International Journal of Clinical Oncology and Cancer Research
2020; 5(1): 1-4
http://www.sciencepublishinggroup.com/j/ijcocr
doi: 10.11648/j.ijcocr.20200501.11
ISSN: 2578-9503 (Print); ISSN: 2578-9511 (Online)

Case Report

Efficacy of CDK4/6 Inhibitor in Treatment of Metastatic Breast Cancer and Colon Cancer

Janet Raycheva[1, *], Teodora Karanikolova[2], Rossitza Krusteva[3], Margarita Taushanova-Hadjieva[1, *]

[1]Department of Medical Oncology, University Hospital "Sofiamed", Sofia, Bulgaria

[2]Department of Medical Oncology, Hospital "Nadezhda", Sofia, Bulgaria

[3]Department of Medical Oncology, Hospital "UniHospital", Panagyurishte, Bulgaria

Email address:

janet.raycheva@gmail.com (J. Raycheva), md_margarita@yahoo.com (M. Taushanova-Hadjieva)

[*]Corresponding author

To cite this article:

Janet Raycheva, Teodora Karanikolova, Rossitza Krusteva, Margarita Taushanova-Hadjieva. Efficacy of CDK4/6 Inhibitor in Treatment of Metastatic Breast Cancer and Colon Cancer. *International Journal of Clinical Oncology and Cancer Research*. Vol. 5, No. 1, 2020, pp. 1-4. doi: 10.11648/j.ijcocr.20200501.11

Received: October 21, 2019; **Accepted**: December 30, 2019; **Published**: January 8, 2020

Abstract: A 52-years old woman was diagnosed with an invasive left-sided ductal breast cancer, G3 – staged as T2N0M0; Estrogen (ER) 3+, Progesterone (PR) +, Human epidermal growth factor receptor 2 (HER 2) negative, Ki67-11%. She underwent a radical mastectomy, followed by adjuvant chemotherapy and hormone treatment with Tamoxifen. A year later she was diagnosed with a colorectal cancer-low grade, G1; histological results of adenocarcinoma - T3N1M1 with liver metastases. After a biopsy, which revealed that the metastases are coming from the breast (ER+/HER 2 (-) Breast cancer - (GATA (3+)), she was restaged as T3N1M0. The patient started treatment with Ribociclib 600mg/d + Letrozole 2,5mg/d with a partial response of the disease after three months of treatment. Due to G3 neutropenia, the dose was adjusted to 400 mg/d. Last restaging: October 2019 – complete response and a good quality of life. This case approves that the CDK (cyclin-dependent kinase) 4/6 inhibitors are able to manage visceral metastases and to provide long-term survival without worsening the quality of life. Her disease is successfully managed with CDK4/6 inhibitor together with hormonal therapy, which proves the effect of the CDK 4/6 inhibitors in treatment not only to breast cancer. Six months after there are no signs of relapse of the colon cancer. Despite the stage of the second cancer – T3N1M0, the patient did not undergo adjuvant treatment for the colon cancer.

Keywords: Metastatic Breast Cancer, Colon Cancer, Hormone Therapy, Efficacy, Safety Profile

1. Introduction

Breast cancer is the most common malignant disease among women – over 2,1 million women are affected annually according to the World Health Organization (WHO) [1]. It is also the most frequent reason for death among women who had suffered once in a lifetime with an oncological disease. Breast cancer is a multifactor heterogeneous disease with epidemiologic significance for the society around the world. It affects most frequently the postmenopausal patients at the age 50-70y. old. However, around 25% of the cases are below the age of 50 and 5% are even under 35 y. old [2].

The standard treatment of breast cancer is complexed. It includes surgical methods, chemo- and radiotherapy, endocrine therapy for hormonal sensitive (HR+) tumors and targeted therapy for HER2-expressing tumors. Breast carcinomas can be classified in different subgroups depending on their histology. This is crucial in the clinical practice in order to create the convenient therapeutic strategy. Main subgroups are: Luminal A (HR+/HER2-); Luminal B-like (HR+/HER2-) high Ki67; Luminal B-like (HR+/HER2+) any Ki67; Non-Luminal (HR-/HER2 overexpression); Basal-like – Triple negative breast cancer (TNBC) (HR-/HER2-); typical basal-like/unclassified [2].

