

# The Therapeutic Effects of Specific CDK4/6-inhibitors in Treating HR-positive, HER2-negative Advanced Breast Cancer

Terapeutické účinky specifických inhibitorů CDK4/6 při léčbě pokročilých HR-positivních a HER2-negativních pokročilých karcinomů prsu

Mendoza L.

IQVIA Solutions a. s.

## Introduction

The current oncology practice recommends that all newly diagnosed breast cancers (BC) be evaluated for PR (progesterone receptor) and OR (oestrogen receptor) protein expression by immunohistochemistry [1]. Approximately 70% of patients with metastatic BC have hormone receptor positive (HR+) disease and are commonly treated with hormone-based therapies that include a non-steroidal aromatase inhibitor (NSAI) such as letrozole, anastrozole, or exemestane [2,3]. However, some patients have intrinsic resistance or acquired tolerance to hormone or endocrine therapy, which hampers their survival prolongation [4]. Thus, novel and effective therapies are urgently required for the BC population treated with endocrine therapy.

Cancer derives from uncontrolled cell division, which results from dysregulation of the cell cycle progression, including four stages, G1 (Gap phase 1), S phase (DNA synthesis), G2 (Gap phase 2), and M phase (mitosis). Cyclin D1 is a major transcriptional target of the ER. The cyclin D1-CDK4-RB pathway regulates cell proliferation by controlling the G1 to S cell cycle checkpoint [5,6]. The OR factor (E2F) family of transcription factors are downstream targets of the RB protein, which function in the cell

cycle control and contribute to tumour development [7]. The combination of RB and E2F causes suppression of E2F transcription modules through inducing recruitment of the chromatin remodelling proteins, histone modifiers, and repressive chromatin marks, resulting in cell cycle block [8]. Therefore, the essential roles of CDK4/6 in the cell cycle regulation make them effective targets for cancer therapeutic intervention, especially in BC [9–11]. Fig. 1 shows details of the mechanism of action of the CDK4/6-inhibitors.

## Clinical Trials

Palbociclib (Ibrance®, Pfizer), the most advanced specific CD4/6-inhibitor, was approved by the US FDA (United States Food and Drug Administration) based on the randomised phase II PALOMA-1 study, where palbociclib in combination with letrozole in the 1<sup>st</sup> line setting substantially improved median progression-free survival (mPSF) and yielded an absolute 10-month benefit [12]. In order to further confirm and extend the efficacy and safety data of PALOMA-1, the double-blind phase III PALOMA-2 study enrolled 666 postmenopausal patients with ER+, HER2– advanced breast cancer (ABC) who had not received any treatment for this deadly disease [13].

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

The Editorial Board declares that the manuscript met the ICMJE recommendation for biomedical papers.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.



Luis Mendoza, MD, PhD.

IQVIA Solutions a. s.

