrine therapy use in the baseline patient populations underlie the different results between FACT and SWOG S0226, specifically, in FACT about 68% of patients had adjuvant endocrine therapy whereas in the SWOG study only 40% did.

Targeting mTOR

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that regulates various growth factor inputs [39]. Everolimus has been evaluated in multiple phase 3 studies in various breast cancer settings, but it is only ER+ breast cancer that it met its primary endpoints of improving PFS (Table 2). BOLERO-2 randomized 724 women with advanced ER+/HER2 negative breast cancer to receive either exemestane and everolimus or exemestane and placebo [4]. All patients were required to have disease that was refractory to nonsteroidal AIs, meaning recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after the end of treatment

Table 2
Positive phase 3 everolimus and alpelisib trials [4,8].

	BOLERO-2 trial (n = 724)	SOLAR-1 trial (n = 341, PI3K mutant cohort)
Drug (target)	Everolimus (mTOR)	Alpelisib (PI3kα)
Combination	Exemestane	Fulvestrant
Prior aromatase inhibitor	100%	100%
Prior fulvestrant	~17%	None
Median PFS	6.9 mos *v* 2.8 mos	11 mos *v* 5.7 mos
HR PFS	0.43 (95% CI, 0.35-0.64) $P < .001$	0.65 (95% CI 0.50-0.85) $P < .001$
Response rate (all patients)	9.5%	26.6%
Most common G3/4 adverse events	Stomatitis, anemia, dyspnea, hyperglycemia, pneumonitis	Hyperglycemia, rash, diarrhea

for advanced disease. Other anticancer endocrine treatments and a single prior chemotherapy regimen for advanced disease were also allowed. PFS with the doublet was 6.9 months versus 2.8 months for exemestane-alone (HR 0.43; 95% CI, 0.35-0.54; $P < .001$). The markedly short PFS in the control arm reflects the minimal activity of exemestane in this pretreated cohort (over have the patients in each arm had more than 3 prior therapies in the early or advanced setting). The study was the first phase 3 study to demonstrate that a novel agent, when added to endocrine therapy can improve PFS. Response rates were also improved; 9.5% and 0.4% in the combination-therapy and exemestane-alone groups, respectively ($P < .001$). OS, a traditionally difficult endpoint to achieve in ER+ breast cancer, however, was not improved; median OS in patients receiving the combination was 31.0 months (95% CI, 28.0-34.6 months) compared with 26.6 months (95% CI, 22.6-33.1 months) in patients receiving exemestane-alone (HR = 0.89; 95% CI 0.73-1.10; log-rank $P = .14$). Toxicity was increased with the combination. The most common grade 3 or 4 adverse events were stomatitis (8% in the combination group *v* 1% in the exemestane-alone group), anemia (6% *v* <1%), dyspnea (4% *v* 1%), hyperglycemia (4% *v* <1%), fatigue (4% *v* 1%), and pneumonitis (3% *v* 0%). Subsequent to the approval, the prophylactic use of dexamethasone mouthwash was shown to significantly diminish the severity of everolimus induced stomatitis [40].

A randomized double-blind phase 2 study also evaluated everolimus in combination with fulvestrant. PrE0102 randomized 131 women between the combination and fulvestrant and placebo. In this study, patients were required to AI-resistant disease (defined here either as relapse while receiving adjuvant AI therapy or disease progression while receiving an AI for metastatic disease), and no more than one prior chemotherapy regimen for metastatic disease. Though a relatively small study, like BOLERO-2 it demonstrated the combination improved median PFS from 5.1 to 10.3 months (HR, 0.61 [95% CI, 0.40-0.92]; stratified log-rank $P = .02$) though the ORRs were similar (18.2% *v* 12.3%; $P = .47$). The side effect profile was similar as in BOLERO-2.

