International Journal of Cancer Therapy and Oncology
www.ijcto.org

The role of CDK inhibitors in breast cancer therapy

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Received January 16, 2016; Revised July 14, 2016; Accepted July 31, 2016; Published Online August 07, 2016

Review Article

Abstract

Cyclin D1 and cyclin-dependent protein kinases CDK4/6 are part of RB-pathway which plays a very important role in the regulation of cell cycle progression and cell death. D-type cyclins associate with cdk4 and 6 to phosphorylate the Rb protein. Hyperphosphorylation of Rb promotes the release of the E2F family of transcription factors that then promotes entry into S phase through activation of key target genes. CDK inhibitors are proteins that suppress CDK-cyclin protein kinase activity in the G1 phase of the cell cycle and promote G1 arrest in response to environmental or intracellular signals. A literature search of these topics was performed through PubMed. Results from preclinical and early-stage clinical trials support the efficiency of CDK inhibitors such palbociclib, abemaciclib and ribociclib for the treatment of human cancers - including breast cancer. The first-in-class CDK4/6 inhibitor, which significantly extended PFS in combination with endocrine therapy in the first and subsequent lines of treatment for steroid receptor -positive, HER2-negative advanced breast cancer is Palbociclib. Other inhibitors (abemaciclib, ribociclib) are still in clinical trials and are a very promising group of drugs.

Keywords: CDK inhibitors, Palbociclib, Abemaciclib, Ribociclib, Breast cancer

1. Introduction

The development of new therapies directed at specific molecular targets within cancer cells is currently an important goal of oncology and a part of treatment individualization. An example of targeted therapies are hormonotherapy (hormone receptors) and immunotherapy (human epidermal growth factor receptor 2 (HER2)).

Targeted therapies cause an increase of patients survival[1,2] and improvement of pathologic complete response (pCR) after neoadjuvant therapy[3]. These results encourage to search new specific molecular targets. One of them is cyclin-dependent kinases (CDK), which play an essential role in the control of the cell cycle and/or proliferation.

The cyclin/cyclin-dependent kinase (CDK)/ retinoblastoma (RB) -axis is a critical modulator of cell cycle entry. The disorders of the axis are observed in many human cancers such as breast cancer. D-type cyclins associate with cdk4 and 6 to phosphorylate the Rb protein. Hyperphosphorylation of Rb promotes the release of the E2F transcription factors which activate key target genes and then promotes entry into S phase of cell cycle.[4] Abnormal accumulation of cyclin D1 is observed in up to 35% of human breast cancer cases. In animal models cyclin D1 overexpression leads to carcinoma in mammary glands.[5, 6]

Many preclinical and clinical trials have confirmed the role of cyclins and CDKs in cancer, both in the development and progression of the disease and as therapeutic targets.[7,8,9] A study conducted on cell culture showed that a selective CDK4/6 inhibitor is preferentially effective in estrogen receptor-positive (ER^+) disease including HER2 amplified and apparently acts synergistically with tamoxifen or trastuzumab. Finn *et al*. have identified a ER^+ luminal subtype as most likely to benefit from CDK4/6 inhibitors because they are the subgroup enriched for cyclin D1 overexpression.[10]

Cyclin-dependent kinases (CDKs) have become a new target for drugs such as CDK 4/6 inhibitors. The first drug in this class is Palbociclib which received Food and Drug Administration (FDA) approval for the treatment of ER positive and HER2 negative metastatic breast

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***Cite this article as**: Huszno J. The role of CDK inhibitors in breast cancer therapy. Int J Cancer Ther Oncol. 2016; 4(3):434.*
***DOI**: 10.14319/ijcto.43.4*

ISSN 2330-4049

cancer, in combination with letrozole in postmenopausal patients.[7,8,9] Other drugs such as abemaciclib and ribociclib are still in clinical trials.

In this article the author described the role of CDK4/6 inhibitors in clinical practice in breast cancer therapy. The review contains the results of completed and ongoing clinical trials.

2. Methods and Materials

2.1. Literature review

A literature search of these topics was performed through PubMed and abstracts of the main cancer congresses of recent years. The author reviews the preclinical and clinical data relating to the activity of Palbociclib, Abemaciclib and Ribociclib in breast cancer.