Hormonal positive (Luminal A; Luminal B) are around 70% of the newly diagnosed tumors. Most of them show good results in treatment with endocrine agents. Despite this fact, 40% of the patients are getting resistant to this treatment, which requires

creating new molecules to prevent and to fight over this resistance. In the last couple of years successfully started the combined therapy with CDK4/6 inhibitors together with endocrine therapy in hormonal sensitive metastatic breast cancer [3]. To the group of the CDK4/6 inhibitors belong Abemaciclib (Verzenio®), Palbociclib (Ibrance®) and Ribociclib (Kisqali®).

2. Case Report

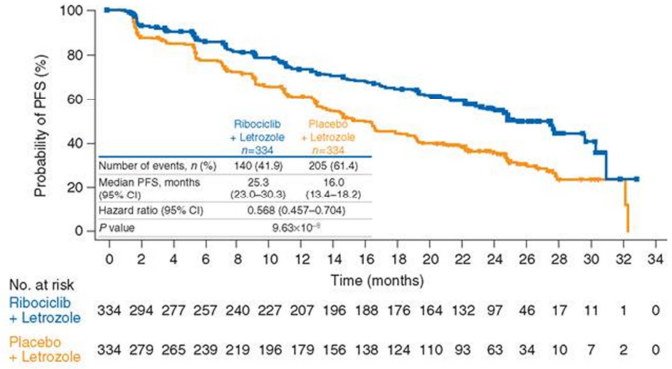
This report presents the case of a 52 years old postmenopausal Caucasian woman, who was diagnosed in February 2017 with an invasive ductal carcinoma. – G3 on the left breast. A radical mastectomy a modo Auchincloss was performed and the staging is as follows – T2N0M0, immunohistochemistry (IHC): ER (3+); PR (+); HER2 (-); Ki67 = 11%; E-cadherin-reduced expression. After the mastectomy the patient had adjuvant chemotherapy – 6 cycles EC (April-August, 2017). The woman started adjuvant hormonal treatment with Tamoxifen. EndoPredict Report provided information for high risk of relapse of the disease: EPclin Score-3.5, EPclin 10 year risk-11%, EPclin Class-high risk**.** In June 2018 a computerized axial tomography (CAT) scan was performed, which did not show any evidence neither for metastatic lesions nor for relapse.

The patient has a negative family history. In the past history, at the age of 50 the patient underwent a total hysterectomy with bilateral salpingoovariectomy due to myoma of the uterus. As co-morbidity the patient has a left-sided thoracic wall Basal-Cell Carcinoma (BCC), which was reevaluated and verified as BCC after excision of the skin lesion in October 2018.

In September 2018 the patient was diagnosed with a colorectal cancer (CRC), which was confirmed as low-grade adenocarcinoma of the colon sigmae. She underwent a laparoscopic resection of the sigma with termino-terminal sigmo-recto anastomosis and resection of the liver metastasis – TNM staging is as follows: T3N1M1 with liver metastases and infiltration of the tumor in the pericolic adipose tissue; metastases were found in 2 out of 13 lymph nodes. The histology of the liver metastases revealed that it is dissemination from the previously treated breast carcinoma – IHC: ER (+)/HER2 (-), non-differentiated breast carcinoma. The colon cancer was restaged as T3N1M0. A CAT scan was performed in October 2018: Multiple hypodense liver lesions of various sizes (the biggest - in 6th segment, 1.44/1.28 cm axial size). In November was performed a full-body skeletal scintigraphy: no SPECT/CT evidence for metabolically active bone metastases.