CDK 4/6 inhibitors

The idea of targeting the cell cycle in cancer medicine is not new, but was limited by the lack of efficacy and toxicity of first-generation compounds that were pan-CDK inhibitors. PD-0332991, now known as palbociclib, was the first of a new generation of CDK 4/6 specific inhibitors that demonstrated preferential preclinical activity in ER+ breast cancer models [41]. These data lead to the PALOMA1/ TRIO-18 study, a proof-of-concept Phase 1/2 of letrozole plus palbociclib versus letrozole alone. This study demonstrated a more than 10-month improvement in PFS with a predictable safety profile, with the most common adverse event being on-target leukopenia and neutropenia. Based on these data, the FDA granted palbociclib and letrozole accelerated approval for the first-line treatment of advanced ER+ breast cancer. Since this time, the importance of CDK 4/6 inhibition in the treatment of advanced breast cancer has been validated in 8 randomized phase 3 studies with palbociclib, ribociclib, and abemaciclib (Tables 3 and 4). While the baseline characteristics of the patients in these studies are somewhat different between compounds, the efficacy is quite comparable. Similarly, they all cause some degree of neutropenia (though the risk of neutropenic fever is less than 2%), but they also have some unique side effects depending on the compound (Table 5).

Targeting PI3-kinase

The PI3-kinase (PI3K) pathway plays a key role in cellular metabolism and growth [42]. Genetic mutations in the pathway are among the most common in breast cancer and are felt to play a role in endocrine resistance [43]. Alpelisib is a specific small molecule inhibitor of the α-specific subunit of PI3K. A phase 3 study evaluated it in combination with fulvestrant versus fulvestrant and placebo in both patients with and without PI3K mutations (Table 2) [8]. The study met its endpoint of improving PFS only in those patient that harbored mutations (11.0 months; 95% CI, 7.5–14.5) in the alpelisib and fulvestrant group, as compared with 5.7 months (95% CI, 3.7-7.4) in the placebo and fulvestrant group (HR for progression or death, 0.65; 95% CI, 0.50-0.85; $P < .001$). The most frequent adverse events of grade 3 or 4 were hyperglycemia (36.6% *v* 0.7%) and rash (9.9% *v* 0.3%) in the combination group versus placebo, respectively. Diarrhea of grade 3 occurred in 6.7% as compared with 0.3%. There was no significant activity seen in those patients without PI3K mutations. These data validate PI3K as a target in ER+ breast cancer and provide another option for this population of patients. Importantly, of the 341 patients with PI3K mutations, only 20 had been treated with a prior CDK 4/6 inhibitor. At ASCO 2020, data from cohort A of the non-comparative BYLieve study was presented [44]. In this arm, 121 women with advanced ER+/HER-2 negative advanced breast cancer that had progressed on an AI and CDK 4/6 inhibitor received alpelisib and fulvestrant as their next line of treatment. The primary endpoint of percent of women that were disease free at 6 months was met with over half the patients (50.4%, 95% CI 41.2-59.6) alive and without disease progression at 6 months. Median PFS was 7.3 months (95% CI, 5.6-8.3) and the ORR was 21% (95% CI, 32.2-52.3) in patients with measurable disease. There were no new safety signals. In regards to the role of CDK 4/6 inhibitors in patients with PI3K mutations, data from studies with CDK 4/6 inhibitors and fulvestrant have shown no difference in benefit in patients with or without PI3K mutations [45].

Cytotoxic chemotherapy

While single-agent or doublet endocrine regimens remain the mainstay of systemic therapy for metastatic ER+ breast cancer, cytotoxic chemotherapy remains a viable option for patients who have progressed on endocrine therapy. While combination chemotherapy regimens may have a higher chance of inducing a response, this comes at significantly increased toxicity compared to single-agent chemotherapy [46], hence single-agent sequential

Table 3
Phase 3 CDK 4/6 inhibitor and AI combination trials.