3. Results and Discussion

3.1. Cyclin-dependent kinase (CDK) 4/6 - mechanism of action

The cell cycle is regulated by many proteins such as CDKs, a group of serine/threonine kinases and cyclins. Cyclin D1 and cyclin-dependent protein kinases CDK4/6 are part of RB-pathway, which consists of inhibitors and activators of cyclin-dependent kinases, the retinoblastoma tumor suppressor (RB) and the E2F-family of transcription factors. RB-pathway plays a very important role in the regulation of cell cycle progression and cell death.[11]

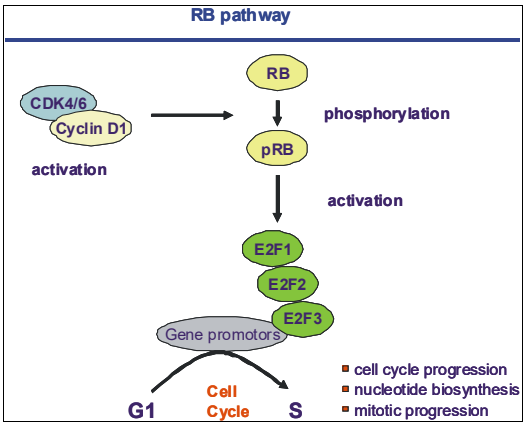

Figure 1: Retinoblastoma (RB)-pathway.

CDK4 and CDK6 are kinases that are activated by D-type cyclins. CDK4/6 forms a complex with cyclin D. Complex cyclin D with kinases (CDK4 and D-CDK6) phosphorylate the retinoblastoma tumor suppressor protein, pRB and pRB-like p107 and p130 proteins, leading to activation or de-repression of E2F transcription factors.[12,13,14] Next, E2F binds to and regulates the promoters of multiple genes involved in cell cycle progression (e.g. cyclin E and cyclin A), nucleotide biosynthesis (e.g. thymidylate synthase and ribononucleotide reductase), DNA replication (e.g. MCM7 and cdc6), and mitotic progression (e.g. cyclin B1 and cdk1) (Figure 1).[11] Complex cyclin D with kinases play also another, noncatalytic function in the G1 phase progression through sequestration of cell cycle inhibitors p27Kip1 and p21Cip1, which cause activation of CDK2-containing complexes. On the contrary, the Ink4 proteins (CDKN) compete with the D-cyclins for cdk4/6 to prevent the formation of the active kinase complex. The Ink4-family and the RB-family proteins function as tumor suppressors, whereas the D-cyclins, cdk4/6 and E2F promote tumor cell proliferation.[11]

Deregulated CDK4/6 activity can induce mammary tumor which was described in the mice model. On the contrary, disruption of its activity will limit tumor development[12]. Amplification at 11q13, the locus of the *CCND1* gene encoding cyclin D1, occurs in 15% to 20% of breast cancers, and cyclin D1 overexpression is even more common (up to 50% of breast cancers).[15, 16]

CDK4/6 are also downstream of the majority of processes causing resistance to HER2 targeted therapy. The deletion of Cyclin D1 will limit the development and maintenance of tumors driven by HER2.[17] Some studies have shown that in models of acquired resistance to HER2 inhibition, cyclin D1 control is deregulated. In such models, xenografts and primary human tumor tissue were all sensitive to CDK4/6 inhibition. In models of acquired resistance to Her2-targeted therapies, Cyclin D1 was inappropriately activated and CDK4/6 inhibition was effective. The role of CDK4/6 inhibitors in cancer therapy were described in some preclinical and clinical trials.[8, 9, 18, 19]

3.2. Inhibitors of cyclin-dependent kinases 4 & 6

Palbociclib is the first-in-class small-molecule inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6 inhibitor). It is dedicated to the therapy of hormone receptor-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. The recommended dose of Palbociclib is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. This drug should be taken with food in combination with letrozole 2.5 mg once daily given continuously throughout the 28-day cycle.[7,8] Palbociclib reduces cellular proliferation of ER-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle. Palbociclib effectiveness has been proven by many clinical trials.

