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Use of CDK4/6 inhibitor in combination with hormone therapy to treat metastatic luminal breast cancer: clinical case

Background: *Breast cancer (BC) is currently the most common cancer in the world. The new methods opened up in the last decade have improved BC treatment and the survival prognosis for this group of patients. Nevertheless, metastatic BC remains an urgent problem of oncology.*

The article presents a clinical case of treatment of luminal BC with metastatic damage to the contralateral breast, liver, and skeleton bones with a CDK4 / 6 inhibitor in combination with hormone therapy in the outpatient of chemotherapy at Kazakh Institute of Oncology and Radiology.

Results: *The clinical studies show the effectiveness of using of cyclin-dependent kinase inhibitors in combination with hormone therapy in pre- and postmenopausal women with hormone-receptor-positive and HER2 negative metastatic BC.*

Conclusion: *the presented clinical case demonstrates more than 1-year survival without disease progression and good quality of life in a patient receiving CDK inhibitors with hormonal therapy as the first line of therapy.*

Keywords: *clinical case, hormone therapy for breast cancer, CDK4 / 6 inhibitors, treatment of luminal breast cancer, metastatic breast cancer.*

Introduction: Today, breast cancer (BC) is the most common cancer in the world. In 2018, more than 2 million new BC cases were reported [1].

Thanks to the achievements of the last decade, new methods of treating BC were opened, which have significantly improved the prognosis for survival of this group of patients. Nevertheless, metastatic BC remains an urgent problem of oncology. The average life expectancy of patients with the progression of the process is about 3 years, and 5-year survival is about 25% [1]. The metastatic BC treatment involves continuous monitoring of the disease, and therefore much attention is paid to the quality of life of patients, which is a priority criterion for any therapy. The development of targeted drugs to regulate the cell cycle in the tumor cell helped to realize the main objectives of the treatment of such patients, such as the increase in the survival rate and the maintaining of a satisfactory quality of life.

Thanks to the successful results of experimental and clinical studies of cyclin-dependent kinases inhibitors, the range of the antitumor therapy for BC has replenished with a fundamentally new class of drugs. The mechanism of action of oral inhibitors is due to the selective suppression of the activity of the cell cycle "motor." The drugs inhibit the formed cyclin D complex - CDK4/6, which leads to the pRB protein hypophosphorylation and the decreasing in the expression of genes that control the cell cycle. Thus, the activity of the Rb-E2F-DP signaling pathway and E2F transcription factor is reduced. Besides, the control process is restored at the "reconciliation point" G1/S, and cells with an unstable genome undergo apoptosis. CDK4/6 inhibitors showed the highest activity against luminal type tumors in experiments on BC cells. Perhaps this is because estrogen receptors can affect transcriptional processes by activating the cyclin D gene similar to classical estrogen-dependent pathway [2, 3]

It is noteworthy that the mutations leading to CDK activation are much more often with the luminal A and B subtypes. Amplification of cyclin D1 was found in 29% and 58%, and CDK4 in 14% and 25% of tumors of the luminal subtype A and B, respectively. Besides, it became clear that tumors of the luminal A-subtype are characterized by the loss of the CDKN2C gene, which encodes a CDK inhibitor protein (p16INK4a) [3]. According to preclinical studies on 47 BC cell lines, the genomic activity of ERα is preserved and provides a CDK4 / E2F-dependent transcription program, even under conditions of estrogen deprivation. Thus, the sensitivity of hormone-receptor-positive BC cell lines to inhibitors of cyclin-dependent kinases has become the main argument for the study of this group of drugs in combination with hormone therapy [3, 4].

The success in therapy with the use of this combination was justified at the stage of clinical trials. An almost 2-fold increase in progression-free survival was achieved in women with luminal HER2 negative metastatic BC in the pre- and postmenopausal period of life in MONALEESA (ribociclib), PALOMA (palbociclib) and MONARCH (abemaciclib) studies. Such stunning results with this biological subtype were obtained for the first time in a long time. According to current recommendations, cyclin-dependent kinase inhibitors, in combination with letrozole or fulvestrant, are recognized as the treatment of choice for wom-

en with hormone-positive and HER2 negative metastatic BC [5]. The effectiveness of cyclin-dependent kinase inhibitors in combination with hormone replacement therapy in women with visceral metastases allows the above combination to be used as an alternative to chemotherapy. The U.S. Food and Drug Administration (FDA) has approved three low-molecular-weight CDK4/6 inhibitors ---- ribociclib, palbociclib, and abemaciclib. The Republican protocols for the treatment of metastatic hormone-positive HER2 negative BC include two CDK4/6 inhibitors - palbociclib and ribociclib.

