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Incorporating CDK4/6 Inhibitors in the Treatment of Advanced Luminal Breast Cancer

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Summary
After optimizing endocrine monotherapy modalities in the setting of advanced luminal breast cancer (BC), dual endocrine/targeted therapy combinations have been tested with positive results, and are transforming this BC subtype treatment landscape. Cell cycle deregulation is a hallmark of cancer that has become a key druggable target in hormone receptor (HR)-positive BC due to its role in endocrine resistance mechanisms. Cyclin dependent kinase (CDK)4/6 inhibitors have experienced a fast development in combination with endocrine therapy and have already been commercialized in some countries. In this review, we will summarize the development of these CDK4/6 inhibitors in luminal BC, from the preclinical data to the pivotal phase III trials that led to their approval, focusing on the efficacy and safety data for each of the treatment settings. Moreover, we will consider the challenges CDK4/6 inhibitors face in their positioning in the algorithm of treatment for advanced luminal BC and the considerations physicians should take into account when selecting these therapies for their patients. However, we are still in need of reliable predictive biomarkers in order to identify patients who will derive the greatest benefit from these drug combinations that are not exempt from toxicity.

Introduction

Both de novo and acquired endocrine resistance mechanisms represent a challenge in hormone receptor (HR)-positive breast cancer (BC) [1]. Dual targeting strategies in advanced luminal BC have emerged as a promising way to overcome this resistance and enhance the sensitivity to endocrine therapy (ET) [2].

CDK4/6 Inhibitors as a Target of Interest in Luminal BC

Cell cycle deregulation is a hallmark of cancer, conferring a proliferative advantage as well as genomic and chromosomal instability on cells [3]. Cyclin dependent kinases (CDKs) modulated by activators (cyclins) and inhibitors closely regulate the cell cycle. For instance, the G1/S checkpoint of the cell cycle (restriction point) is tightly controlled by CDK4/6 and cyclin D interactions. Different mitogenic signals converge at this level leading to the phosphorylation of the Rb protein by CDK4/6 and the subsequent release of the E2F transcription factor from pRb. E2F then triggers cell cycle progression through the transcription of key genes involved in the G1/S transition [4, 5].

The cyclin D/CDK4 axis deregulation is of significant relevance in estrogen receptor-positive (ER+) BC, as cyclin D1 is an ER gene product and there is significant crosstalk between steroidal HRs and the cell cycle [6]. Cyclin D1 is overexpressed in up to 50% of all BC [7], and luminal tumors are particularly enriched in *CCND1* amplifications and/or *CDK4* gains. In particular, luminal A tumors have low expression of *CDKN2C* and high expression of *RB1* [8]. Rb dysfunction has been associated with endocrine resistance in luminal BC [9]. CDK4/6 inhibitors have been shown to induce G1 arrest and decrease the phosphorylation of the Rb protein, with a subsequent down-regulation of E2F downstream effectors.

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Table 1. Preclinical data and early-phase trial dosage results

	IC50		
	Palbociclib [13, 23]	Ribociclib [15, 25]	Abemaciclib [18]
CDK4	11 nmol/l	10 nmol/l	2 nmol/l
CDK6	16 nmol/l	39 nmol/l	10 nmol/l
CDK1	> 10,000 nmol/l	113,000 nmol/l	1,627 nmol/l
CDK2	> 10,000 nmol/l	76,000 nmol/l	504 nmol/l
CDK9	NA	NA	57 nmol/l
CDK7	NA	NA	3,910 nmol/l
MTD	125 mg qd 3/4wk	900 mg 3/4wk	200 mg bid continuous
RDE	125 mg 3/4wk	600 mg 3/4wk	200 mg bid continuous

IC50 = Half-maximal inhibitory concentration; MTD = maximum tolerated dose; RDE = recommended dose for expansion; NA = not applicable; qd = daily; 3/4wk = 3-weeks-on/1-week-off; Bid = twice daily.

The CDK inhibitor development has been a long and challenging process [4, 10], until the arrival of CDK4/6 inhibitors [5, 9]. Palbociclib (Ibrance®, Pfizer, New York, NY, USA), Ribociclib (Kisqali®, Novartis, Basel. Switzerland), and Abemaciclib (Lilly, Indianapolis, IN, USA) are members of this new generation of serine/threonine kinase inhibitors, and their combination with ET in luminal BC has provided promising results which we will review below.