PALOMA-1/TRIO-18 is an open-label, randomized, phase 2 trial, in which participated postmenopausal women with advanced estrogen receptor-positive and HER2-negative breast cancer who had not received any systemic treatment for their advanced disease. Patients were randomly assigned 1:1 to receive letrozole (2.5 mg orally daily) alone or letrozole plus palbociclib 125 mg

 ISSN 2330-4049

daily for 3 weeks, followed by 1 week off, as initial therapy for advanced breast cancer. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population. The investigator-assessed median progression-free survival was 20. 2 months for the combination therapy versus 10.2 months for letrozole alone (hazard ratio [HR] = 0.488; 95% CI = 0.319-0.748; 1-sided P = 0.0004).[9]

The most common adverse events in patients receiving palbociclib plus letrozole was neutropenia. Grade 3-4 neutropenia was reported in 45 (54%) of 83 patients in the palbociclib plus letrozole group and in one (1%) of 77 patients in the letrozole group, leucopenia in 16 (19%) versus none, and fatigue in four (4%) versus one (1%). Serious adverse events that occurred in more than one patient in the palbociclib plus letrozole group were pulmonary embolism (4% patients), back pain (2%), and diarrhoea (2%). No cases of febrile neutropenia or neutropenia-related infections were reported during the study. 11 (13%) patients in the palbociclib plus letrozole group and two (2%) in the letrozole group discontinued the study because of adverse events.[8, 9] Based on the results of this trial, the FDA recently (February 2015) provided accelerated approval of palbociclib in combination with letrozole for the treatment of metastatic ER positive and HER2 negative breast cancer in postmenopausal patients.

A confirmatory phase III trial, PALOMA-2, is comparing the combination of palbociclib and letrozole with letrozole alone as a frontline treatment for postmenopausal women with ER-positive, HER2-negative advanced breast cancer who have not received prior systemic anti-cancer therapies for their advanced/metastatic disease. The primary end point was investigator-assessed progression-free survival. This study is still under way and the initial results are expected in 2016.[18]

The next study was PALOMA-3 trial. This phase III trial involved 521 patients with advanced hormone-receptor –positive and HER2 negative breast cancer that had relapsed or progressed during a prior endocrine therapy. Patients were in a 2:1 ratio to receive palbociclib and fulvestrant or placebo and fulvestrant. The primary end point was investigator-assessed progression-free survival. Secondary end points included overall survival, objective response, rate of clinical benefit, patient-reported outcomes, and safety. The investigator-assessed median progression-free survival at the time of a preplanned analysis as 9.2 months with palbociclib-fulvestrant compared with 3.8 months with placebo-fulvestrant (HR = 0.42; 95% CI = 0.32-0.56; P < 0.001).[9]

The most common grade 3 or 4 adverse events in the palbociclib–fulvestrant group were neutropenia (78.8%, vs. 3.5% in the placebo–fulvestrant group), leukopenia (45.5% vs. 4.1%), anemia (2.6% vs. 3.5%), thrombocytopenia (2.3% vs. 0%), and fatigue (2.0% vs. 1.2%). Febrile neutropenia was reported in 0.6% of palbociclib-treated patients and 0.6% of placebo-treated patients. The rate of discontinuation due to adverse events was 2.0% with palbociclib and 1.7% with placebo[19].

Based on the results of this trial, the FDA recently (February 19, 2016) approved palbociclib in combination with fulvestrant for the treatment of women with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced or metastatic breast cancer with disease progression following endocrine therapy. There are also conducted many other clinical trials recruiting breast cancer patients, such as PEARL trial (Palbociclib and Exemestane vs. Capecytabine), PATRICIA trial (Palbociclib and Trastuzumab vs. Palbociclib and Trastuzumab with Letrozol) or phase IB study (Palbociclib and TDM1). Clinical studies of cdk4/6 inhibitor - Palbociclib (LEE011) in breast cancer are shown in Table 1.

Palbociclib was also examined for other different tumor types, which include colorectal cancer[20], germ cell tumors[21], multiple myeloma[22] and lung adenocarcinoma[23].

