

Why CDK 4/6 Inhibitors are Practice Changing in Advanced Breast Cancer

Nicholas P McAndrew and Kelly E McCann

Division of Hematology/Oncology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

DOI: <https://doi.org/10.17925/OHR.2020.16.1.23>

Systemic therapy for advanced, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-unamplified (HER2-) breast cancer has drastically evolved over the past several decades, from oophorectomy to combination endocrine and molecularly targeted therapy. Cyclin-dependent kinase (CDK) 4/6 inhibitors are the latest addition to this arsenal of therapies, and while they have been rapidly adopted by most oncologists, many still question whether they belong in the first-line metastatic setting. Recent reporting of overall survival data, however, has re-invigorated the debate and strongly supports first-line use of CDK 4/6 inhibitors. This article will provide an overview of the evolution of systemic therapy in HR+, HER2- breast cancer, summarize the data that led to the approval of CDK 4/6 inhibitors, detail the new overall survival data reported in the PALOMA-3, MONALEESA-7, MONALEESA-3, and MONARCH-2 trials, and then discuss why our patients should receive these drugs in the first-line setting for advanced disease.

Keywords

Breast cancer, CDK 4/6, endocrine therapy, metastatic, targeted therapy

Disclosure: Nicholas P McAndrew has received research funding from Novartis and Daiichi Sankyo; advisory board honoraria from Novartis, Daiichi Sankyo, and Genomic Health; travel accommodation from TRIO, Daiichi Sankyo, and Roche; consulting honoraria from Daiichi Sankyo; and is on a speaker's bureau for Novartis. Kelly E McCann has received research funding from H3 Biomedicine and Immunomedics; advisory board honoraria from Daiichi Sankyo, Eli Lilly, and Biotheranostics; is a member of a strategic council for Puma Biotechnology; and is on a speaker's bureau for Eli Lilly.

Review Process: Double-blind peer review.

Compliance with Ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Authorship: The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Received: January 29, 2020

Accepted: June 22, 2020

Published Online: July 28, 2020

Citation: *Oncology & Hematology Review (US)*. 2020;16(1):23-9

Corresponding Author: Nicholas P McAndrew, 2336 Santa Monica Blvd, Suite 304, Santa Monica, CA 90404, USA. E: nmcandrew@mednet.ucla.edu

Support: No funding was received in the publication of this article.

Since the approval of palbociclib in 2015,¹ cyclin-dependent kinase (CDK) 4/6 inhibitors have been a heavily researched and discussed class of medication for the management of metastatic, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-unamplified (HER2-) breast cancer. Because their approval and rise to prominence was based on benefit seen in progression-free survival (PFS), the ideal sequencing of therapy has been debated amongst oncologists. More recently, overall survival (OS) data from several studies have matured, hopefully putting to rest concerns about the appropriateness of CDK 4/6 inhibition in the first-line setting. This article will review the evolution of systemic therapy for advanced HR+ breast cancer leading up to the development and rise of CDK 4/6 inhibitors, followed by an overview and discussion of the recently reported survival data in these studies.

Evolution of systemic therapy for metastatic, hormone receptor positive breast cancer

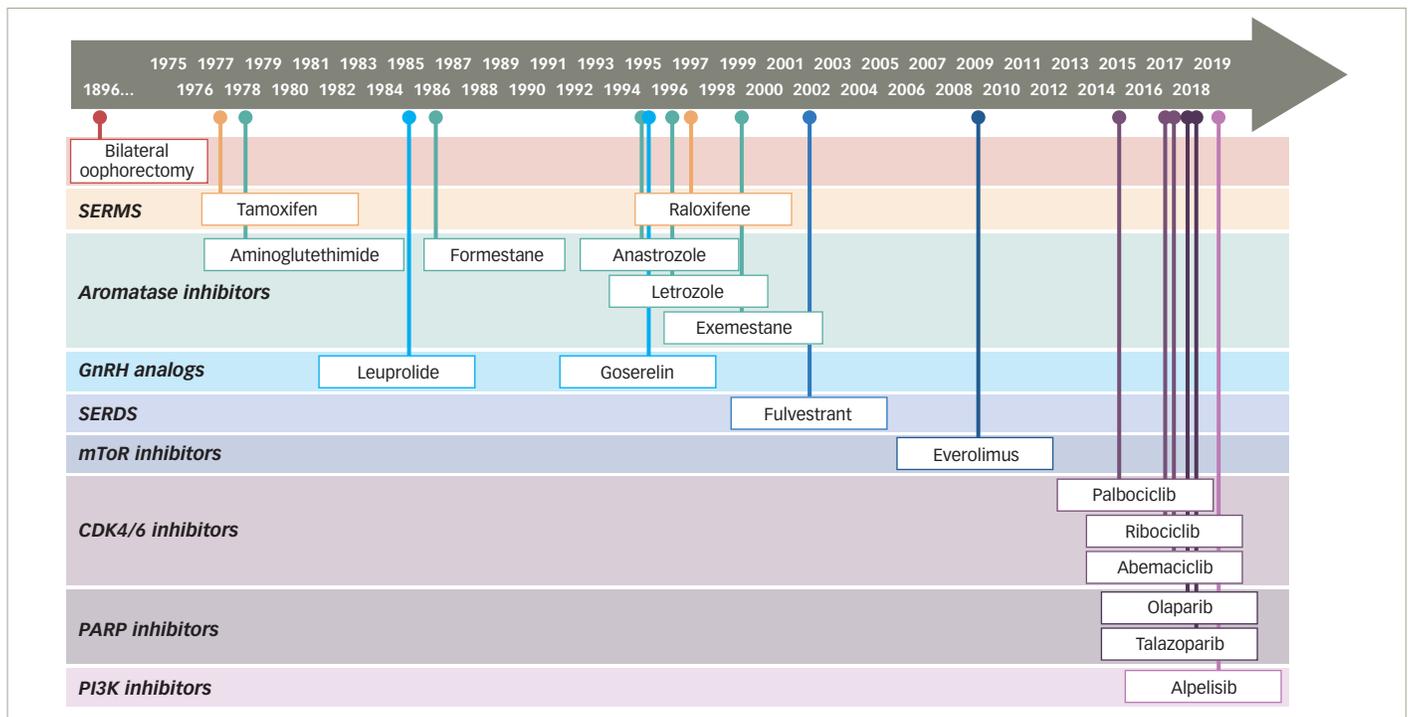
In the textbook "Popular Medicine or The American Family Physician" published by Drs. George Capron and David Slack in 1854, the entry on "Cancer" comprises 2.5 pages in a 705-page tome, and breast cancer is the paradigm:²