Senior Medical Advisor

Radlicka 714/113 Praha 5

158 00 Czech Republic

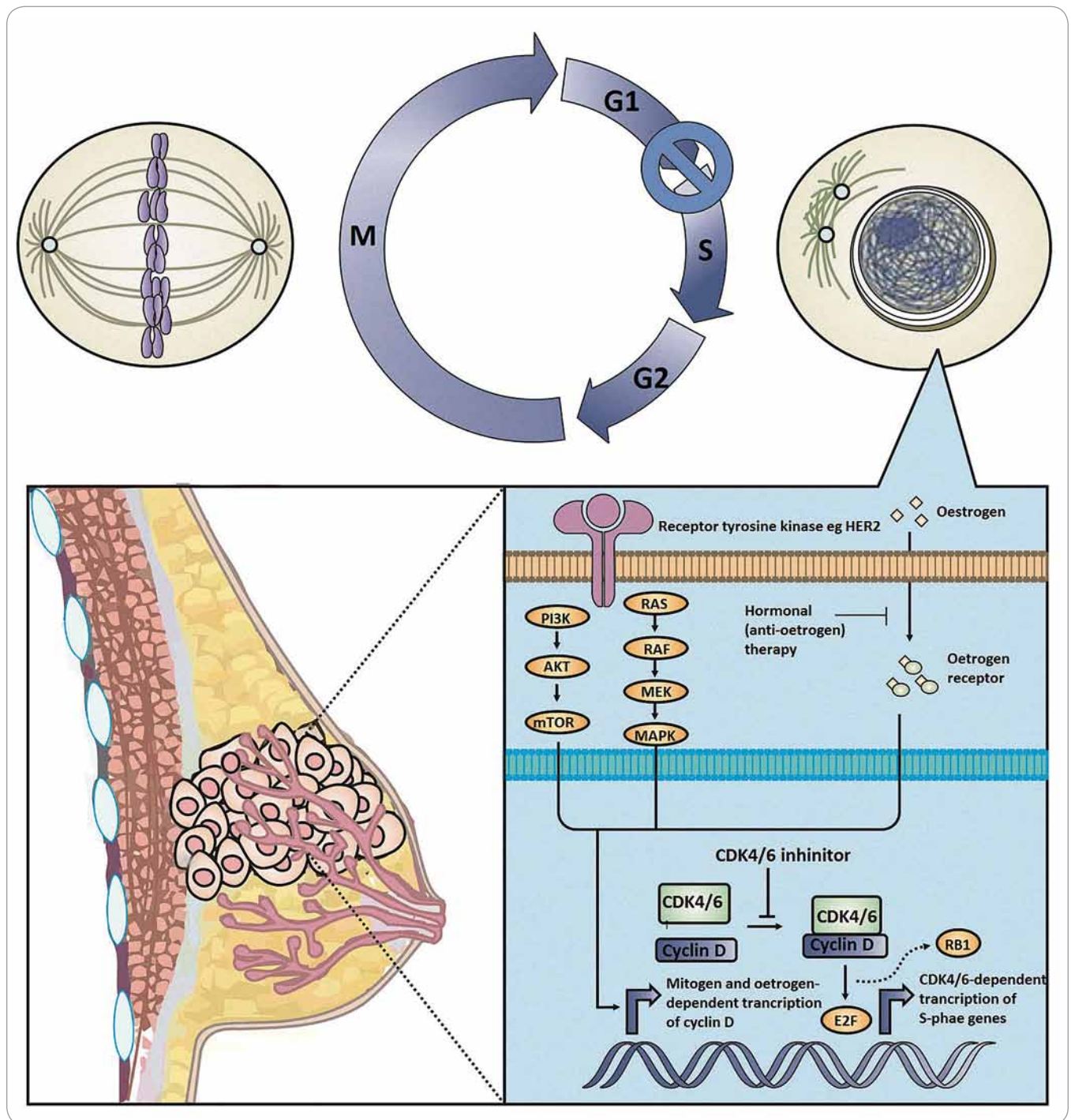
e-mail: luis.mendoza@iqvia.com

Submitted/Obdrženo: 3. 2. 2018

Accepted/Přijato: 28. 5. 2018

doi: 10.14735/amko2018305

A total of 444 patients were randomly assigned to receive letrozole (2.5 mg/d oral) + palbociclib (125 mg/d oral in 4-week cycles, 3 weeks of treatment followed by 1 week off), and the other patients received letrozole + placebo. The overall response rate (ORR) was 42.1% in the letrozole + palbociclib arm and 34.7% in the letrozole + placebo arm. In patients with measurable



**Fig. 1. Mechanism of action of CDK4/6 inhibitors.**

In brief, the CDK4/6-cyclin D axis is hyperactive in hormone receptor-positive breast cancer (BC) because estrogen receptor signaling induce the expression of cyclin D1. Selective CDK4/6 inhibitors prevent the assembly of the CDK4/6-cyclin D1 complex, which normally functions to phosphorylate the retinoblastoma (RB) protein in order to liberate transcription factor E2F from the inactive RB-E2F complex. Administration of anti-CDK4/6 agents therefore suppresses the bioavailability of the E2F transcription factor, resulting in decreased transcription and translation of S-phase-related gene sets, causing BC cells to undergo G1 arrest and/or death.