3.3. Abemaciclib in Metastatic Breast Cancer

Abemaciclib is a small molecule inhibitor with selectivity against cyclin-dependent kinases 4 and 6 (CDK4/6). The safety and antitumor activity of abemaciclib was evaluated in Phase I study in 2 cohorts of patients with metastatic breast cancer. One cohort of unselected population of patients with metastatic breast cancer received a single-agent abemaciclib while the combination of abemaciclib plus fulvestrant was evaluated in patients with hormone receptor positive metastatic breast cancer. In this trial patients were treated with abemaciclib at 150 or 200mg orally every 12 hours on a continuous schedule. In the combination cohort, patients with hormone receptor positive metastatic breast cancer (n = 18) were treated with abemaciclib and fulvestrant. They received abemaciclib at 200mg orally every 12 hours on a continuous schedule and fulvestrant at 500mg intramuscularly every month. The primary goal of this cohort of the study was to examine the safety profile of the combination treatment. The most common grade 3 adverse events (greater than 5% incidence) were neutropenia (33%), leukopenia (22%), abdominal pain (11%), diarrhea (6%) and fatigue (6%). No grade 4 toxicities were reported and no patients discontinued due to adverse events. This trial demonstrated that Abemaciclib is an oral cell cycle inhibitor that demonstrates single-agent activity against metastatic breast cancer, especially for hormone receptor positive disease[24].

Table 1: Clinical studies of cdk4/6 inhibitor - Palbociclib (LEE011) in breast cancer.

CDK4/6 inhibitors	Clinical study	Phase	Condition	Study group	Primary end points	Results
Palbociclib (PD-0332991)	PALOMA-1/TRIO-18	Open-label, randomised phase II trial	Postmenopausal women with advanced oestrogen receptor positive and HER2-negative breast cancer who had not received any systemic treatment for their advanced disease	letrozole alone vs. letrozole plus palbociclib	Progression free Survival (PFS)	10.2 vs. 20.2 months
	PALOMA-2 trial	Phase III trial	Post menopausal patients with ER+ and HER2- advanced breast cancer	palbociclib and letrozole with letrozole alone	Progression free Survival (PFS)	study is still under way
	PALOMA-3 trial	Phase III trial	Advanced hormone-receptor–positive, human epidermal growth factor receptor 2–negative breast cancer that had relapsed or progressed during prior endocrine therapy	palbociclib and fulvestrant or placebo and fulvestrant	Progression free Survival (PFS)	9.2 vs. 3.8 months
	PENELOPE-B trial	Phase III trial	Patients with hormone receptor positive, HER2 normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy	standard anti-hormonal therapy + palbociclib vs. placebo	Invasive disease free survival (iDFS)	study is still under way
	PALLAS trial	Phase III trial	Premenopausal and postmenopausal women or men with stage II or stage IIIHR+ /HER2- early breast cancer.	Palbociclib + Standard Adjuvant Endocrine Therapy vs. Adjuvant Endocrine Therapy	Invasive Disease Free Survival (iDFS)	Recruiting
	PEARL trial	Phase III trial	Hormonal Receptor (HR) Positive/HER2 Negative Metastatic Breast Cancer (MBC) Patients With Resistance to Non-steroidal Aromatase Inhibitors	Palbociclib + Exemestane vs. Chemotherapy (Capecitabine)	Progression free Survival (PFS)	Recruiting
		Phase II Randomized trial	Premenopausal Women With Hormone Receptor-Positive Metastatic Breast Cancer	Palbociclib in Combination + Exemestane + Goserelin vs. Capecitabine	Progression free survival (PFS)	Not yet recruiting

Table 1: Clinical studies of cdk4/6 inhibitor - Palbociclib (LEE011) in breast cancer.