"The scirrhous... is a hard and irregular lump, which forms under the skin, in the breasts of women" and when "attended with a burning, shooting pain and the skin over it has become dusky, purple, or livid, it has become a confirmed cancer. [...] The axillary glands and the arms will swell and become stiff and hard, and the whole body will partake of the disease. [...] In some, the progress of the disease is rapid, and in others, exceedingly slow. [...] Almost the only hope of a cure in this disease is found in having it removed by the knife. [...]"²

Fortunately, astute observers of the time noted that the size of some breast tumors changed during the menstrual cycle and that progression of disease might slow if a woman with breast cancer underwent menopause, leading to the hypothesis that ovarian hormones were linked to breast cancer progression. Dr. George Thomas Beatson of Glasgow Cancer Hospital published the results of bilateral oophorectomy in three women in *The Lancet* in 1896.³ Having miraculously survived surgery in the late 19th century, one of his patients, a pre-menopausal, 40-year-old woman with inoperable breast cancer, had complete remission of disease and lived for another 4 years.

Professor Elwood Jensen's work, defining the role of estrogen and estrogen receptors in the 1950s–1970s, set the stage for development of targeted treatment for estrogen receptor-positive breast cancer,^{4,5} the first of which was tamoxifen (*Figure 1*). In the 1980s, the use of tamoxifen prior to chemotherapy, with chemotherapy, or after chemotherapy in women with advanced breast cancer was explored in

Figure 1: Timeline of targeted therapies for HR+, HER2- breast cancer



Targeted therapies for HR+, HER2- breast cancer have evolved over the last and current centuries from bilateral oophorectomy for pre-menopausal women with breast cancer to more targeted therapies as more has been discovered about the biology of HR+, HER2- breast cancer. Aminoglutethimide and formestane were early aromatase inhibitors studied in clinical trials that were never FDA-approved for use. Raloxifene is a SERM that is not FDA-approved for use in patients with breast cancer. Leuprolide and goserelin were first FDA-approved for prostate cancer in 1985 and 1989, respectively. Leuprolide is used off-label for ovarian suppression in pre-menopausal women with breast cancer; goserelin was FDA-approved for this purpose in 1995. Everolimus is approved for use in combination with exemestane. The CDK 4/6 inhibitors are approved for use in combination with the non-steroidal aromatase inhibitors anastrozole and letrozole or with fulvestrant. Abemaciclib is also approved for use as a monotherapy. Olaparib and talazoparib are approved for use in breast cancers associated with pathogenic germline BRCA1 or BRCA2 mutations. Alpelisib is approved for use in breast cancers with activating PIK3CA mutations in combination with fulvestrant. CDK 4/6 = cyclin-dependent kinases 4 and 6; FDA = US Food and Drug Administration; GnRH = gonadotropin-releasing hormone; HER2- = human epidermal growth factor receptor 2 unamplified; HR+ = hormone receptor positive; mTOR = mammalian target of rapamycin; PARP = poly(ADP-ribose) polymerase; PI3K = phosphoinositide 3-kinase; SERD = selective estrogen receptor degrader; SERM = selective estrogen receptor modulator.

clinical trials with results showing that although the overall response rate to first-line cytotoxic chemotherapy is higher than that of tamoxifen, OS is virtually the same if chemotherapy is given prior to tamoxifen, tamoxifen prior to chemotherapy, or if tamoxifen and chemotherapy are given in combination.⁶⁻⁹ Being far less toxic compared with cytotoxic chemotherapies (prior to the advent of powerful anti-emetics and granulocyte growth factors), tamoxifen became a preferred first-line therapy.

Aromatase inhibitors were originally studied and developed for clinical use by Harry and Angela Brodie, who were studying the enzyme, aromatase.¹⁰ Aromatase inhibitors block estrogen biosynthesis by preventing the peripheral conversion of androgens to estrogens by the enzyme aromatase. The current generation of aromatase inhibitors are anastrozole, letrozole, and exemestane, with anastrozole being US Food and Drug Administration (FDA)-approved in 1995, letrozole in 1996, and exemestane in 1999. These aromatase inhibitors improved upon the tolerability and ease of administration of earlier generations of aromatase inhibitors.^{11,12} The use of aromatase inhibitors in pre-menopausal women requires chemical ovarian suppression, oophorectomy, or ablation by radiation. Goserelin, a gonadotropin-releasing hormone analog, causes estrogen depletion via suppression of the hypothalamic-pituitary-gonadal hormone axis, and was approved for use in pre-menopausal women with breast cancer in 1995.¹³⁻¹⁵ All three aromatase inhibitors have been evaluated in phase III clinical trials in post-menopausal patients with HR+, HER2- breast cancer in the first-line

metastatic setting versus tamoxifen, with results demonstrating superiority in terms of median PFS; however, there are no clinical trials demonstrating the superiority of one aromatase inhibitor over another.¹⁶⁻²¹