An open, randomized phase II trial of PALOMA-1 / RIO-18, which included 165 patients with hormone-positive and HER2 negative metastatic BC in menopause who had not previously received any treatment for the progression of the process, yielded impressive results [5]. Adding palbociclib to letrozole in the 1st line of therapy allowed us to double the progression-free survival (PFS) of the disease: in the entire population of this study, median PFS was 20.2 and 10.2 months for the combination of palbociclib + letrozole and one letrozole, respectively (p=0.0004). Patients were randomized by the duration of the relapse-free interval and the localization of metastases. The first group included patients with only immunohistochemical data (RE+HER2–), and the second group, designed to assess the effect of biomarkers, included cases with cyclin D1 amplification and / or loss of p16 (INK4A or CDKN2A). In the experimental group (n = 84), palbociclib was prescribed in the standard regime (125 mg 1 time per day for 3 weeks, then a 7-day break) and letrozole (2.5 mg per day daily), in the control group (n=81) - only letrozole. It is important to note that in all patients of this study, letrozole monotherapy provided a median of PFS comparable to previous studies, but the results of the combined approach were more impressive. The subgroup analysis showed that gains from the addition of palbociclib to letrozole were recorded in all patient subgroups, regardless of age (younger or older than 65 years), status on the ECOG scale - (0 or 1 point), localization of metastases (visceral or only in bones), previous chemotherapy (yes/no) or HT (yes/no), as well as from the time from the end of adjuvant treatment to the progression of the disease [6]. The frequency of objective response was also higher in the group of therapy with palbociclib compared with one letrozole and for the whole population was 43% vs. 33% (p=0.13), and for the population with measurable foci - 55% vs. 39% (p=0.047). When a complete or partial objective response was achieved, its duration in the group with palbociclib was 2 times higher than when using letrozole in mono mode (median DOO - 20.3 months vs. 11.1 months). The final results on overall survival were presented at the ASCO Congress in 2017, where there was a tendency to increase life expectancy in the combination therapy group with an absolute increase in median overall survival (4.2 months), as well as the fact that the differences did not reach statistical significance (median OM - 37.5 months vs. 34.5 months, OR=0.813; p=0.42). These results might be associated with the differences in the subsequent treatment: more patients from the letrozole group vs. the palbociclib group had to continue treatment after leaving the stud (86.4% vs. 78.6%), as well as had to receive 3 or more lines of treatment (37% vs. 18%). It is noteworthy that palbociclib significantly increased the time from randomization to the start of subsequent chemotherapy (medians 26.7 months vs. 17.7 months, RR=0.662; 95% CI 0.445-0.989), and the maximum duration of palbociclib in the study is currently 76+ month [6.7]. It should be noted that such prolonged treatment was not accompanied by cumulative toxicity: most adverse events were recorded within 1 year; no new adverse events were recorded in the future.

In the registration study of MONALEESA-2 phase III, an almost twofold increase in the median progression-free survival was also demonstrated with a combination of ribociclib with letrozole (25.3 months) compared with letrozole monotherapy (16 months) [7]. The follow-up period in this study was more than 2 years (26.4 months).

In 2018, the FDA approved the use of ribociclib in first-line therapy in pre- / perimenopausal patients with metastatic hormone-positive HER2 negative BC based on the MONALEESA-7 study. The new drug has been studied in combination with aromatase inhibitors or tamoxifen. All patients in this study underwent ovarian suppression.

An important result of the MONALEESA-3 study was that ribociclib proved its efficiency in combination with both aromatase inhibitors and fulvestrant. The median follow-up in this group was 20.4 months. The study evaluated combination therapy in the first and second lines. When prescribing combination therapy in the first line, median progression-free survival was not achieved at the end of the study. While in the monotherapy group, fulvestrant was 18.3 months. In the second line, combination therapy was almost 1.5 times better compared to fulvestrant monotherapy (PFS 14.6 and 9.1 months, respectively).