	PALOMA-2 [68,69]	MONALEESA-2 [6,70]	MONARCH-3 [7,71]	MONALEESA-7 [72,73]
Drug	Palbociclib	Ribociclib	Abemaciclib	Ribociclib
Partner/control	Letrozole	Letrozole	Letrozole or anastrozole	Tamoxifen, letrozole, or, anastrozole (+ goserilin)
Size (n)	666	668	493	672
Randomization	2:1	1:1	2:1	1:1
Menopausal status	Post	Post	Post	Pre
Study population	First-line advanced	First-line advanced	First-line advanced	First-line advanced
Response rate (measurable)	55.3% *v* 44.4%	52.7% *v* 37.1%	59% *v* 44%	50.9% *v* 36.4%
PFS	27.6 mos *v* 14.5 mos (HR 0.563; 1-sided $P < .0001$)	25.3 mos *v* 16.0 mos (HR 0.568; 95% CI 0.457-0.704; $P = 9.63 \times 10\text{-}8$)	28.18 mos *v* 14.76 mos (HR 0.540, 95% CI 0.418-0.698; $P = .000002$	23.8 mos *v* 13.0 mos (HR 0. 55, 95% CI 0.44-0.69; $P < .0001$)
OS (ITT)	Not reported yet	Not reported yet	Not reported yet	Not estimatable *v* 40.9 mos (HR 0.71 (95% CI, 0.54-0.95, $P = .00973$)

ITT = intent-to-treat population; PFS = progression-free survival.

Table 4
Phase 3 CDK 4/6 inhibitor and fulvestrant combination trials.

	PALOMA-3 (n = 521) [74,75]	MONALEESA-3 (n = 725) [76,77]	MONARCH-2 (n = 669) [78,79]
Drug	Palbociclib	Ribociclib	Abemaciclib
Menopausal status	Pre-/peri + post	Post	Pre-/peri+post
Study population	-Progression on previous ET on/within 1 year of adjuvant therapy or on therapy for aBC (any number of lines)	- Newly diagnosed aBC treatment-naïve or progressed after first-line of ET - Progressed at any time during/after (neo)adjuvant ET, no treatment for metastatic disease - Progressed >12 months after adjuvant ET and then progressed after first-line of ET for metastatic disease	- Progression on previous ET on/within 1 year of adjuvant therapy or on therapy for aBC - Only one prior line of ET
Prior chemotherapy	One-line for advanced disease	None for advanced disease	None for advanced disease
PFS (ITT)	9.5 mos *v* 4.6 mos (HR 0.46,CI 0.38-0.59, $P < .0001$)	20.5 mos *v* 12.8 mos (HR 0.593,CI 0.480-0.732, $P < .0001$)	16.4 mos *v* 9.3 mos (HR 0.553,CI 0.449-0.681, $P < .0001$)
OS	34.9 mos *v* 28.0 months (HR 0.81; CI, 0.64 to 1.03; $P = .09$)	Not reached *v* 40.0 mos (HR 0.72; CI, 0.57 to 0.92; P = 0.00455)	46.7 mos *v* 37.3 mos (HR 0.757; CI, 0.606-0.945; P = .01)

aBC = advanced breast cancer; ET = endocrine therapy; ITT = intent-to-treat population; PFS = progression-free survival.

Table 5
Common adverse events of CDK 4/6 inhibitors.

	Palbociclib	Ribociclib	Abemaciclib
Dosing	125 mg daily, 3 weeks on/ 1 week off	600 mg daily, 3 weeks on/ 1 week off	150 mg twice daily
Most common adverse event	Neutropenia	Neutropenia	Diarrhea
Common grade 3/4 adverse events	Neutropenia, leukopenia	Neutropenia, leukopenia	Neutropenia, leukopenia, diarrhea
FDA label warnings and precautions	Neutropenia	Neutropenia, QT prolongation, hepatobiliary toxicity	Neutropenia, diarrhea, hepatotoxicity, venous thromboembolism

regimens are generally preferred. There is a paucity of data regarding the optimal sequencing of these agents, and the optimal regimen will depend on a number of patient-specific factors. There are a number of available agents to consider, some highlighted below, but other agents commonly used in the metastatic setting, including vinorelbine [47], ixabepilone [48], gemcitabine [49], and anthracyclines [50] (Table 6).