Fulvestrant is a selective estrogen receptor degrader/downregulator administered by depot intramuscular (IM) injection with a first-month loading dose followed by a monthly maintenance dose. FDA-approved in 2002 for use in the HR+, HER2- metastatic setting, fulvestrant was originally studied in clinical trials at a maintenance dosage of 250 mg IM monthly, which in 2010 was found to be suboptimal to a maintenance dosage of 500 mg IM monthly.²² In the interim period between 2002–2010, fulvestrant 250 mg IM monthly was found to have efficacy similar to oral tamoxifen 20 mg daily in the first-line setting,²³ oral anastrozole 1 mg daily in the second-line setting,^{24,25} and oral exemestane 25 mg daily in the second-line setting.²⁶ The FALCON study, published in 2016, compared fulvestrant 500 mg IM every 2 weeks x2 doses, followed by 500 mg every 28 days, to oral anastrozole 1 mg daily in the first-line metastatic HR+, HER2- setting, demonstrating a statistically significant median PFS of 16.6 months in the fulvestrant group versus 13.8 months in the anastrozole group.²⁷

In 2012, the concept of combining endocrine therapy with an additional molecular target was ushered in by the BOLERO-2 trial. BOLERO-2 was a phase III clinical trial studying the combination of everolimus, a mammalian target of rapamycin (mTOR) inhibitor, with exemestane in the

second-line HR+, HER2- metastatic setting after progression on a non-steroidal aromatase inhibitor (NSAI). The median PFS was 6.9 months with everolimus + exemestane versus 2.8 months for placebo + exemestane ($p < 0.001$).³⁸ However, poor tolerability of everolimus stunted widespread clinical adoption. Subsequent molecularly targeted agents, such as poly(ADP-ribose) polymerase (PARP) inhibitors olaparib and talazoparib, as well as the phosphoinositide 3-kinase inhibitor alpelisib, have been shown to be effective in specific germline (*BRCA1/2*) or somatic (*PIK3CA*) mutations, respectively.^{29,30} While these agents are not options for all patients with HR+, HER2- breast cancer, they are good options for those who are candidates.

Outcome measures for first-line chemotherapy in metastatic HR+, HER2- breast cancer are not as clear as those for hormonal therapies because (1) triple negative and HR+, HER2- breast cancers have typically been combined into one group of “HER2-negative” breast cancers, and (2) many or most of the HR+, HER2- patients have previously been exposed to hormonal therapies in the metastatic setting (i.e., the cytotoxic chemotherapy is not truly first-line). For example, the RIBBON-1 trial directly compared common and currently-used cytotoxic therapies—capecitabine, taxane (docetaxel or nab-paclitaxel), or anthracycline-based therapy (epirubicin or doxorubicin with cyclophosphamide plus or minus fluorouracil)—with or without the addition of bevacizumab in the “first-line” metastatic setting in persons with HER2- breast cancer.³¹ The taxane and anthracycline cohorts were pooled. Approximately 75% of the patients were HR+ in both cohorts, with over half of the capecitabine patients and more than one-third of the taxane/anthracycline cohort already having received hormonal therapy in the metastatic setting. Median PFS was 5.7 months with capecitabine ($n=206$) and 8.0 months in the combined taxane or anthracycline-based chemotherapy arm ($n=207$). Patients in the anthracycline cohort had not had previous exposure to anthracycline.

Rise of CDK 4/6 inhibitors

Though endocrine therapy had been the mainstay of treatment for HR+ breast cancer for decades, eventual endocrine resistance was almost universal. Alterations of key checkpoints in the cell cycle, including the CDK 4/6 pathway, were identified to be commonly associated with resistance to endocrine therapy.³² Within the cell cycle, the transition between G1 and S phase is heavily regulated, and only occurs if the cell can proceed past the restriction point, or the “R point”.³³ In its active, de-phosphorylated state, retinoblastoma protein (Rb) prevents this transition. CDK 4 and CDK 6, when associated with cyclin-D, regulate Rb by hyperphosphorylating and de-activating it, thereby allowing progression through the cell cycle. CDK 4/6 inhibitors restrict progression through the cell cycle by preventing hyperphosphorylation of Rb, resulting in an active form of Rb that can effectively restrict progression through the cell cycle.³⁴

Pre-clinical studies by Finn et al. suggested that HR+ breast cancer cell lines were sensitive to growth inhibition with a CDK 4/6 specific inhibitor, palbociclib, in both endocrine-sensitive and endocrine-resistant cell lines.³⁵ This growth inhibition was synergistic with endocrine therapy. While the majority of palbociclib-sensitive cell lines were HR+, some HER2+ and triple-negative cell lines exhibited varying degrees of sensitivity to palbociclib.

These promising pre-clinical findings led to the development of randomized, controlled clinical trials with CDK 4/6 inhibitors in the first- and second-line metastatic HR+ HER2- breast cancer settings. First-line studies, such as PALOMA-2³⁶ (palbociclib), MONALEESA-2³⁷ (ribociclib), and MONARCH-3³⁸

(abemaciclib), randomized post-menopausal women who had not received prior endocrine therapy in the metastatic setting to receive either a NSAI plus either a CDK 4/6 inhibitor or placebo. Importantly, 22% of patients in PALOMA-2 had a disease-free interval of less than 12 months, compared with 2% of patients in MONALEESA-2 and 0% in MONARCH-3. MONALEESA-7 was the only first-line study to compare endocrine therapy with endocrine therapy + a CDK 4/6 inhibitor (ribociclib) in pre-menopausal patients.³⁹ The second-line studies, such as PALOMA-3,⁴⁰ MONALEESA-3,⁴¹ and MONARCH-2,⁴² all randomized patients who had progressed or relapsed on endocrine therapy to receive fulvestrant plus either placebo or a CDK 4/6 inhibitor. MONALEESA-3 only allowed post-menopausal women and men, while PALOMA-3 and MONARCH-2 also included pre-menopausal women. Additionally, MONALEESA-3 also included patients who were treatment naïve in the metastatic setting. A fourth trial in the second-line setting, MONARCH-1,⁴³ was the only larger trial to investigate a CDK 4/6 inhibitor as a single agent after progression on prior chemotherapy and endocrine therapy.