Subgroup analysis was performed in all MONALEESA studies. More than half of the patients in each study had an established metastatic lesion of visceral organs, mainly the lungs and liver, and patients with metastatic brain damage were also included in the MONALEESA-3 study. In all three studies, a subgroup analysis showed that with the addition of CDK 4/6 inhibitors to hormone therapy, all patients benefit, regardless of the type of metastasis.

Such impressive results of clinical studies allow us to talk about an important achievement - lengthening the period before chemotherapy, which was made possible by achieving persistent and long-term remissions [8]. Another important argument in favor of more active use of new drugs in clinical practice is their proven safety. Most patients tolerate well the daily oral administration of these drugs. Despite a similar spectrum of toxicity, inhibitors

of cyclin-dependent kinases differ in severity and certain types of adverse events. Studies have shown that insignificant differences can be associated with different selectivity of effects on CDK4 and CDK6 enzymes [9]. For example, palbociclib and ribociclib, to a greater extent, inhibit the enzyme CDK6, which often leads to leukopenia and neutropenia compared with abemaciclib [10].

The results of a clinical study of cyclin-dependent kinase inhibitors in patients with hormone-receptor-positive and HER2 negative metastatic BC in pre- and postmenopausal women indicate the effectiveness of the combination of this group of drugs with hormone therapy. The above studies have shown that half of the women in the group of CDK inhibitors with hormone therapy in the first line live more than 2 years without signs of disease progression and with a good quality of life. However, it should be remembered that any effective treatment can be long-term, provided that the risk of developing adverse events is reduced. And although side effects are not a significant problem for a new class of drugs, experts recommend careful monitoring of patients during treatment. This approach is the key to successful treatment, minimizing side effects, and achieving the proven effectiveness of any innovative treatment method.

Patient Information:

Female patient, born in 1981, since March 2014, has been undergoing a clinical examination with a diagnosis of C-r of the left breast St IIb (T2N1M0).

Clinical data: the patient consulted suspicious for mass in the left mammary gland, which she founded herself. Objectively, the general condition is satisfactory. Consciousness is clear; adequacy is preserved. No data were found for pulmonary, cardiac, and gastrointestinal pathology. There was no weight loss in dynamics. A dense mass 2.0×2.0 cm in size was detected by palpation of the left breast. On palpation, painless, fused with surrounding tissues, the skin above the knot was not changed; there was no nipple discharge.

Diagnostics:

According to the breast ultrasonography of May 26, 2014: Cancer of the left breast with metastases to the axillary lymph nodes on the left, cytological conclusion No. 2477-80 of 05/26/2014 - material from the formation of the left breast - carcinoma, from axillary lymph nodes - metastases of carcinoma.

According to mammograms dated June 12, 2014: cancer of the left breast, lower outer quadrant with a seal behind the nipple of the breast. Breast hyperplasia on both sides, as well as cystic hyperplasia of the lower outer quadrant of the left breast.

An infiltrating carcinoma was diagnosed during the trepanobiopsy of the mass of the left breast.

Treatment:

The patient sought medical attention at the oncological center of the city of Urumqi (China), where on June 16, 2014, an operation was performed: radical resection of the left breast with regional lymphatic dissection. The postoperative histological conclusion is represented by ductal carcinoma of the left breast; the tumor invaded the nipple cells, with a metastatic lesion of the lymph nodes.

According to an immunohistochemical test, estrogen receptors - 90 points (positive), progesterone receptors - 80 points (positive), Her2/neu - 2+ (when FISH is negative), Ki 67 - 20% of internal iliac artery. P53 (site +), SC 5/6 (-), P63 (-).

In the postoperative period, the patient gave a course of external-beam radiotherapy in the area of the postoperative scar and regional metastasis zone, as well as 4 courses of adjuvant polychemotherapy (PCT) with epirubicin in combination with docetaxel, were given from July to October 2014.

Then the patient continued taking hormonal therapy: Zoladex + tamoxifen and was followed up for two years.

Since September 2016, the patient began to worry about pain in the right leg, in the projection of the coccyx, more on the left. Skeleton scintigraphy was performed (from September 13, 2016), where no data were found for the presence of the pathological bone formation site.