Capecitabine

Capecitabine, a prodrug of fluorouracil, is a popular first line chemotherapeutic agent due to the convenience of oral dosing, lack of alopecia and neuropathy, and potential for blood-brain barrier penetration [51]. The approval for capecitabine was based on a single arm, phase II study after progression on a taxane and anthracycline in the metastatic setting [52]. Capecitabine was dosed at 2510 mg/m^2/d split into 2 doses, and was associated with a 20% ORR, including a few complete responses. Median PFS was approximately 3 months. Capecitabine is well known to be associated with significant gastrointestinal toxicity as well as hand-foot syndrome, and frequently requires dose reduction if starting at the 1250 mg/m^2 dose.

Taxanes

Taxanes, a staple of cytotoxic regimens in the early stage setting, are also frequently used in metastatic disease, with paclitaxel, nab-paclitaxel, and docetaxel all being reasonable and frequently utilized options. Data are limited on comparative effectiveness between taxanes [53]. Weekly dosing regimens are more commonly used because of the favorable toxicity profile compared to every 3-week doses. Nanoparticle albumin-bound (nab)-paclitaxel carries the advantage of not requiring steroid premedication. However, weekly nab-paclitaxel was shown to have similar, even trending toward inferior median PFS (9.3 months) when compared head-to-head with weekly paclitaxel (11 months, HR 1.20, 95% CI 1.00-1.45, $P = .054$). Nab-paclitaxel was also associated with increased toxicity (both hematologic, nonhematologic, and neuropathic) when compared to paclitaxel. Of note, ixabepilone was one of the arms in this trial, but stopped early for futility.

Eribulin

Eribulin is one of the more recently approved chemotherapeutic agents in metastatic breast cancer. Eribulin is a nontaxane inhibitor of microtubule polymerization in the halichondrin class of drugs

Table 6
Select single-agent cytotoxic chemotherapy regimens in advanced breast cancer.

Trial	Regimens	Prior Lines	N	Outcomes	Notes
Blum et al [52]	C	P, An	162	ORR 20%; mDoR 12.8 months	3 complete responses; grade 3 HFS 10%, diarrhea 14%
CALGB 40502 [64]	P *v* nabP *v* Ix (all with Bev)	HT only	783 (275 *v* 267 *v* 241)	mPFS 11 *v* 9.3 months (P = .054) *v* 7.4 months (P < .001)	Hematologic and non-hematologic toxicity worse with nab-paclitaxel
EMBRACE [54]	Er *v* TPC	HPT	762 (508 *v* 254)	mOS 13.1 *v* 10.6 months (P = .041); mPFS 3.7 *v* 2.2 months (P = .137)	5% discontinuation rate for peripheral neuropathy
Kaufman et al [55]	Er *v* C	P, An	1102 (554 *v* 548)	mOS 15.9 *v* 14.5 months (P = .056); mPFS 4.1 *v* 4.2 months (P = .30)	Allowed first line metastatic patients; similar QOL scores between 2 groups
Jones et al [47]	V *v* Mel	HPT	179 (115 *v* 64)	mTTP 12 *v* 8 weeks (P < .001); mOS 35 *v* 31 weeks (P = .034)	Hematologic toxicities most common in V
Perez et al [48]	Ix	HPT	126	ORR 11.5%; mPFS 3.1 months; mOS 8.6 months	Median cycles received: 4; 25% received ≥ 8 cycles; 14% G3/4 neuropathy
Rha et al [49]	G	HPT	41	Response rate 20%, mDoR 9 months, mOS 11 months	OS third line 12 months; OS fourth line 7 months
O'Brien et al [50]	PLD *v* Dxo	FLT	509 (254 *v* 255)	mPFS 6.9 *v* 7.8 months (HR 1.00); mOS 21 *v* 22 months (HR 0.94)	Risk of cardiotoxicity over 3 times higher in Dxo group; also higher risk of myelosuppression, emesis, and alopecia