PALOMA-2 and PALOMA-3 both showed improved PFS when palbociclib was added to first-line letrozole (median PFS 24.8 versus 14.5 months, hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.46–0.72, $p < 0.001$) and second-line fulvestrant (PFS 9.2 versus 3.8 months, HR 0.42, 95% CI 0.32–0.56, $p < 0.001$), respectively.^{36,40} MONALEESA-2 and MONALEESA-3 similarly showed improved PFS with the addition of ribociclib to first-line letrozole (18 month PFS rate 63% versus 42.2%, HR 0.56, 95% CI 0.43–0.72, $p < 0.001$) and first- or second-line fulvestrant (median PFS 20.5 versus 12.8 months, HR 0.59, 95% CI 0.48–0.73, $p < 0.001$), respectively.^{37,41} MONARCH-1 evaluated single-agent abemaciclib in a single-arm, phase II trial of abemaciclib in heavily pre-treated patients with advanced HR+ breast cancer, showing a meaningful clinical benefit rate (42.4%) and objective response rate (19.7%).⁴³ Based on MONARCH-1, abemaciclib is the only CDK 4/6 inhibitor approved as monotherapy.⁴⁴ MONARCH-2 and MONARCH-3 were randomized phase III trials showing improved PFS when abemaciclib was added to second-line fulvestrant (median PFS 16.4 versus 9.3 months, HR 0.55, 95% CI 0.45–0.68, $p < 0.001$) and first-line NSAI (median PFS not yet reached versus 14.7 months, HR 0.54, 95% CI 0.41–0.82, $p < 0.001$), respectively.^{38,42} Across these studies, all subgroups seemed to derive benefit. Interestingly, patients with traditionally high-risk features such as high grade, visceral involvement, and younger age, seemed to show benefit of CDK 4/6 inhibition with most consistency. MONALEESA-7 was unique in that its patient population was exclusively pre-menopausal, and also showed significant PFS benefit when ribociclib was added to either tamoxifen or a NSAI + ovarian suppression (median PFS 23.8 versus 13.0 months, HR 0.55, 95% CI 0.44–0.69, $p < 0.001$).³⁹

Overall survival with CDK 4/6 inhibitors

These studies led to the widespread approval of palbociclib, ribociclib, and abemaciclib by regulatory agencies and the subsequent widespread adoption of these agents in the first-line metastatic setting. Over the last 2 years, OS data from some of these trials have matured (summarized in *Table 1*). The first trial to report on OS data was PALOMA-3.⁴⁵ The prespecified threshold of significance, taking into account a planned interim analysis, was a two-sided p -value of 0.047. The median OS in the palbociclib–fulvestrant group was longer than that of the placebo–fulvestrant group (34.9 versus 28.0 months). This 6.9-month absolute difference translated into a HR for death of 0.81 with a 95% CI 0.64–1.03 and a p -value of 0.09, and was therefore not considered statistically significant.

Table 1: Summary of major CDK 4/6 inhibitor trials (overall survival)

Trial	N	Regimens	Median OS*	Hazard ratio (95% CI)	p-value
PALOMA-3 ⁴⁵	521	Placebo + fulvestrant	28.0 months	0.81 (0.64–1.03)	0.09
		Palbociclib + fulvestrant	34.9 months		
MONALEESA-3 ⁴¹	726	Placebo + fulvestrant	40.0 months	0.72 (0.57–0.92)	0.00455
		Ribociclib + fulvestrant	NR		
MONALEESA-7 ⁴⁶	672	Placebo + tamoxifen or NSAI	40.9 months	0.71 (0.54–0.95)	0.00973
		Ribociclib + tamoxifen or NSAI	NE		
MONARCH-2 ⁴⁸	669	Placebo + fulvestrant	37.3 months	0.76 (0.61–0.95)	0.01
		Abemaciclib + fulvestrant	46.7 months		

*OS results for MONALEESA-3 and MONALEESA-7 reported as % of patients estimated to be alive at 42 months.

CI = confidence interval; N = number of patients; NE = not estimable; NR = not reached; NSAI = non-steroidal aromatase inhibitor; OS = overall survival.

The median time to receipt of chemotherapy, however, was significantly improved in the fulvestrant–palbociclib group (17.6 versus 8.8 months, HR 0.58, 95% CI 0.47–0.73, $p < 0.001$).

Subsequently, two trials with ribociclib reported significantly improved OS. First, MONALEESA-7 showed a 24.2% absolute increase in 42-month OS rate, with median OS not yet being reached in the ribociclib group at a median duration of follow-up of 34.6 months.⁴⁶ This survival benefit held true across all subgroups. Interestingly, 18.6% of patients in the placebo group subsequently received a CDK 4/6 inhibitor, with time to progression on second-line therapy also being significantly longer in the ribociclib group.

Shortly after these results were presented at the 2019 American Society of Clinical Oncology Annual Meeting, the OS results of MONALEESA-3 were announced at the 2019 Annual European Society of Medical Oncology (ESMO) Meeting. Similarly, the ribociclib group in MONALEESA-3 experienced significantly improved 42-month survival rate (57.8% versus 45.9%, HR 0.72, 95% CI 0.57–0.92, $p = 0.00455$).⁴⁷ MONALEESA-3 is unique among these studies in that it allowed patients in both the first- and second-line setting, giving insight into how two different populations responded to an intervention, which would typically require a cross-trial comparison. A subgroup analysis of the first-line population showed a 10.1% increased OS benefit, with an updated median PFS of 33.6 months in the ribociclib group versus 19.2 months in the fulvestrant-alone group (HR 0.55, 95% CI 0.42–0.72).⁴⁷