CDK4/6 inhibitors	Clinical study	Phase	Condition	Study group	Primary end points	Results
	PYTHIA trial	Phase II trial international, multicenter, randomized, double-blind, placebo-controlled.	Metastatic Breast Cancer	Palbociclib + Fulvestrant vs. Placebo Plus Fulvestrant	Progression free Survival (PFS)	Not yet recruiting
	PALLET trial	Phase II Randomized trial	Neoadjuvant Therapy in Post-Menopausal Women With Estrogen-Receptor Positive Primary Breast Cancer	palbociclib and letrozole	Clinical Complete Response (cCR) Measurement of the proliferation marker Ki67	study is still under way
		Phase I/II Trial	Triple negative, androgen receptor positive metastatic breast cancer (MBC)	Palbociclib in Combination With Bicalutamide	recommended phase II dose (RP2D) (phase I) progression free survival (phase II)	Recruiting
	PATRICIA trial	Phase II, prospective, open-label, multicentre	Post-menopausal patients with HER2-positive locally advanced or metastatic breast cancer (MBC) who have received chemotherapy and treatment with trastuzumab for their metastatic disease	(ER -, HER2 +) palbociclib plus trastuzumab vs. (ER +, HER2+) palbociclib plus Trastuzumab vs. (ER+, HER2+) palbociclib plus Trastuzumab + letrozol	Progression-Free Survival at 6 months (PFS6)	Recruiting
	PARSIFAL trial	Randomized, Multicenter, Open-label, Phase II Trial	Patients With HER2 Negative, ER+ Metastatic Breast Cancer	Palbociclib and Letrozole vs. Palbociclib and Fulvestrant	1-year Progression Free Survival	Recruiting
		Phase 3 trial	Post-Menopausal Women With Hormone Receptor Positive, HER2 Negative Advanced Breast Cancer	Palbociclib with Letrozole	Percentage of patients with treatment-emergent averse events (AEs) or serious adverse events	Not yet recruiting

(SAEs)

Table 1: Clinical studies of cdk4/6 inhibitor - Palbociclib (LEE011) in breast cancer.

CDK4/6 inhibitors	Clinical study	Phase	Condition	Study group	Primary end points	Results
	PREDIX LumB trial	Phase II trial	Early-Stage Breast Carcinoma. Estrogen Receptor Positive Tumor With High Proliferation or Low Proliferation With Metastatic Nodes	weekly treatment with paclitaxel +Palbociclib vs. endocrine treatment +Palbociclib	Radiological Objective Response Rate	Recruiting
		Phase 1/2, Open-label, Randomized Study	Er Positive, Her2 Negative Advanced Breast Cancer In Postmenopausal Women	Letrozole + Palbociclib vs. letrozol	TEAEs, Progression-Free Survival (PFS)	Recruiting
		Phase 1B Study	Advanced HER2 (Human Epidermal Growth Factor Receptor 2)-Positive Breast Cancer	T-DM1 + Palbociclib	Maximum Tolerated Dose (MTD), Dose Limiting Toxicities (DLT)	Recruiting

Table 2. Clinical studies of cdk4/6 inhibitor - Abemaciclib (LY2835219) in breast cancer.

CDK4/6 inhibitors	Clinical study	Phase	Condition	Study group	Primary end points	Results
Abemaciclib (LY2835219)	MONARCH 2 study	Randomized, double-blind, placebo-controlled, phase 3 study	Women with hormone receptor positive (HR+), human epidermal growth factor receptor (HER2) negative advanced breast cancer	Abemaciclib + Fulvestrant vs. Placebo + Fulvestrant	Progression Free Survival (PFS)	study is still under way
	MONARCH 3 study	Randomized, double-blind, placebo-controlled, phase III study	Postmenopausal Women With Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer With No Prior Systemic Therapy in This Disease Setting	abemaciclib + NSAI vs placebo + NSAI*	Progression Free Survival (PFS)	study is still under way
	neoMONARCH	A Phase 2 Neoadjuvant Trial	Postmenopausal Women With Hormone Receptor Positive, HER2 Negative Breast Cancer	Abemaciclib + Anastrozole vs. Abemaciclib Monotherapy and Anastrozole Monotherapy	Change from Baseline to 2 Weeks in Ki67 Expression	study is still under way

*NSAI (Anastrozole or Letrozole).

Table 3: Clinical studies of cdk4/6 inhibitor - Ribociclib (LEE011) in breast cancer.