Since then, the patient had started therapy with Ribociclib 600mg/d + Letrozole 2,5mg/d for the first two cycles. Later, due to a Grade III neutropenia the dose of Ribociclib was adjusted to 400mg/d. In February 2019 an abdominal contrast enhanced ultrasonography (CEUS) states: "the findings correspond to simple liver cysts and responding to the ongoing therapy (regressing) former metastases". A colonoscopy in March 2019 found a polypus of the sigma and internal hemorrhoids. In May 2019 a CAT scan was performed, which showed reduction in the size of the liver metastases – 0.81/0.76cm compared to previously 1.44/1.28cm. Also, there is no evidence for newly occurred lesions in the liver - partial response (PR). In October 2019 a PET/CT was performed, which showed no evidence for metabolically active lesions in the liver – complete response (CR) of the treatment. The patient benefits from this type of treatment, as she is not exposed to additional effects of chemotherapy. Moreover, she has stable disease regarding the colon cancer and good response from the liver lesions. The treatment is still ongoing and the quality of life is not changed. Figures 1 and 2.

3. Discussion



Annals of Oncology, Volume 29, Issue 7, July 2018, Pages 1541–1547, https://doi.org/10.1093/annonc/mdy155

Figure 1. *Kaplan–Meier graph of investigator-assessed PFS for ribociclib plus letrozole versus placebo plus letrozole. CI, confidence interval; PFS, progression-free survival. Data cut-off: 2 January 2017.*

More recent data has been published about the combination of antiestrogenes with other targeted agents in the first and later lines in the treatment of HR+ metastatic breast cancer. CDK4/6 inhibitor Palbociclib and Letrozole have demonstrated a PFS advantage for treatment of metastatic disease [7]. In the PALOMA-2 phase III trial the addition of Palbociclib to Letrozole treatment resulted in a 10-month improvement in PFS compared to Letrozole alone (24, 8 vs. 14,5 months; p=0,0004) in postmenopausal women with previously untreated metastatic disease with a hazard ratio (HR) for disease progression or death of 0,58 (95%; 0,46-0,72; p<0,001) No OS benefit has been reported [4, 8].

The phase III trial MONALEESA-2 compares treatment of metastatic HR+/HER2 (-) breast cancer with Ribociclib 600mg + Letrozole 2,5mg/d compared to Letrozole alone, who had received no prior treatment of the advanced disease [4]. It shows a median progression free survival (PFS) of 26,4 months for the combination and 16,0 months for placebo + Letrozole (26,4 vs. 16 months, hazard ratio 0.568; 95% CI 0.457–0.704; log-rank $P = 9.63 \times 10{-}8$). Hematologic adverse events (Aes) continue to represent the most common grade 3/4 AEs in the Ribociclib plus Letrozole arm, consistent with other CDK4/6 inhibitors [5, 6]. Using a dose reduction of Ribociclib 400mg the overall safety profile of the CDK4/6 inhibitor improves. The data on overall survival (OS) remain immature with 23 deaths in the Ribociclib plus Letrozole arm and 20 deaths in the placebo plus Letrozole arm [7, 9]. Figure 1.