Concurrent with the results of MONALEESA-3, MONARCH-2 also reported OS data at ESMO 2019. The addition of abemaciclib to fulvestrant in the second-line setting was associated with significantly improved median OS (46.7 versus 37.3 months, HR 0.757, 95% CI 0.606–0.945, $p = 0.01$).⁴⁸ Subgroups with especially improved survival were those with visceral disease as well as those with primary resistance to endocrine therapy, and all subjects in the abemaciclib arm also experienced improved time to chemotherapy, time to second progression, and chemotherapy-free survival. A meta-analysis of data from PALOMA-3, MONALEESA-3, and MONARCH-2 confirmed that OS, as well as PFS, is superior in patients receiving a CDK 4/6 inhibitor + fulvestrant compared with fulvestrant alone (HR 0.77, 95% CI 0.67–0.89, $p < 0.001$).⁴⁹ A second meta-analysis of PALOMA 1, 2, and 3; MONALEESA 2, 3, and 7; and MONARCH 2, 3, and MONARCH plus, additionally showed that the addition of a CDK 4/6 inhibitor to endocrine therapy improved overall survival, regardless of menopausal status, endocrine resistance, visceral versus bone-only disease, and age.⁵⁰

Since the approval of CDK 4/6 inhibitors, oncologists have questioned the appropriate sequencing of endocrine therapy in the metastatic setting. Is it best to start with aromatase inhibitor monotherapy and then add CDK 4/6 inhibition upon progression, or to start with the combination at the outset? Prior to the CDK era, everolimus was the only approved agent that could be added to endocrine therapy, and it was common to utilize this only upon progression after NSAI and fulvestrant. The major reason for this choice of sequencing was due to the substantial side effect profile of everolimus. Additionally, BOLERO-2 did not show significant OS benefit with the addition of everolimus.⁵¹ Given the lack of OS benefit and more challenging side effect profile, adding mTOR inhibition seemed appropriate to delay until a later line of therapy.

However, with multiple studies now showing OS benefit of CDK 4/6 inhibition, especially with two studies showing benefit in the first-line setting, all patients should receive these drugs in combination with endocrine therapy for first-line treatment of metastatic, HR+, HER2-breast cancer. Additionally, the comparatively favorable and manageable side-effect profile of these drugs facilitates first-line treatment, even in patients who are asymptomatic from their disease.⁵² With palbociclib and ribociclib, the most common adverse event is neutropenia, which is largely asymptomatic, and very rarely associated with neutropenic fever.⁵² Dose modification for neutropenia does not seem to impact survival outcomes,⁵³ and palbociclib-associated neutropenia may in fact be associated improved PFS (though more data are needed to confirm this).⁵⁴

While it is clear that these agents should be used in the first-line metastatic setting, several important clinical questions remain unanswered. Firstly, since the OS benefit seen in PALOMA-3 was not statistically significant, can the OS benefit seen with ribociclib and abemaciclib be extrapolated to palbociclib? While the Kaplan–Meier PFS curves were nearly interchangeable, suggesting equivalent efficacy, the three drugs differ in their chemical structure and have different side-effect profiles (i.e., QT prolongation with ribociclib, more diarrhea with abemaciclib). Therefore, it is possible that the observed differences in OS are related to these varying biochemical properties. However, it is important to keep in mind that while the OS benefit seen in PALOMA-3 was not statistically significant, it bordered on significance, and differences in outcomes could also be explained by differing patient populations in the two trials. Additionally, a real-world retrospective comparative effectiveness analysis of the Flatiron Health database by DeMichele and colleagues did show a statistically significant difference in OS in patients receiving first-line palbociclib and

letrozole (n=772, 2 year OS rate 80.1%) compared with first-line letrozole alone (n=658, 2 year OS rate 63.9%).⁵⁵

A second unanswered question is what to do about patients presenting with significant visceral disease burden. Traditionally, cytotoxic chemotherapy has been considered the standard of care for these high-risk patients in need of a rapid response, and remains the recommended treatment modality for patients in visceral crisis.⁵⁶ However, it is not clear that chemotherapy is superior to hormone therapy + a CDK 4/6 inhibitor in patients with visceral disease without visceral crisis. Giuliano et al. recently published a systemic review and meta-analysis for endocrine treatment versus chemotherapy in post-menopausal women with HR+, HER2-metastatic breast cancer in the first- or second-line.⁵⁷ They concluded that there is no chemotherapy regimen that is significantly better than hormone therapies in combination with CDK 4/6 inhibitors in terms of median PFS. Additionally, the only regimen with a significantly better overall response than aromatase inhibitor + CDK 4/6 inhibitor was paclitaxel + bevacizumab, a regimen no longer in clinical use. While the Schettini meta-analysis also suggested that CDK 4/6 + endocrine therapy showed improved OS benefit compared with endocrine therapy alone in visceral disease, the studies in this analysis did not include chemotherapy.⁵⁰ The Young-PEARL study was a small phase II trial randomizing pre-menopausal patients to either capecitabine or palbociclib, exemestane, and leuprolide.⁵⁸ There was no significant difference in overall response rate between the two arms, and in patients with visceral disease there was no difference in PFS. In patients without visceral disease, median PFS was significantly improved in the palbociclib arm compared with the capecitabine arm (20.7 versus 14.4 months, HR 0.496, 95% CI 0.26–0.94, p=0.0272). The larger PEARL trial similarly compared endocrine therapy + palbociclib versus capecitabine, and found no difference in PFS or OS between the two arms.⁵⁹ An ongoing trial (ClinicalTrials.gov identifier: NCT04031885) is studying abemaciclib + fulvestrant versus chemotherapy of physician's choice exclusively in patients with visceral metastases.