CDK4/6 inhibitors	Clinical study	Phase	Condition	Study group	Primary end points	Results
Ribociclib (LEE011)	SIGNATURE trial	Phase II trial	Tumors With CDK4/6 Pathway Activation	ribociclib	clinical benefit rate associated with Ribociclib treatment	recruiting
	MONALEESA-1	Phase II trial multi-center, open-label	Primary Breast Cancer	ribociclib and letrozole versus letrozole alone	response rate	terminated
	MONALEESA-2	Phase III trial	Postmenopausal Women With Hormone Receptor Positive, HER2 Negative, Advanced Breast Cancer Who Received no Prior Therapy for Advanced Disease	Letrozole and ribociclib vs. Letrozole and placebo	Progression Free Survival (PFS)	still under way.
	MONALEESA-7	Phase III randomized, double-blind, placebo-controlled trial	Premenopausal Women With Hormone Receptor Positive, HER2-negative, Advanced Breast Cancer	Ribociclib + Tamoxifen and Goserelin or a non-steroidal aromatase Inhibitor and Goserelin	Progression Free Survival (PFS)	Recruiting
	The TEEL Study	Phase I Trial	premenopausal women who have a type of breast cancer known as hormone receptor positive/HER2-breast cancer.	Tamoxifen With Ribociclib	dose limiting toxicity (DLT)	Recruiting
		Phase Ib trial	Adult Patients With Advanced ER+ Breast Cancer	Ribociclib with Letrozole	dose limiting toxicities DLTs	Recruiting
		Phase II trial			PFS	

MONARCH 2 is a randomized, double-blind, placebo-controlled, phase 3 study which compares progression-free survival for women with hormone receptor positive, HER2 negative advanced breast cancer receiving either abemaciclib+fulvestrant or fulvestrant alone. Patients are randomized in ratio 2:1 to abemaciclib or placebo. Inclusion criteria are: a diagnosis of hormone receptor positive, HER2 negative breast cancer and locally advanced disease not amenable to curative treatment by surgery or metastatic disease. Additionally, patients must meet one of the other criteria such as: relapsed with radiologic evidence of progression while receiving neoadjuvant or adjuvant endocrine therapy, relapsed with radiologic evidence of progression within 1 year from completion of adjuvant endocrine therapy both with no subsequent endocrine therapy received following progression or relapsed more than 1 year from completion of adjuvant endocrine therapy and then subsequently relapsed after receiving treatment with either an antiestrogen or an aromatase inhibitor as first-line endocrine therapy for metastatic disease. Patients have postmenopausal status either due to natural menopause or ovarian suppression (a gonadotropin-releasing hormone (GnRH) agonist). This study is still under way[25].

Another clinical trial is MONARCH 3 study which evaluates the combination of abemaciclib and a nonsteroidal aromatase inhibitor (anastrozole or letrozole) in patients with hormone receptor positive, HER2 negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting. The aim of this study is to assess clinical efficacy of NSAI (anastrozole or letrozole) and abemaciclib. MONARCH 3 is a randomized, double-blind, placebo-controlled, phase III study. Patients are randomized 2:1 to abemaciclib + NSAI vs placebo + NSAI and stratified by the nature of the disease (visceral vs bone-only metastases vs other) and prior (neo)adjuvant endocrine therapy (aromatase inhibitor vs other vs none). Abemaciclib 150 mg or placebo will be given continuously every 12 hours until progression, along with anastrozole 1 mg or letrozole 2.5 mg once daily at the investigator's discretion, and assessments will occur every 28 days. Inclusion criteria are; postmenopausal women with hormone receptor positive, HER2 negative disease, a disease-free interval > 12 months after completion of (neo)adjuvant endocrine therapy, ECOG PS ≤ 1, adequate organ function, and measurable disease or nonmeasurable bone-only disease (RECIST v1.1). The primary endpoint is progression-free survival; a key secondary endpoint is overall survival. Enrollment began in November 2014; planned enrollment is 450 patients[26]. Clinical studies of cdk4/6 inhibitor - Abemaciclib (LEE011) in breast cancer are shown in Table 2.