An = anthracycline; C = capecitabine; DoR = duration of response; Dxo = doxorubicin; Er = eribulin; FLT = first-line therapy; G = gemcitabine; HPT = heavily pretreated; HT = hormone therapy; Ix = ixabepalone; Mel = melphalan; nabP = nanoparticle albumin-bound paclitaxel; ORR = objective response rate; OS = overall survival; P = paclitaxel; PFS = progression-free survival; PLD = pegylated liposomal doxorubicin; QOL = quality of life; TTP = time to progression; V = vinorelbine

(named after the sea sponge, *Halichondria okadai*, from which the compound is derived) [54]. In the EMBRACE trial, eribulin demonstrated an improved PFS and OS when compared against treatment of physician's choice in heavily pretreated patients (median 4 prior lines of therapy) [54]. However, when eribulin was compared against capecitabine in patients who had progressed on prior chemotherapy, no difference in PFS or OS was observed [55].

Future directions

There is little doubt that we are continuing to improve OS in advanced ER+ breast cancer. Still, there are several unanswered question in ER+ breast cancer for which many studies are currently ongoing (Box 3).

Box 3. Future directions in advanced ER+ breast cancer treatment.

- Targeting CDK 4/6 inhibitor resistance (PI3K, CDK 2, and mTOR)
- Role of continued CDK 4/6 inhibition after progression
- Optimal sequence of therapies
- Oral SERDs
- Combination immunotherapy/endocrine/molecular therapy
- HER2 targeted antibody-drug conjugates with "bystander effect" in HER2 low cancers

One of the most pressing and heavily studied topics is how to best address progression on or after CDK 4/6 inhibitors. Proposed mechanisms of resistance include loss or mutation of RB1, overexpression of cyclin E1/2 or CDK6, alterations in the AKT/PI3K pathway, mTOR activation, and alterations in KRAS/HRAS/NRAS [56,57]. The use of a CDK 4/6 inhibitor beyond progression cannot be recommended at this time as there is no strong data to support this. Nor are there strong data to suggest that there is a lack of cross-resistance between the 3 approved CDK 4/6 inhibitors. An area of active interest is adding additional targeted agents to CDK 4/6 inhibition at progression. The TRINITI-1, a phase 1/2 study was one of the first trials to evaluate continued CDK 4/6 inhibition beyond progression with the addition of everolimus. The triplet regimen of ribociclib 300 mg continuous dosing, everolimus 2.5 mg, and exemestane 25 mg demonstrated a promising efficacy signal with a 40% clinical benefit rate [58]. Many other trials including the PACE trial (NCT03147287) continue to investigate to role of continued CDK inhibition beyond progression [59]. The TRIO B-11 study is evaluating the addition of copanlisib (a selective PI3K-α/δ inhibitor) to letrozole/palbociclib in the first-line metastatic setting to delay progression (NCT03128619) and after progression on prior AI/CDK 4/6 inhibitor, TRIO-27 (NCT02756364) is investigating the use of fulvestrant plus the mTOR inhibitor MLN0128.

Another unanswered question, which becomes increasingly important as more therapies are approved in the metastatic setting, is what sequence of drugs is ideal to achieve optimal disease control? A recent retrospective review of over 6,000 patients in the SEER-Medicare database revealed that 56% of patients received a treatment sequence that fewer than 11 other patients also received, and 2,985 individuals received a unique treatment sequence [60]. The investigators also found differential survival upon performing sequencing visualization, with longer survival among patients starting on endocrine therapy in the first line, as compared to those receiving chemotherapy as the first line of treatment. Interestingly, despite this improved OS in the endocrine therapy first group, the median time on first-line treatment was similar between the chemotherapy and endocrine therapy groups. While the majority of patients will be started on first-line endocrine plus CDK 4/6 inhibitor therapy, the patient populations studied in the trials that defined the benefit in the second- and third-line settings may be considered "obsolete," as many of these earlier trials did not enroll patients who had received a prior CDK 4/6 inhibitor. It is possible that the resistance mechanisms that develop with CDK 4/6 inhibitors may alter the likelihood of response to later line therapies, and more research is needed to clarify the current benefit of our armamentarium of drugs in a modern patient population.