Much lies ahead on the horizon for CDK 4/6 inhibitors. Currently, data are insufficient to recommend continued CDK 4/6 inhibition beyond progression on a CDK 4/6 inhibitor. The TRINITY-1 trial did show a promising clinical benefit rate of 40% in patients receiving ribociclib, everolimus, and exemestane who had progressed on prior CDK 4/6 inhibitor.⁶⁰ The ongoing PACE trial (ClinicalTrials.gov identifier: NCT03147287) will hopefully shed further light on the role of continuing CDK 4/6 inhibitors beyond progression. Another important, and as of yet unanswered, question is whether or not any biomarkers exist that predict response or resistance to CDK 4/6 inhibitors. Aside from hormone receptor positivity and HER2 negativity, there do not seem to be any clear biomarkers that predict response to these drugs. Biomarkers in the cell-cycle pathway have been suggested as natural candidates to predict response.⁶¹ A small, retrospective study of two single-arm phase II trials of single-agent palbociclib suggested that early grade 1+ neutropenia associated with single-agent palbociclib was associated with improved PFS in both breast and non-breast cancers.⁵⁵ However, early neutropenia does not seem to predict response to abemaciclib,⁶² and data from PALOMA-3 did not suggest a PFS difference with development of grade 3+ neutropenia.⁵⁴

Finally, much work has been done, and is still ongoing, with CDK 4/6 inhibitors in early stage breast cancer. The large, international, phase III PALLAS, monarchE, and NATALEE trials will explore whether or not the

addition of palbociclib, abemaciclib, and ribociclib (respectively) to adjuvant aromatase inhibitor-based endocrine therapy will improve invasive disease-free survival.^{63–66} These trials differ slightly with regard to eligibility criteria, duration of CDK 4/6 inhibitor administration, and starting dose of CDK 4/6 inhibitor, and have the potential to change the face of adjuvant endocrine therapy for early-stage HR+ breast cancer. Recently, press releases from PALLAS and monarchE suggest conflicting results with regard to the benefit of adding CDK 4/6 inhibitors to adjuvant endocrine therapy. PALLAS has reported at the first pre-planned efficacy and utility analysis that the trial is unlikely to show any benefit of adding palbociclib to endocrine therapy.⁶⁷ However, the monarchE trial is reporting that the addition of abemaciclib seems to result in improved invasive disease-free survival compared with endocrine therapy alone.⁶⁸ The NATALEE trial is currently still enrolling and the initial results have yet to be reported (ClinicalTrials.gov identifier: NCT03701334).

The role, if any, of CDK 4/6 inhibitors in the neoadjuvant setting has yet to be defined. NeoPalAna and PALLET demonstrated that adding CDK 4/6 inhibition increases the rate of complete cell cycle arrest (Ki67 \leq 2.7%), though no pathologic complete responses were seen in NeoPalAna, and no difference in the low pathologic complete response rate was seen between the letrozole versus palbociclib groups in PALLET.^{69,70} The neoMONARCH trial similarly combined a CDK 4/6 inhibitor (abemaciclib) with pre-operative endocrine therapy, and also found a greater change in Ki67 in the abemaciclib arm after 2 weeks of treatment, with a pathologic complete response rate of 4%.⁷¹ Interestingly, additional findings of neoMONARCH also demonstrated increased immune response activation, as well as downregulation of genes associated with estrogen response and cell-cycle pathways. The neoadjuvant CORALLEEN study compared 24 weeks of neoadjuvant ribociclib/letrozole to neoadjuvant chemotherapy (dose dense doxorubicin and cyclophosphamide followed by weekly paclitaxel), and found comparable rates of “molecular downstaging” between the two arms, as defined by a decrease in the PAM50 risk of relapse from high to low risk.⁷² While these neoadjuvant studies have demonstrated changes at the molecular level, the clinical utility of neoadjuvant CDK 4/6 inhibitors is unclear, especially with most systemic therapy in early-stage HR+, HER2- breast cancer taking place in the adjuvant setting.

Conclusions

Systemic therapy for HR+, HER2- breast cancer has steadily evolved over the past several decades. While the relatively recent introduction of CDK 4/6 inhibitors has resulted in rapid adoption of these agents, many oncologists rightfully questioned whether or not it was appropriate to use them in the first-line setting or upon progression. OS reporting of MONALEESA-7, MONALEESA-3, and MONARCH-2 all show significantly improved survival when ribociclib or abemaciclib is added to endocrine therapy. While the results of PALOMA-3 suggested a non-significant trend towards benefit with the combination, this may be due to differences in patient population, and a recent real-world database analysis suggests that there may be an OS benefit with palbociclib. Most importantly, the findings from MONALEESA-7 and MONALEESA-3 included data for patients receiving the combination in the first line, suggesting that waiting to administer these medications until after progression may negatively impact OS. While the purpose of this article was to provide a historical overview of the important trials leading to the current standard of care for HR+, HER2- metastatic breast cancer, it is not a systematic review,

though these findings have been confirmed in a prior systematic review and meta-analysis.⁵⁰ These medications have helped patients live longer, with an acceptable side-effect profile, and have changed the game in the treatment of metastatic breast cancer. Ongoing trials will hopefully

identify biomarkers that may predict response to these drugs, as well as understand whether or not these agents will improve disease-free survival in early stage breast cancer, potentially helping more patients live free of this disease. □