Abemaciclib was also examined for other different tumor types, which include glioblastoma, melanoma and non-small cell lung cancer (NSCLC).[27, 28, 29, 30] Results from preclinical and early-stage clinical trials support the efficiency of abemaciclib for the treatment of human cancers - including breast cancer and lung cancer.[31]

3.4. Ribociclib

Another CDK 4/6 inhibitor evaluated in clinical trials was ribociclib. It is an orally available cyclin-dependent kinase (CDK) inhibitor targeting the cyclin D1/CDK4 and cyclin D3/CDK6 cell cycle pathway.

Phase I study showed an acceptable safety profile, dose dependent plasma exposure, evidence of target inhibition and preliminary signs of clinical activity of ribociclib in advanced solid tumors and lymphoma. In this study, partial response was confirmed in 2 ER-positive breast cancer patients among 70 evaluable pts, (2.9%) treated with single-agent ribociclib. The most common study drug-related AEs (all grades) reported were neutropenia (40%), leukopenia (36%), nausea (35%), and fatigue (27%). G3/4 AEs included neutropenia (19%), lymphopenia (14%), and leukopenia (12%).[32] In phase 1b study, six patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer were treated with ribociclib in combination with letrozole. In one case neutropenia grade 4 was reported. A 67% clinical benefit rate was reported in six patients[33].

Currently, there are conducted some phase 2 trials such as SIGNATURE, MONALEESA-1 and other. In the SIGNATURE trial participate adult patients with a diagnosis of a solid tumor or hematological malignancy that have been pre-identified as having relevant CDK4/6, cyclin D1/3, or p16 aberrations. Patients must receive at least one prior treatment for their recurrent, metastatic and/or locally advanced disease and have no remaining standard therapy options anticipated to result in a durable response. Primary end point is clinical benefit rate associated with Ribociclib treatment. Second end points are overall response, progression free survival, overall survival, duration of response and safety and tolerability. This study is still under way[34]. In phase II trial - MONALEESA-1 patients with hormone receptor positive, HER2 negative invasive breast cancer (stage II or III) received the combination of ribociclib and letrozole versus letrozole alone before surgery. The primary end point was cell cycle response rate, defined as the proportion of patients who have a natural logarithm of Ki-67 percentage of baseline that is < 1 at the time of surgery. The secondary end point was safety[35]. The most frequent adverse events were neutropenia, nausea, hyperglycemia, diarrhea, decreased appetite and asymptomatic QTc prolongation. Side effects in grade IV was neutropenia[36].

 ISSN 2330-4049

MONALEESA-2 is a phase III trial randomizing 500 patients with treatment-naive hormone receptor positive, HER2 negative advanced breast cancer to receive letrozole combined with either ribociclib dosed at 600 mg daily for 3 of every 4 weeks or with placebo. Primary end point is progression free survival. Secondary end points are overall survival, overall response rate, clinical benefit rate, safety and tolerability[37]. Next phase III trial is MONALEESA-7 randomized, double-blind, placebo-controlled study which evaluates the efficacy and safety of Ribociclib in combination with Tamoxifen and Goserelin or a non-steroidal aromatase Inhibitor (NSAI) and Goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer. Primary end point is progression free survival. Secondary end points are overall survival, clinical benefit rate, safety and tolerability, time to response, duration of response and overall response rate[38]. Both trials are still under way. There are also some phase I and phase II clinical trials such as TEEL study which are recruiting patients. Clinical studies of cdk4/6 inhibitor - Ribociclib (LY2835219) in breast cancer are shown in Table 3.

Ribociclib was also examined for other different tumor types, which include prostate cancer[39], advanced solid tumors, lymphomas [40, 32], neuroendocrine tumors[41] and non-small cell lung cancer[42].

4. Conclusion

In summary, CDK inhibitors are a very promising group of drugs. Currently, numerous clinical trials are conducted to evaluated the efficiency of the cyclin-dependent kinases 4/6 inhibitors in both solid tumors and lymphomas. Nowadays the CDK inhibitor which is used in clinical practice is Palbociclib. This drug was approved by FDA for use in combination with letrozole and in combination with fulvestrant for the treatment of postmenopausal women with estrogen receptor - positive, human epidermal growth factor receptor 2 - negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. Other drugs are still in clinical trials.

Conflict of interest

The author declares that author has no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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