Development of CDK4/6 Inhibitors in BC

First Steps of CDK4/6 Inhibitors at the Preclinical Level

Palbociclib (PD0332991) is a potent and highly selective CDK4/6 inhibitor (table 1). In vivo trials revealed antitumor activity in a variety of tumors, including BC, although palbociclib was found to be inactive in Rb-negative BC tumors [11]. Among a large panel of BC cell lines, ER+ cell lines, including luminal HER2+, showed the greatest sensitivity in contrast to basal subtypes. In addition to luminal markers, sensitive cell lines showed overexpression of RB1 and cyclin D1, as well as underexpression of p16 [12].

Ribociclib (LEE011) is a selective CDK4/6 inhibitor with preclinical activity via the induction of cytostasis and senescence [13, 14]. Enhanced tumor growth inhibition in BC was observed when combined with ET, and was further improved with PI3K inhibitor triple combination [15].

Abemaciclib (LY2835219) is a selective CDK inhibitor with a higher selectivity towards CDK4 than towards CDK6 [16]. Abemaciclib's activity was observed only in Rb-proficient cells [16, 17], inducing reversible cell cycle arrest and senescence [18]. Abemaciclib has been shown to cross the blood-brain barrier in a more effective way than palbociclib [19].

Early-Phase Clinical Trials with CDK4/6 Inhibitors Focused on Luminal BC

The first-in-human trial of palbociclib was conducted in a population of Rb-positive advanced solid tumors and lymphomas [20]. Palbociclib 125 mg per day was evaluated in a 3-weeks-on/1-week-off (3/4 wk) schedule phase I trial [21] demonstrating an adequate safety profile. Subsequent studies in combination with ET confirmed a favorable safety and efficacy profile [22].

A first-in-human trial of single-agent ribociclib established the recommended dose for expansion at 600 mg/day on a 3/4 wk schedule [23]. The combination of ribociclib and ET also showed a favorable safety and efficacy profile [24, 25]. Triple combination trials with PI3K/Akt/mTOR inhibitors are currently ongoing (NCT01872260 and NCT01857193).

A dose-escalation trial fixed the maximum tolerated dose for single-agent abemaciclib at continuous 200 mg twice daily, and the combination of fulvestrant and abemaciclib showed a similar safety profile [26]. Resistance to abemaciclib was associated with *TP53* mutations, and no impact of *PI3KCA* mutation was observed in terms of response to abemaciclib.

CDK4/6 Inhibitor Development in the Clinical Setting of Advanced Luminal BC: Phase II–III Trials

Following promising early-phase trial results, the agents were evaluated in phase II–III studies. We will review the most relevant data for each of the drugs currently available (table 2), as well as provide a summary of ongoing trials (table 3).

Palbociclib

This agent was the first CDK4/6 inhibitor approved by the regulatory authorities. The PALOMA-1 trial [27] was a randomized phase II trial designed to evaluate the addition of palbociclib to letrozole in HR+/HER2- advanced BC (ABC) patients with no prior treatment for metastatic disease. While patients who received mono-ET obtained a median progression-free survival (PFS) of 10.2 months, letrozole plus palbociclib treatment reached a PFS of 20.2 months (hazard ratio (HR) 0.488, $p < 0.001$).

The PALOMA-2 trial [28] was a randomized phase III trial designed to confirm and add to the results of PALOMA-1. This trial allocated 666 HR+/HER2- ABC patients with no prior treatment for advanced disease to receive letrozole plus palbociclib or placebo. Palbociclib increased PFS from 14.5 to 24.8 months (HR 0.58, $p < 0.001$). Neutropenia occurred in 79% of patients in the palbociclib arm and was the most common grade (G) 3–4 adverse event (AE) (66.4 vs. 1.4%).

The PALOMA-3 trial [29, 30] was a double-blind randomized trial that assigned 521 patients (2:1) to fulvestrant plus palbociclib or placebo. Eligibility criteria included ER+/HER2- ABC patients who had progressed during ET for advanced disease or within 12 months of completing adjuvant therapy. Median PFS was 9.5 versus 4.6 months in the palbociclib and control arm, respectively (HR 0.46, $p < 0.001$), with a similar benefit among premenopausal women [31]. G 3–4 neutropenia occurred in 65% of the patients in the palbociclib arm, with a less than 1% febrile neutropenia rate [32].