- Inman S. FDA approves palbociclib for metastatic breast cancer. Available at: www.onclive.com/web-exclusives/fda-approves-palbociclib-for-metastatic-breast-cancer, 2015 (accessed June 24, 2020).
- Capron G, Slack DB, Cancer. In: Capron G. *Popular medicine, or, The American family physician: a work in which the principles and practice of medicine are familiarly explained: comprising a complete and comprehensive description of diseases, with full and definite directions for their treatment: the properties of many new and important medicines, with their doses and mode of administration, are accurately described: designed for general use and adapted to all climates*. New York, NY: Ray & Brother. 1854;105–8.
- Beaton GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *Lancet*. 1896;148:162–65.
- Jensen EV, DeSombre ER. Estrogen-receptor interaction: estrogenic hormones effect transformation of specific receptor proteins to a biochemically functional form. *Science*. 1973;182:126–34.
- Jensen EV, DeSombre ER, Junblut PW. Estrogen receptors in hormone-dependent tissues and tumors. In: Wissler RW, Dao TL, Wood S, (eds). *Endogenous factors influencing host-tumor balance*. Chicago, IL: University of Chicago Press. 1967;15–30.
- A randomized trial in postmenopausal patients with advanced breast cancer comparing endocrine and cytotoxic therapy given sequentially or in combination. The Australian and New Zealand Breast Cancer Trials Group, Clinical Oncological Society of Australia. *J Clin Oncol*. 1986;4:186–93.
- Cavalli F, Beer M, Martz G, et al. Concurrent or sequential use of cytotoxic chemotherapy and hormone treatment in advanced breast cancer: report of the Swiss Group for Clinical Cancer Research. *Br Med J (Clin Res Ed)*. 1983;286:5–8.
- Taylor SGT, Gelman RS, Falkson G, Cummings FJ. Combination chemotherapy compared to tamoxifen as initial therapy for stage IV breast cancer in elderly women. *Ann Intern Med*. 1986;104:455–61.
- Viladiu P, Alonso MC, Avella A, et al. Chemotherapy versus chemotherapy plus hormone therapy in postmenopausal advanced breast cancer patients. A randomized trial. *Cancer*. 1985;56:2745–50.
- Chumsri S, Howes T, Bao T, et al. Aromatase, aromatase inhibitors, and breast cancer. *J Steroid Biochem Mol Biol*. 2011;125:13–22.
- Goss PE, Powles TJ, Dowsett M, et al. Treatment of advanced postmenopausal breast cancer with an aromatase inhibitor, 4-hydroxyandrostenedione: phase II report. *Cancer Res*. 1986;46:4823–6.
- Wells SA, Santen RJ, Lipton A, et al. Medical adrenalectomy with aminoglutethimide. *Ann Surg*. 1978;187:475–84.
- Blamey RW, Jonat W, Kaufmann M, et al. Goserelin depot in the treatment of premenopausal advanced breast cancer. *Eur J Cancer*. 1992;28:810–4.
- Blamey RW, Jonat W, Kaufmann M, et al. Survival data relating to the use of goserelin depot in the treatment of premenopausal advanced breast cancer. *Eur J Cancer*. 1993;29:1498.
- Kaufmann M, Jonat W, Kleeberg U, et al. Goserelin, a depot gonadotropin-releasing hormone agonist in the treatment of premenopausal patients with metastatic breast cancer. German Zoladex Trial Group. *J Clin Oncol*. 1989;7:1113–9.
- Milla L, Portella J, et al. Anastrozole versus tamoxifen as first-line therapy in postmenopausal patients with hormone-dependent advanced breast cancer. *Am J Clin Oncol*. 2003;26:317–22.
- Nabholtz JM, Arimidex Study Group. Advanced breast cancer updates on anastrozole versus tamoxifen. *J Steroid Biochem Mol Biol*. 2003;86:321–5.
- Thurlimann B, Hess D, Koberle D, et al. Anastrozole (Arimidex) versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: results of the double-blind cross-over SAKK trial 21/95—a sub-study of the TARGET (Tamoxifen or 'Arimidex' Randomized Group Efficacy and Tolerability) trial. *Breast Cancer Res Treat*. 2004;85:247–54.
- Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol*. 2003;21:2101–9.
- Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: The European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol*. 2008;26:4883–90.
- Iwata H, Masuda N, Ohno S, et al. A randomized, double-blind, controlled study of exemestane versus anastrozole for the first-line treatment of postmenopausal Japanese women with hormone-receptor-positive advanced breast cancer. *Breast Cancer Res Treat*. 2013;139:441–51.
- Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol*. 2010;28:4594–600.
- Howell A, Robertson JFR, Abram P, et al. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. *J Clin Oncol*. 2004;22:1605–13.
- Howell A, Robertson JFR, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol*. 2002;20:3396–403.
- Osborne CK, Pippen J, Jones SE, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. *J Clin Oncol*. 2002;20:3386–95.
- Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFFECT. *J Clin Oncol*. 2008;26:1664–70.
- Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *Lancet*. 2016;388:2997–3005.
- Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366:520–9.
- Robson M, Im S-A, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377:523–33.
- Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med*. 2018;379:753–63.
- Robert NJ, Diéras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol*. 2011;29:1252–60.
- Finn RS, Aleshin A, Slamon DJ. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. *Breast Cancer Res*. 2016;18:17.
- Lundberg AS, Weinberg RA. Control of the cell cycle and apoptosis. *Eur J Cancer*. 1999;35:1886–94.
- Fry DW, Harvey P, Keller PR, et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther*. 2004;3:1427–38.
- Finn RS, Dering J, Conklin D, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Res*. 2009;11:R77.
- Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375:1925–36.
- Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med*. 2016;375:1738–48.
- Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35:3638–46.
- Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol*. 2018;19:904–15.
- Turner NC, Ro J, André F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2015;373:209–19.
- Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol*. 2018;36:2465–72.
- Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35:2875–84.
- Dickler MN, Tolane SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2– metastatic breast cancer. *Clin Cancer Res*. 2017;23:5218.
- US Food and Drug Administration. FDA approves abemaciclib as initial therapy for HR-positive, HER2-negative metastatic breast cancer, 2018. Available at: www.fda.gov/drugs/informationondrugs/approveddrugs/ucms98404.htm (accessed June 24, 2020).
- Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379:1926–36.
- Im SA, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med*. 2019;381:307–16.
- Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. 2020;382:514–24.
- Sledge GW, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy-MONARCH 2: a randomized clinical trial. *JAMA Oncol*. 2019;6:116–24.
- Ramos-Esquivel A, Hernández-Romero G, Landaverde DU. Cyclin-dependent kinase 4/6 inhibitors in combination with fulvestrant for previously treated metastatic hormone receptor-positive breast cancer patients: a systematic review and meta-analysis of randomized clinical trials. *Cancer Treat Res Commun*. 2020;23:100175.
- Schettini F, Giudici F, Giuliano M, et al. Overall survival of CDK4/6-inhibitors-based treatments in clinically relevant subgroups of metastatic breast cancer: systematic review and meta-analysis. *J Natl Cancer Inst*. 2020;dja071.
- Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: overall survival results from BOLERO-2. *Ann Oncol*. 2014;25:2357–62.
- Spring LM, Zangardi ML, Moy B, Bardia A. Clinical management of potential toxicities and drug interactions related to cyclin-dependent kinase 4/6 inhibitors in breast cancer: practical considerations and recommendations. *Oncologist*. 2017;22:1039–48.
- Verma S, Bartlett CH, Schnell P, et al. Palbociclib in combination with fulvestrant in women with hormone receptor-positive/HER2-negative advanced metastatic breast cancer: detailed safety analysis from a multicenter, randomized, placebo-controlled, phase III study (PALOMA-3). *Oncologist*. 2016;21:1165–75.
- McAndrew NP, Dickson MA, Clark AS, et al. Neutropenia and response to single agent palbociclib. *J Clin Oncol*. 2018;36(Suppl. 15):1043.
- DeMichele A, Cristofanilli M, Brufsky A, et al. Overall survival for first-line palbociclib plus letrozole vs letrozole alone for HR+/HER2– metastatic breast cancer patients in US real-world clinical practice. *Cancer Res*. 2020;80(Suppl. 4):P1-19-02.
- Rugo HS, Rumble RB, Macrae E, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology Guideline. *J Clin Oncol*. 2016;34:3069–103.
- Giuliano M, Schettini F, Rognoni C, et al. Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis. *Lancet Oncol*. 2019;20:1360–9.
- Park YH, Kim TY, Kim GM, et al. Palbociclib plus exemestane with gonadotropin-releasing hormone agonist versus capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer (KCSG-BR15-10): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2019;20:1750–9.
- Martin M, Zielinski C, Ruiz-Borrego M, et al. Abstract GS2-07: results from PEARL study (GEICAM/2013-02_CECOG/BC.1.3.006): a phase 3 trial of palbociclib (PAL) in combination with endocrine therapy (ET) versus capecitabine (CAPE) in hormonal receptor (HR)-positive/human epidermal growth factor receptor (HER) 2-negative metastatic breast cancer (MBC) patients (pts) whose disease progressed on aromatase inhibitors (AIs). *Cancer Res*. 2020;80(Suppl. 4):GS2-07.
- Bardia A, Hurvitz SA, DeMichele A, et al. Triple therapy (continuous ribociclib, everolimus, exemestane) in HR+/HER2– advanced breast cancer postprogression on a CDK4/6 inhibitor (TRINITI-1): Efficacy, safety, and biomarker results. *J Clin Oncol*. 2019;37(Suppl. 15):1016.
- McCartney A, Migliaccio I, Bonechi M, et al. Mechanisms of resistance to CDK4/6 inhibitors: potential implications and biomarkers for clinical practice. *Front Oncol*. 2019;9:666.
- Rugo HS, Sledge GW, Johnston SRD, et al. The association of early toxicity and outcomes for patients treated with abemaciclib. *J Clin Oncol*. 2018;36(Suppl. 15):1053.
- Mayer EL, Demichele AM, Pfeiler G, et al. PALLAS: PALbociclib Collaborative adjuvant study: a randomized phase 3 trial of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+/HER2– early