Other exciting new agents are being explored in the ER+, "HER2 low" expressing population. Trastuzumab deruxtecan (Daiichi Sankyo, Inc), is an antibody-drug conjugate that binds to HER2, releases its topoisomerase I inhibitor payload once the linker is cleaved intracellularly by the lysosome, which is then able to also leak outside the cell to adjacent cells. This leaking of the payload

to surrounding cells is known as a "bystander effect" [61]. While trastuzumab deruxtecan was shown to have an impressive 60% ORR in heavily pretreated HER2+ metastatic breast cancer [62], a phase I study suggested a 40% response rate in heavily pretreated patients with HER2 low expressing (IHC 1-2+, FISH negative) tumors [63]. The DESTINY-Breast04 study is an ongoing phase 3 trial comparing the efficacy of trastuzumab deruxtecan against treatment of physician's choice in patients with HER2 low-expressing tumors after progression on endocrine therapy (NCT03734029). If approved, trastuzumab deruxtecan would be the first HER2 targeted therapy to show efficacy in a patient population previously thought not to receive benefit from HER2 targeted agents.

Finally, as with many subtypes of breast cancer, immune checkpoint inhibitors targeting the programmed death receptor 1 (PD-1) pathway, as well as other forms of immunotherapy, have been studied in ER+ breast cancer, with many more trials currently underway. The KEYNOTE-028 trial enrolled 25 patients with PD-L1 positive, ER+/HER2- tumors who progressed on prior therapy, and administered the PD-1 inhibitor pemrbolizumab [64]. However, the ORR was quite low at 12%, and the drug's development has since been more focused on triple negative tumors [65]. In another trial, the PD-L1 inhibitor avelumab was administered to patients with metastatic breast cancer (including HER2+ and triple negative subtypes) after progression on prior therapy. [66] About 43% of patients had tumors that were either ER+ and/or PR+ and HER2-. ORR for the overall population was 3.0%, with a slightly higher rate of 5% among patients with triple negative disease. While single-agent immunotherapy trials have been disappointing in the ER+ population, ongoing trials are looking into novel combinations of immunotherapy with targeted therapy. RB1 is postulated to induce multiple immune-related genes, and studies are seeking to combine CDK 4/6 inhibitors with immune checkpoint inhibitors [67]. Another approach taken by some trials is to induce a better immune response by promoting neo-antigen production through intratumoral injection of the oncolytic virus talimogene laherparepvec, in combination with dual immune checkpoint inhibition with nivolumab and ipilimumab (NCT04185311). These combination trials will attempt, either through molecular or neo-antigen generating pathways, to overcome the problem of immunotherapy resistance in ER+ breast cancer, and hopefully identify the setting in which patients can gain benefit from these exciting drugs.

Conclusions

As compared to most advanced solid tumors, ER+ breast cancer has a much different prognosis. The survival for women with advanced ER+ breast cancer has been getting longer because of the increasing number of active treatments we have available. Changing paradigms are resulting in the delay of onset of symptoms and the need for cytotoxic chemotherapy resulting in a better quality of life for our patients. With the introduction of CDK 4/6 inhibitors, front-line treatment is now an endocrine-based doublet for most patients. Still, we have not seen the OS readouts from the three large phase 3 studies in postmenopausal women, but the results of the fulvestrant studies and the MONALEESA-7 trial suggests that there could be an improvement in OS from these studies as well. The rapid change in the past 5 years has raised questions on the optimal sequencing of all the available agents including everolimus and alpelisib. Until there are prospective data to guide us, clinicians will have to extrapolate from available data, considering a patients prior treatments, disease-free interval, and clinical characteristics to choose the best option for each individual patient. Despite the gains made, the research community remains engaged in moving the benchmark further along with efforts to incorporate novel agents including antibody drug candidates and checkpoint/immunotherapy options, among others. If the current trend continues, women with this disease will continue to benefit from a prolonged survival and maintained quality of life.

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