The TREND trial [33] was a randomized phase II trial comparing single-agent palbociclib versus palbociclib in combination with the same ET that patients were receiving prior to disease progression. This trial included ER+/HER2- ABC patients who had previ-

Table 2. Main phase II–III clinical trials evaluating CDK4/6 inhibitors in advanced luminal breast cancer (BC) patients with data reported by June 2017

	PALOMA-1	PALOMA-2	PALOMA-3	TREND	MONALEESA-2	MONARCH-1	MONARCH-2
Trial ID	(NCT00721409) [27]	(NCT01740427) [28]	(NCT01942135) [29–31]	(NCT02549430) [33]	(NCT01958021) [36, 37]	(NCT02102490) [39]	(NCT02107703) [40]
Trial phase	II	III	III	II	III	II	III
population	postmenopausal ER+HER2- ABC with no prior therapy for ABC	postmenopausal ER+HER2- ABC with no prior therapy for ABC	pre/postmenopausal ER+HER2- ABC who had progressed on ET (tamoxifen or AIs)	postmenopausal ER+HER2- ABC who had progressed on ET (AIs or fulvestrant)	postmenopausal ER+/ HER2- recurrent or ABC with no prior therapy for ABC	postmenopausal ER+HER2- ABC who had progressed on or after prior ET and CT for ABC	posmenopausal ER+HER2- BC who had progressed to ET for adjuvant, neoadjuvant, or ABC
Patients, n	165	666	521	115	668	132	669
Treatment arms	palbociclib 125 mg/d 3/4wk+letrozole vs. letrozole+placebo	palbociclib 125 mg/d 3/4wk+letrozole + vs. letrozole+placebo	palbociclib 125 mg/d 3/4wk+fulvestrant 500 mg vs. fulvestrant+placebo	palbociclib 125 mg/d 3/4wk vs. palbociclib 125 mg/d 3/4wk + same ET as prior to disease progression (AIs or fulvestrant)	ribociclib 600 mg/d 3/4wk+letrozole vs. letrozole+placebo	abemaciclib 200 mg BID continuous	abemaciclib 150 mg BID+fulvestrant 500 mg vs. fulvestrant+placebo
Primary endpoint	PFS	PFS	PFS	clinical benefit	PFS	ORR	PFS
Line of treatment	first	first	second	second	first	pretreated patients MBC (median 3 lines)	first
Visceral disease, %	22.4 vs. 26	48.2 vs. 45.5	59 vs. 60	74 vs. 78	59 vs. 58.7	90.2	54.9 vs. 57.4
Prior therapy for MBC	no	no	yes	yes	no	yes	no
Median follow-up, months	29.6	23	8.9	–	26.4	12	19.5

ER = Estrogen receptor; HER2 = human epidermal growth factor receptor 2; ABC = advanced breast cancer; ET = endocrine therapy; AI = aromatase inhibitor; CT = chemotherapy; d = day; 3/4wk: 3-weeks-on/1-week-off; BID = twice daily; PFS = progression-free survival; ORR = overall response rate; MBC = metastatic breast cancer.

Table 3. Selection of ongoing phase II–III clinical trials evaluating CDK4/6 inhibitors in advanced luminal breast cancer patients

	PALOMA-4	PEARL	FLIPPER	FATIMA	BTCRC BRE15-016	MONALEESA-3	MONALEESA-7	MONARCH-3	MONARCH PLUS
Trial ID	(NCT02297438)	(NCT02028507)	(NCT02690480)	(NCT02917005)	(NCT02668666)	(NCT02422615)	(NCT02278120)	(NCT02246621)	(NCT02763566)
Phase	III	III	II	II	II	III	III	III	III
Trial population	Asian menopausal	menopausal progressed on AIs in early BC or for ABC	menopausal at least >12 months after the end of adjuvant ET or de novo	premenopausal	pre/ postmenopausal	menopausal	premenopausal	menopausal	menopausal
Line of treatment	first	first or second	first	first or second	first	first or second	first or second	first	first
Primary endpoint	PFS	PFS	PFS	PFS	ORR	PFS	PFS	PFS	PFS
Treatment	palbociclib 125 mg/d (d1–21/q28d)+ letrozole vs. letrozole+ placebo	palbociclib 125 mg/d (d1–21/q28d)+ exemestane 25 mg/d vs. capecitabine (1,250 mg/m^2 BID d1–14/q21)	palbociclib 125 mg/d (d1–21/q28d)+ fulvestrant 500 mg vs. fulvestrant+ placebo	palbociclib 125 mg/d (d1–21/q28d)+ exemestane + goserelin vs. exemestane+ placebo	palbociclib 125mg/d (d1–21/q28d)+ tamoxifen	ribociclib 600 mg/d (d1–21/q28d)+ fulvestrant vs. fulvestrant+ placebo	ribociclib 600 mg/d (d1–21/ q28d)+ET (tamoxifen or NSAIs – letrozole or anastrozole) + goserelin vs. ET+placebo	abemaciclib 150 mg BID+ NSAIs (letrozole or anastrozole) vs. NSAIs+placebo	Cohort A: abemaciclib 150 mg BID+NSAIs (letrozole or anastrozole) vs. NSAIs+placebo Cohort B: abemaciclib BID+fulvestrant 500 mg vs. fulvestrant+ placebo