- breast cancer. *Ann Oncol.* 2017;28(Suppl. 5):V66.
64. ClinicalTrials.gov. Endocrine therapy with or without abemaciclib (LY2835219) following surgery in participants with breast cancer (monarchE), 2018. Available at: www.clinicaltrials.gov/ct2/show/NCT03155997 (accessed June 24, 2018).
 65. Slamon DJ, Fasching PA, Patel R, et al. NATALEE: Phase III study of ribociclib (RIBO) + endocrine therapy (ET) as adjuvant treatment in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) early breast cancer (EBC). *J Clin Oncol.* 2019;37(Suppl. 15):TPS597.
 66. Translational Research in Oncology. TRIO awarded NATALEE study, largest single phase III breast cancer clinical trial in its history, 2018. Available at: <https://globenewswire.com/news-release/2018/07/09/1534927/0/en/TRIO-Awarded-NATALEE-Study-Largest-Single-Phase-III-Breast-Cancer-Clinical-Trial-in-its-History.html> (accessed June 24, 2020).
 67. Pfizer, Inc. Pfizer provides update on phase 3 PALLAS trial of IBRANCE® (palbociclib) plus endocrine therapy in HR+, HER2-early breast cancer. Available at: <https://investors.pfizer.com/investor-news/press-release-details/2020/Pfizer-Provides-Update-on-Phase-3-PALLAS-Trial-of-IBRANCE-palbociclib-Plus-Endocrine-Therapy-in-HR-HER2-Early-Breast-Cancer/default.aspx> (accessed July 16, 2020).
 68. Eli Lilly and Company. Verzenio® (abemaciclib) significantly reduced the risk of cancer returning in people with high risk HR+, HER2- early breast cancer. Available at: www.prnewswire.com/news-releases/verzenio-abemaciclib-significantly-reduced-the-risk-of-cancer-returning-in-people-with-high-risk-hr-her2-early-breast-cancer-301077315.html (accessed July 16, 2020).
 69. Ma CX, Gao F, Luo J, et al. NeoPalAna: neoadjuvant palbociclib, a cyclin-dependent kinase 4/6 inhibitor, and anastrozole for clinical stage 2 or 3 estrogen receptor-positive breast cancer. *Clin Cancer Res.* 2017;23:4055–65.
 70. Johnston S, Puhalla S, Wheatley D, et al. Randomized phase II study evaluating palbociclib in addition to letrozole as neoadjuvant therapy in estrogen receptor-positive early breast cancer: PALLET trial. *J Clin Oncol.* 2019;37:178–89.
 71. Hurvitz SA, Martin M, Press MF, et al. Potent cell-cycle inhibition and upregulation of immune response with abemaciclib and anastrozole in neoMONARCH, phase II neoadjuvant study in HR+/HER2- breast cancer. *Clin Cancer Res.* 2020; 26:566–80.
 72. Prat A, Saura C, Pascual T, et al. Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEN): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol.* 2020;21:33–43.