The picture was a courtesy of Dr. Nicholas Syn from the National University of Singapore with small modifications.

disease, the ORR was 55.3% and 44.4%, resp. Evaluation of the primary endpoint, mPFS, indicated that palbociclib in

combination with letrozole dramatically prolonged mPFS (24.8 months) in comparison with letrozole + placebo

(14.5 months) (HR0.58; 95% CI0.46–0.72;  $p < 0.001$ ) [13]. In addition to the combination of palbociclib and letrozole,

**Tab. 1. Outcomes of treatment with CD4/6 inhibitors in HR+, HER2- advanced or metastatic breast cancer patients.**

Clinical trial name (trial identifier)	Treatment arms	ORR (%)	ORR (%) in patients with measurable disease	mPFS (months)	Hazard ratio (95% CI)	Ref.
<b>1<sup>st</sup> line setting</b>						
PALOMA-2 (NCT01740427)	letrozole + palbociclib vs. letrozole + placebo	42.1 34.7	55.3 44.4	24.8 14.5	0.58 (0.46–0.72) p < 0.001	[13]
MONALEESA-2 (NCT01958021)	letrozole + ribociclib vs. letrozole + placebo	40.7 27.5	52.7 37.1	NR** 14.7	0.59 (0.41–0.85)	[15]
MONARCH-3 (NCT02246621)	NSAI* + abemaciclib vs. NSAI* + placebo	48.2 34.5	59.2 43.8	NR 14.7	0.54 (0.41–0.72)	[17]
<b>After prior hormonal treatment</b>						
PALOMA-3 (NCT01942135)	fulvestrant + palbociclib vs. fulvestrant + placebo	19 9	25 11	9.5 4.6	0.46 (0.36–0.59) p < 0.001	[14]
MONARCH-2 (NCT02107703)	fulvestrant + abemaciclib vs. fulvestrant + placebo	35.2 16.1	48.1 21.3	16.4 9.3	0.55 (0.45–0.68) p < 0.001	[16]

HR – hormonal receptor, HER2 – human epidermal growth factor receptor 2, NSAI – non-steroidal aromatase inhibitor, ORR – overall response rate, mPFS – median progression-free survival, NR – not reached

\*letrozole or anastrozole

\*\* after 24 months, the mPFS was 25.3 months for the ribociclib arm (updated data)

the efficacy of fulvestrant + palbociclib was also studied in HR+, HER2- ABC that progressed in the process of prior hormone therapy [14]. In the PALOMA-3 study, 347 patients received palbociclib (with the same dosage scheme as PALOMA-2) + fulvestrant (500 mg intramuscularly on day 1 and 15, and on day 1 of subsequent cycles every 28 days) and 174 patients received fulvestrant + placebo. The ORR was 19% in the fulvestrant + palbociclib arm and 9% in the fulvestrant + placebo arm. In patients with measurable disease, fulvestrant + palbociclib achieved an ORR of 25 % compared with 11% in the control arm (Tab. 1). There was a clinically meaningful and statistically significant improvement in mPFS in patients receiving palbociclib + fulvestrant (9.5 months) in comparison with the placebo group (4.6 months) (HR 0.46; 95% CI 0.36–0.59; p < 0.001). The most common grade 3 or 4 adverse events observed in palbociclib-treated arms of the PALOMA-2 and -3 studies were neutropenia, leukopenia, and fatigue. The myelotoxicity effect > grade 3 or

higher was observed in > 50% of the palbociclib-treated patients, but the rate of febrile neutropenia was low. The myelotoxicity effects were successfully managed with appropriate supportive care and dose reductions.

Next to become FDA-approved was ribociclib (Kisqali®, Novartis), which when combined with letrozole in the MONALEESA-2 trial met its primary endpoint – after 18 months, mPFS was not reached in the ribociclib (600 mg/d oral in 4-week cycles, 3 weeks of treatment followed by 1 week off) arm vs. 14.7 months in the letrozole (2.5 mg/d oral) + placebo arm [15]. In this randomised, placebo-controlled, phase III trial, 668 postmenopausal (334 assigned to receive ribociclib + letrozole and 334 assigned to receive placebo + letrozole) women with HR+, HER2- ABC who had not received previous systemic therapy for advanced disease were eligible. The data were updated, and after 24 months, the mPFS for the ribociclib arm showed 25.3 months. The mPFS of the placebo arm remained the same. The ORR was

40.7% in the letrozole + ribociclib arm and 27.5% in the letrozole + placebo arm. The ORR for patients with measurable disease was 52.7% vs. 37.1%, resp. [15] (Tab. 1). The most common grade 3 or 4 adverse events were neutropenia (59.3%), leukopenia (21%), hypertension (9.9%), lymphopenia (6.9%), and increase of liver enzymes in < 10% of the patients treated in the ribociclib arm. A few cases of febrile neutropenia were also reported.