AI = Aromatase inhibitor; ABC = advanced breast cancer; PFS = progression-free survival; ORR = overall response rate; d = day; ET = endocrine therapy; BID = twice daily; NSAIs = nonsteroidal aromatase inhibitors.

ously received 1 or 2 lines of ET (only 1 for ABC). The primary endpoint was the clinical benefit rate, which was similar for both arms (54 and 60% in the combination and monotherapy groups, respectively). However, median duration of clinical benefit was 11.5 versus 6 months (HR 0.35, p = 0.002), and median PFS was 10.8 versus 6.5 months (HR 0.69, p = 0.12). This trial suggests that palbociclib could reverse acquired resistance and that palbociclib monotherapy harbors clinical activity in moderately pretreated patients.

Both the PALOMA-2 and the PALOMA-3 trial explored ER positivity as a biomarker of response, and while ER+ tumors did benefit from palbociclib, the level of ER expression did not discriminate for this benefit [30, 34]. *CCND1* amplification, loss of *p16*, or Ki67 levels did not help in predicting response to palbociclib [27, 34]. *ESR1* mutations were related to worse outcomes, and despite a reduction in the *ESR1* mutational burden along treatment, it did not predict for PFS benefit, nor was the *PIK3CA* mutational status discriminative [30]. A decrease in circulating tumor (ct)DNA levels at day 15 was significantly associated with PFS [35].

Ribociclib

Ribociclib was the second CDK4/6 inhibitor to be commercialized. The MONALEESA-2 trial [36] was a double-blind phase III trial that randomized 668 ER+/HER2- ABC patients with no prior treatment for advanced disease to receive letrozole plus or placebo. Median PFS was 25.3 versus 16 months (HR 0.58, p < 0.001) [37]. The most common G 3–4 AE was neutropenia (59.3 vs. 0.9%), and QTcF interval increases (> G 2) occurred in 3% of the patients.

Parallel with the palbociclib data, biomarker analysis of the MONALEESA-2 trial did not demonstrate the value of Rb, p16, or ki-67 levels, or *CDKN2A*, *CCND1* or *ESR1* gene expression levels, as biomarkers of ribociclib benefit [38].

Abemaciclib

In October 2015, abemaciclib obtained the designation of Innovative Therapy by the Food and Drug Administration (FDA). The MONARCH-1 [39] phase II trial of single-agent abemaciclib included ER+/HER2- ABC women who had progressed on or after ET and had received no more than 3 lines of chemotherapy for advanced disease. The primary endpoint was the overall response rate (ORR). At 12 months of follow-up, the ORR was 19.7% and PFS was 6 months.

The MONARCH-2 trial [40] was a double-blind phase III study that included ER+/HER2- ABC patients who had progressed while receiving or within 12 months of completion of adjuvant/neoadjuvant ET, or during first-line ET for metastatic disease. Patients were randomized to receive fulvestrant plus abemaciclib or placebo. Median PFS were 16.4 and 9.3 months in the abemaciclib and placebo arms, respectively (HR 0.553, p < 0.001). The most frequent AEs were gastrointestinal (GI) symptoms and neutropenia. Diarrhea occurred in 73% of patients in the abemaciclib arm (13.4% G 3); this was an early event and was easily managed with antidiarrheal medication. Increases in serum creatinine levels occurred in 25% of the patients in the abemaciclib group, with no renal impairment.

A phase II trial evaluated the potential benefit of abemaciclib in brain metastases (NCT02308020) (HR+ BC, melanoma, and non-small cell lung cancer) with preliminary evidence of antitumor activity [41].

Advanced Luminal BC – Current Treatment Status: CDK4/6 Inhibitors in Context

The advanced luminal BC landscape is continuously evolving, and CDK4/6 inhibitors are promising drugs that have come to stay. Palbociclib has rapidly progressed from its accelerated FDA approval [27] to its inclusion in international treatment guidelines for HR+/HER2- ABC [42, 43]. Similarly, ribociclib has just been approved by the FDA in 2017 [36], and abemaciclib is heading towards its final approval.

ABC treatment goals should be present when evaluating the expansion of our treatment armamentarium [44, 45]. To date, international ABC guidelines for HR+/HER2- patients uniformly recommended endocrine-based regimens over chemotherapy unless there is a visceral crisis in need of rapid response [43, 46]. The balance between disease-specific characteristics and patient-related factors forms the basis for the decision-making process; however, other external factors such as social support, healthcare coverage, and research opportunities are also worth considering. In view of the significant gains in PFS with CDK4/6 inhibitors [27, 28, 30, 36, 40], the mono-ET paradigm is being challenged, although overall survival (OS) data are still too immature to draw solid conclusions. So far, the PALOMA-1 trial is the only trial to report a non-statistically significant increase in OS for the combination of letrozole and palbociclib [47]. Nevertheless, this co-targeting strategy has demonstrated the ability to delay the use of chemotherapy [47] and global quality of life deterioration [48].