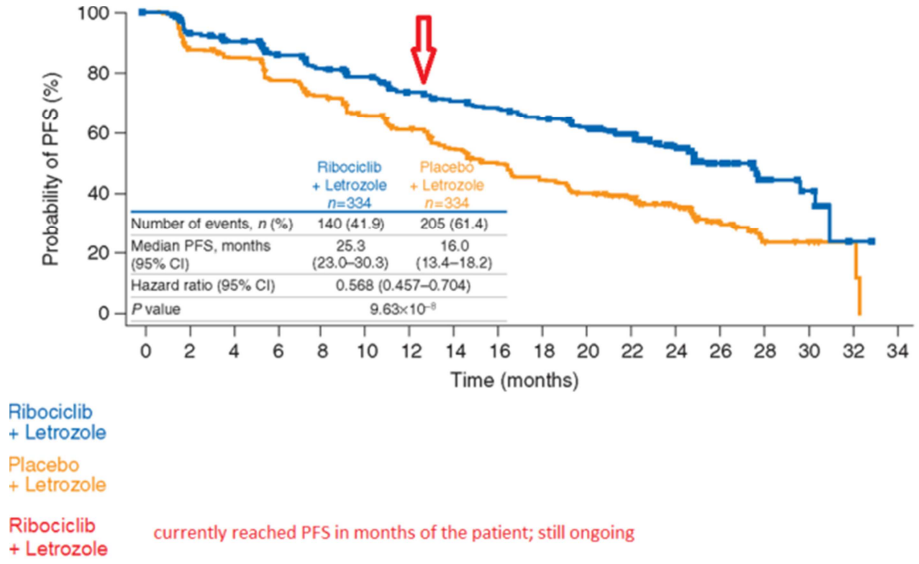


Figure 2. *Kaplan–Meier graph of investigator-assessed PFS for ribociclib plus letrozole versus placebo plus letrozole. CI, confidence interval; PFS, progression-free survival compared to the reported PFS in the clinical case.*

Lately there have been published numerous studies in-vitro and in-vivo (using xenografts) on the effects of CDK4/6 inhibitors to other malignancies, namely because of the safety profile and the large expression of cyclin-depending kinases in the tumors. These agents are involved in many studies for treatment of other types of cancer – more often colorectal (CRC), non-small cell lung cancer (NSCLC) and even for melanoma.

In February 2019 a study of C. L. Lee, S Toomey, A Farrelly, B Hennessy was examining the combined effect of CDK4/6 inhibitor together with PI3K-inhibtors [5]. The study found that the combination between Palbociclib + Gedatolisib has clear synergistic antiproliferative effect in CRC cell lines with common mutations arising from MAPK (mitogen-activated protein kinases) & P13K (phosphoinositide 3-kinase) pathways [6, 10]. These mutations might play crucial role in the future when the treatment against colorectal cancer simply does not show any effect.

In another study Abemaciclib was found to have positive effects in patients dealing with gynaecological malignancies, but also brain glioblastomas, non-small cell lung cancer, melanoma and colorectal carcinoma. This study showed that 3 out of the enrolled 17 patients glioblastoma (n=17) have benefited from Abemaciclib [11], same with one patient with EGFR and another with TP53-mutation in the NSCLC-group (n=68); in the melanoma group one patient achieved RECIST partial response and 6 patients achieved stable disease (n=26), these patients with metastatic melanoma expressed molecular alterations (NRAS mutation and copy-number loss at the INK4 locus), which have induced aberrant kinase activity of CDK4 and CDK6. In the colorectal cancer cohort (n=15) 2 patients have achieved stable disease as one of them with a tumor that harbored both KRAS and TP53 mutations.

Combination of CDK4/6 inhibitor and MEK-inhibitor is not studied only for breast cancer treatment [8]. A study published in 2016 reveals that Palbociclib together with Trametinib is a well tolerated treatment combination for colorectal cancer in xenograft models for both KRAS/BRAF wild-type and even BRAF mutation (+). In 2017 another study proves the correlation between KRAS-mutation and co-targeting of CDK4/6 and MEK inhibitors. [13, 14] The study was done in cell line models with KRAS m (+), BRAF m (+) and normal

colon cancer cell lines. In this study was found out that Palbociclib together with a MEK-inhibitor (PD0325901) has a beneficial effect in both KRAS m (+) and BRAF m (+), but not in normal epithelial cells. This was proven through observation both in vitro and in vivo with downregulation of the KRAS-associated gene signature [15].

4. Conclusion

CDK4/6 inhibitors combined with hormonal agents successfully treat HR (+)/HER2 (-) metastatic breast cancer (mBRCA). The MONALEESA-2 trial proves the combination between Ribociclib + Letrozole as a first line treatment for mBRCA, as well as PALOMA-2 respectively Palbociclib + Letrozole. Both combinations prove the efficacy in the treatment of breast cancer with visceral metastases and assuring a good quality of life and PFS of more than 20 months.

The safety profile and the proven efficacy of the CDK 4/6 inhibitors are making them preferred treatment option together with aromatase inhibitors, compared to hormonal treatment alone. Despite the severe adverse event related to the hematological toxicity, that can be managed with a dose reduction, the CDK 4/6 inhibitors are well tolerated by most of the patients.