However, two months later, when conducting a PET/CT study from 11/21/2016, the following picture was obtained:

1) According to PET/CT data, relapse in the postoperative region and regional metastatic lesions with high metabolic activity were not detected;

2) PET/CT: signs of distant secondary blast (metastatic) lesion of the wing of the left iliac bone.

A histological conclusion was obtained when conducting a trepanobiopsy from the formation of the iliac wing on the left: blood elements, scraps of capillaries, bare nuclei with dystrophy were detected in smears.

According to MRI of the lumbar spine with the capture of the pelvic bones from 12/14/2016: MR-picture of the protrusion of the intervertebral disc L5-S1. A limited focal lesion of the iliac wing on the left. Condition after trepan-biopsy of the iliac wing on the left (12/07/2016).

According to the results of the studies, the progression of the process was established, and in December 2016, a course of PCT was conducted according to the scheme: doxorubicin + cyclophosphamide. After a course of chemotherapy, the patient developed a polyvalent allergy as a result of which further specialized treatment was canceled. The patient visited the allergist for 2 months. In February 2017, a PET/CT study was performed (Urumqi, China) according to which the progression of the process was not established. The patient continued hormone therapy but noted an irregular intake of the drug.

Since January 2018, she began to notice increasing general weakness, fatigue, pain in the lower extremities.

PET/CT study in March 2018, showed metastatic lesions of the contralateral breast, liver, and skeleton bones.

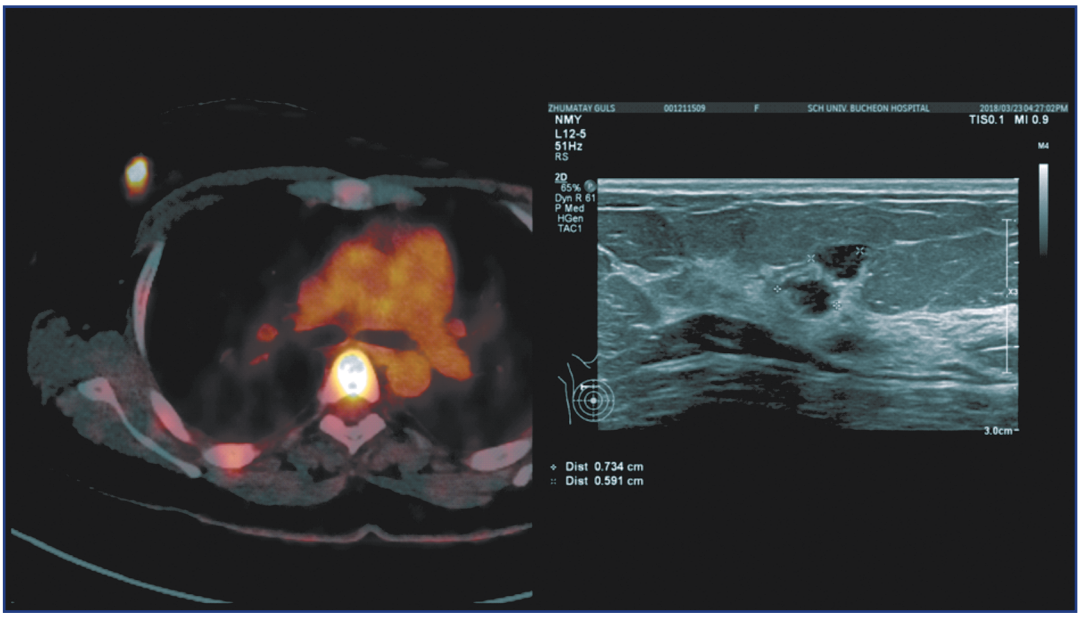

Figure 1 – PET/CT. The site of the RP (radiopharmaceutical) abnormal uptake in the right mammary gland is determined; according to the ultrasound data - at 11 o'clock, a hypoechoic formation of irregular shape, with uneven contours.