The benefits of new CDK4/6 inhibitor/ET combinations should be counterbalanced with the AEs derived from their use. While palbociclib dose-limiting toxicities were mainly hematologic, ribociclib added liver alterations and QTc prolongation as relevant AEs, and in contrast, fatigue, anorexia, and GI AEs appeared in the toxicity spectrum of abemaciclib more commonly than with the other inhibitors. Hematologic toxicity is a key issue to be aware of, but it is manageable with dose delays and reductions, does not require routine use of granulocyte-colony stimulating factor, and is associated with a low rate of febrile neutropenia and severe infections. This probably is the result of palbociclib's bone marrow suppression mechanism, through a temporary cell cycle arrest, as opposed to permanent DNA damage or cell death with cytotoxic chemotherapy [49]. Close monitoring of blood counts and signs of infection is a necessary precaution during palbociclib treatment. Precautions to be observed with the use of ribociclib include electrocardiogram, serum electrolyte, and liver function monitoring, adding to the previous set of recommendations. Given the abemaciclib toxicity profile, diarrhea and GI toxicity management strategies need to be implemented to optimize treatment dose intensity.

Many of the ABC luminal population is over 60 years of age, and with an increased prevalence of comorbidities and polypharmacy, close monitoring of concomitant medication is mandatory.

Finally, financial toxicity is an unavoidable barrier for the widespread use of CDK4/6 inhibitors over mono-ET strategies, and must be addressed in the treatment individualization process [50].

Future Prospects and Open-Ended Questions for CDK4/6 Inhibitors in Luminal BC Treatment

CDK4/6 inhibitors have opened a new chapter in the luminal ABC treatment historical timeline, although many unanswered questions remain. In the ABC setting, do we need to adopt combination strategies or is there still a role for mono-ET? We have long been searching for the right endocrine sequence, and the current advances, with the integration of mTOR and CDK4/6 inhibitors, just expand the picture. The arrival of new CDK4/6 combinations opens the possibility to delay the development of endocrine resistance but also to overcome this resistance once established. Up to this point, the 3 CDK4/6 inhibitors have followed a parallel development strategy, but there is no head-to-head comparison that allows us to decide between the different options. With positive data from palbociclib and ribociclib in the frontline setting, they represent a valuable option that can be offered to many patients, with benefit either for visceral or non-visceral involvement and irrespective of the interval from the end of adjuvant ET. However, as we are still awaiting OS results, single-agent ET still has a role in this setting, particularly fulvestrant in non-visceral recurrences for ET-naïve patients [51]. The benefits obtained with fulvestrant and either palbociclib or abemaciclib in the resistant setting indicate that treatment with CDK4/6 inhibitors should seriously be considered at some point in advanced luminal BC. Besides, the definition of the optimal therapy upon progression on CDK4/6 inhibitors plus aromatase inhibitors (AIs) in the first line is still pending, and the combination of everolimus and ET is still a valuable choice in the resistant setting before moving on to chemotherapy [2, 52].

In addition, data from direct comparisons of CDK4/6 inhibitor plus ET versus chemotherapy are limited, and clinical trials either in the first-line real-world setting (PADMA, EudraCT 2016–004482–89) or in a non-steroidal AI-resistant population (PEARL, NCT02028507) are still underway.

More importantly, will these achievements be translated into the early luminal BC setting? There is intensive work currently in progress in a potentially curable population, which is undoubtedly the ultimate and most important goal to attain. Currently, there are ongoing adjuvant trials with palbociclib (PENELOPE-B/NCT01864746 and PALLAS/NCT02513394), ribociclib (EarLEE-1/NCT03078751 and EarLEE-2/NCT03081234), and abemaciclib (monarchE/NCT03155997), and the final results are eagerly awaited.

Finally, advances in biomarker identification beyond clinical criteria will enable us to select the best treatment regimen for each patient. This constitutes an unmet clinical need in this area, and many efforts are devoted to this aspect. Nevertheless, ER expression remains the best marker to select patients for CDK4/6 inhibition. Further insights into the resistance mechanisms of this new family of drugs (reviewed in this same issue by Migliaccio et al.) will surely enhance their future development by indicating new potential strategies to overcome the problem.

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