As the cyclin-dependent kinases are expressed in many tumor types, the CDK4/6 inhibitors open new horizons in general oncological treatment of not only hormone sensitive breast cancer, but also NSCLC, colorectal cancer, melanomas and glioblastomas.

Yet there are no clinical trials proving benefits in treating colorectal cancer patients with CDK4/6 inhibitor only or combined with a MEK-inhibitor or PI3K-inhibitor. Despite this fact there are promising results from study trials on xenograft models, which may lead to further trials involving cancer patients with the certain genetic mutational status.

References

[1] WHO Breast Cancer statistics, 2018.

[2] E. Senkus, S. Kyriakides, S. Ohno, F. Penault-Llorca - "Primary Breast Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" doi: 10.1093/annonc/mdv298.

[3] Koehler M, VanArsdale TL, Shields D, Arndt K, Yuan J, Lee N, Eisele K, Chionis J, Cao J, Painter CL. Mechanism of action for combined CDK4/6 and ER inhibition in ER positive breast cancer. Ann Oncol. 2014; 25: i21–i2.

[4] Richard S. Finn, M. D., Miguel Martin, M. D., Hope S. Rugo, M. D. "Palbociclib and Letrozole in Advanced Breast cancer".

[5] Hortobagyi G, Stemmer S, Burris H et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016 375 (18): 1738 –1748.

[6] Michael S. Lee, Timothy L. Helms, Ningping Feng, Jason Gay, Qing Edward Chang "Efficacy of the combination of MEK and CDK4/6 inhibitors in vitro and in vivo in KRAS mutant colorectal cancer models.

[7] Finn RS, Martin M, Rugo HS et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016; 375 (20): 1925–1936.

[8] Cristofanilli M, Turner NC, Bondarenko I et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 2 randomised controlled trial. Lancet Oncol 2016; 17 (4): 425– 439.

[9] Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer - G N Hortobagyi, S M Stemmer, H A Burris, Y S Yap, G S Sonke, S Paluch-Shimon, M Campone, K Petrakova, K L Blackwell, E P Winer.

[10] C L Lee, S Toomey, A Farrelly, B Hennessy "Preclinical drug testing and clinical trial planning of palbociclib (CDK4/6 inhibitor) drug combination with a PI3K or MAPK inhibitor for colorectal cancer (CRC); " Annals of Oncology, Volume 30, Issue Supplement_1, February 2019, mdz029.012, https://doi.org/10.1093/annonc/mdz029.012; Published: 27 February 2019.

[11] Amita Patnaik, Lee S. Rosen, Sara M. Tolaney, Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non–Small Cell Lung Cancer, and Other Solid Tumors.

[12] Elizabeth K. Ziemke, Joseph S. Dosch, Joel D. Maust, Amrith Shettigar, Ananda Sen, Theodore H. Welling, Karin M. Hardiman and Judith S. Sebolt-Leopold DOI: 10.1158/1078-0432. CCR-15-0829 Published January 2016: Sensitivity of KRAS-Mutant Colorectal Cancers to Combination Therapy That Cotargets MEK and CDK4/6.

[13] Migliardi G, Sassi F, Torti D, Galimi F, Zanella ER, Buscarino M, Ribero D, Muratore A, Massucco P, Pisacane A, Risio M, Capussotti L, Marsoni S, et al. Inhibition of MEK and PI3K/mTOR suppresses tumor growth but does not cause tumor regression in patient-derived xenografts of RAS-mutant colorectal carcinomas. Clin Cancer Res. 2012; 18: 2515–25.

[14] Mendoza MC, Er EE, Blenis J. The Ras-ERK and PI3K-mTOR pathways: cross-talk and compensation. Trends Biochem Sci 2011; 36: 320–328.

[15] M Pek, S M J M Yatim, Y Chen, J Li, M Gong Oncogenic KRAS-associated gene signature defines co-targeting of CDK4/6 and MEK as a viable therapeutic strategy in colorectal cancer.