A third selective CDK4/6 inhibitor is abemaciclib (Verzenio®, Eli Lilly and Company), which was granted a breakthrough designation after the positive results from the MONARCH-2 study in HR+, HER2- ABC who had progressed while receiving neoadjuvant or adjuvant endocrine therapy [16]. The MONARCH-2 study enrolled 669 patients of whom 446 were randomly assigned to receive abemaciclib (150 mg 2x daily) + fulvestrant (500 mg intramuscularly on day 1 and 15, and on day 1 of subsequent cycles every 28 days) and 223 placebo + fulvestrant. The ORR was 35.2% in the abemaciclib arm



and 16.1% in the control arm. Patients with measurable disease achieved an ORR of 48.1% in the abemaciclib arm and 21.3% in the control arm. Abemaciclib + fulvestrant significantly extended the mPFS vs. fulvestrant alone (16.4 vs. 9.3 months; HR 0.553; 95% CI 0.4449–0.681;  $p < 0.001$ ) (Tab. 1). In September 2017, the US FDA approved abemaciclib based on the results of the phase III MONARCH-3 trial, which was a double-blind, randomised study of abemaciclib or placebo plus a NSAI in 493 postmenopausal women with HR+, HER2– ABC who had no prior systemic therapy [17]. Patients were randomly assigned 2 : 1 to receive abemaciclib or placebo (150 mg 2x daily orally) or matching placebo plus a NSAI (either 1 mg anastrozole or 2.5 mg letrozole). The ORR was 59.2% in the abemaciclib + NSAI arm and 43.8% in the NSAI + placebo arm. Patients with measurable disease achieved an ORR of 59.2% in the abemaciclib arm and 43.8% in the control arm. The mPFS for the abemaciclib arm was not reached compared with 14.7 months in the placebo arm (0.54; 95% CI 0.41–0.72;  $p = 0.00021$ ) (Tab. 1). In both MONARCH studies, the percentages of grade 3 or 4 myelotoxicity events were lower than those observed in the palbociclib and ribociclib studies.

It is worth noting that individual trials have not been powered to detect a difference in the overall survival, and the follow-up data for survival of the trials are currently immature to conclude the real benefit for these patients in this aspect.

### Conclusions

From the results presented above, it can be concluded that the addition of the three selective approved CDK4/6-inhibitors in CDK4/6-containing regimens enhances ORR and mPFS in the 1<sup>st</sup> line or relapsed setting for HR+, HER2– ABC patients. For this reason, the National Comprehensive Cancer Network (NCCN) added the following recommendations in the NCCN guidelines version 4 (2017) for BC – the use of CDK4/6-containing regimens

in the 1<sup>st</sup> line setting for the treatment of premenopausal and palbociclib or ribociclib for the treatment of postmenopausal HR+, HER2– ABC patients; and CDK4/6-containing regimens in the 2<sup>nd</sup> line setting for pre- and postmenopausal HR+, HER2– ABC patients [18]. It has to be noted that the concomitant use of CDK4/6 inhibitors to standard adjuvant treatments considerably aggravates the toxic effects of endocrine therapy. Serious haematologic toxicities are inevitably common, consistent with the on-target inhibition of CDKs 4 and 6, which are highly expressed in haematopoietic stem and progenitor cells.

### Discussion

Despite the acceptance of anti-CDK4/6-containing regimens as a new therapeutic benchmark, several questions remain unresolved, especially whether the CDK4/6 inhibitor-containing regimens are more efficient compared with cytotoxic chemotherapy or what is the impact on the overall quality of life due to the toxicity. In fact, there is still a lot to know about the safety and efficacy of CDK4/6-containing regimens across various categories defined by the menopausal status, age, HER2 positivity and biomarkers (RB expression, p16 status). Ongoing clinical trials explore the potential of these agents outside the HR+, HER2– ABC setting, including as adjuvant and neoadjuvant treatments and in combination with chemotherapy and targeted agents. The CDK4/6 inhibitors are being evaluated in women with triple-negative BCs, and since abemaciclib crosses the blood-brain barrier, it is also being evaluated as a treatment for brain metastases, including metastatic BC patients. Finally, CDK4/6 inhibition may result in favorable modulation of the immune microenvironment, and thus combination trials with immune checkpoint blockers have also been initiated.

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