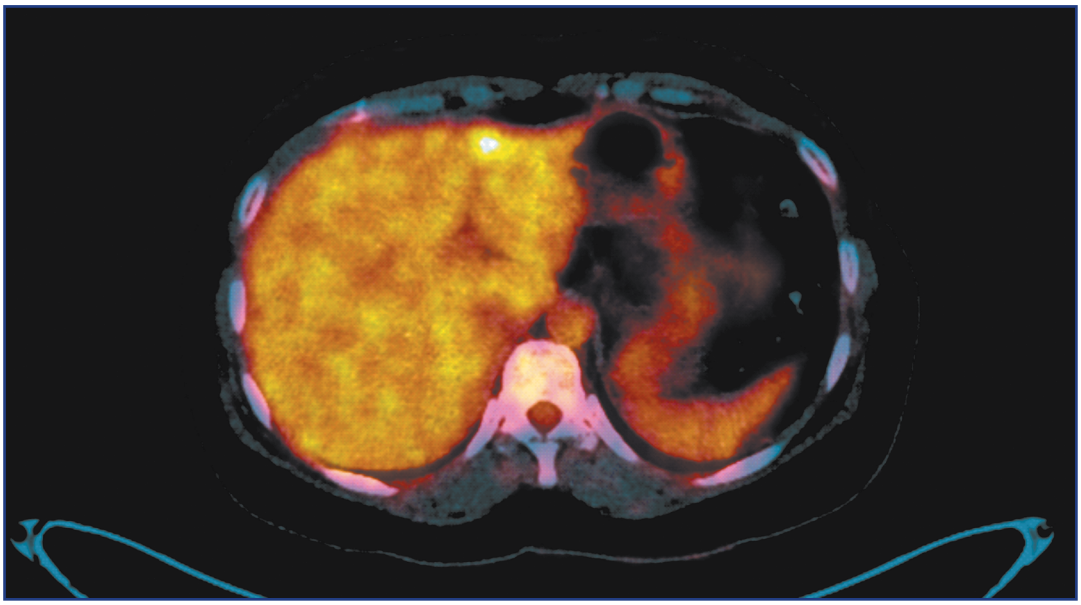

Figure 2 – PET/CT. - The metastatic lesion in the parenchyma S1 of the liver segment

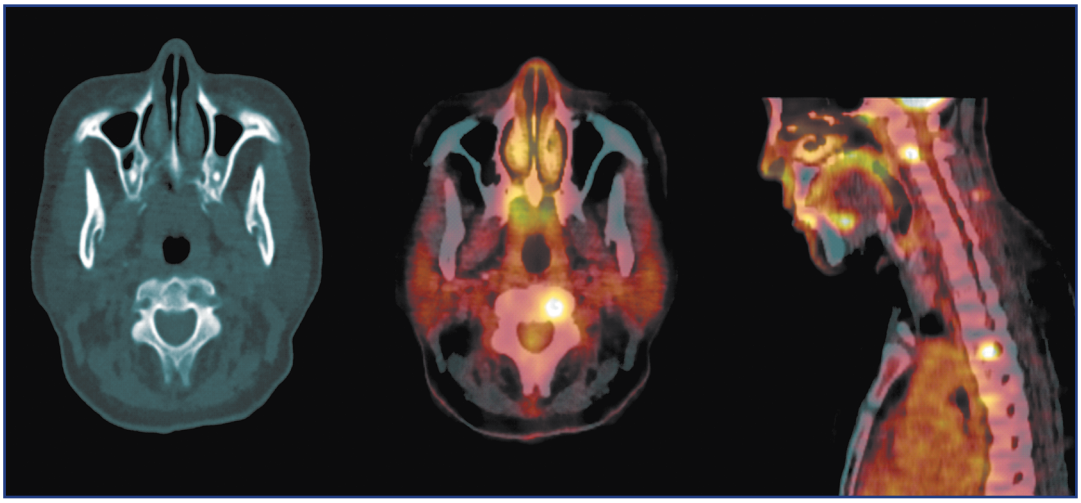

Figure 3 – PET/CT. Metastatic lesions of the lateral mass of the C2 vertebra on the left lateral mass of the C2 vertebra on the left.

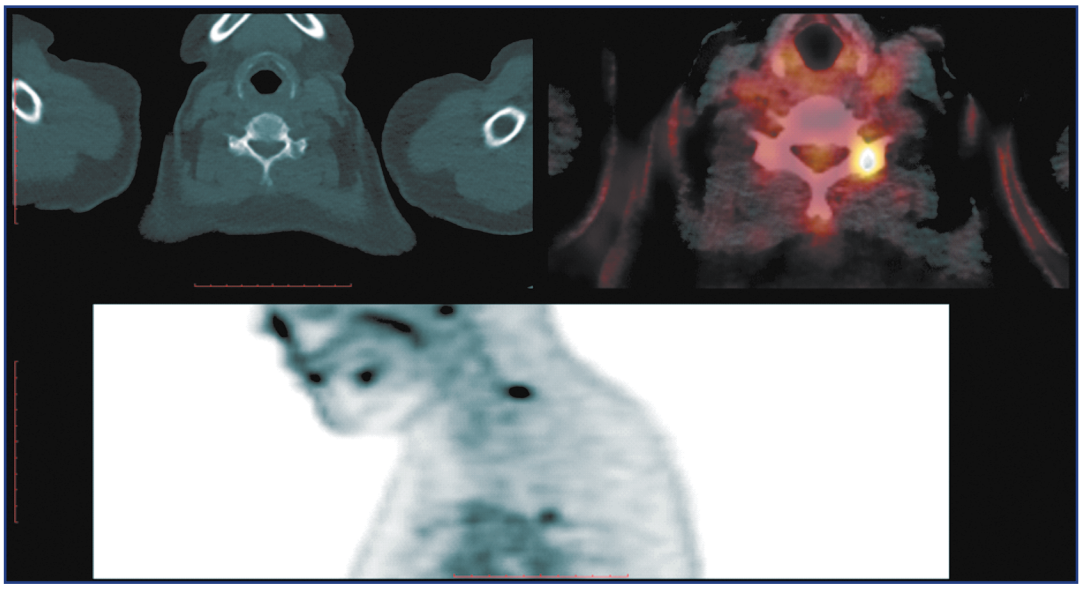

Figure 4 – PET/CT. Metastasis in the arm of the C6 vertebra on the left.

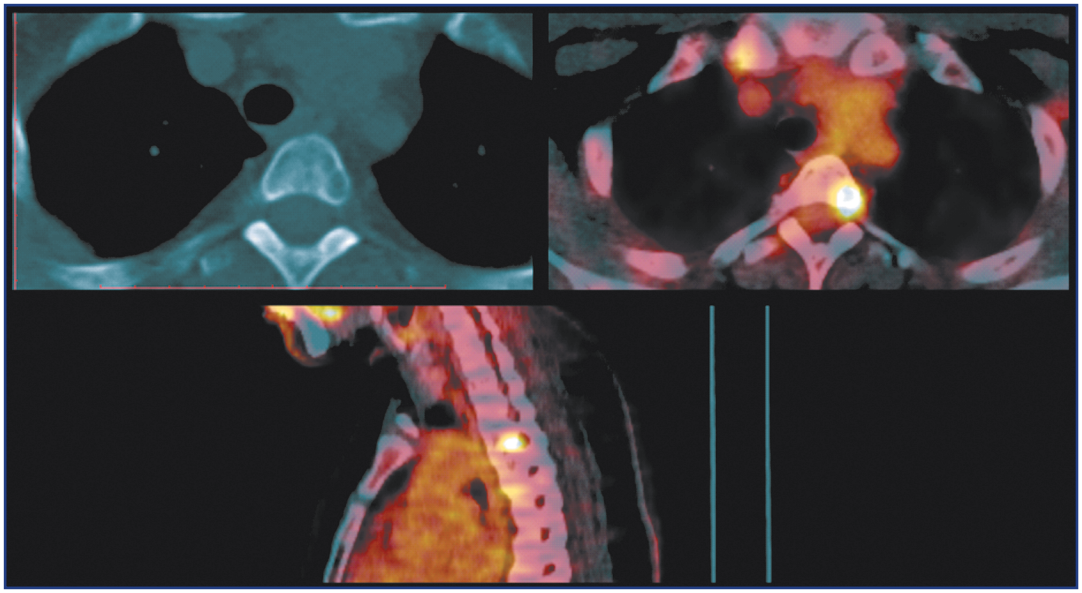

Figure 5 – PET/CT. Metastasis to the arch Th4 root on the left.

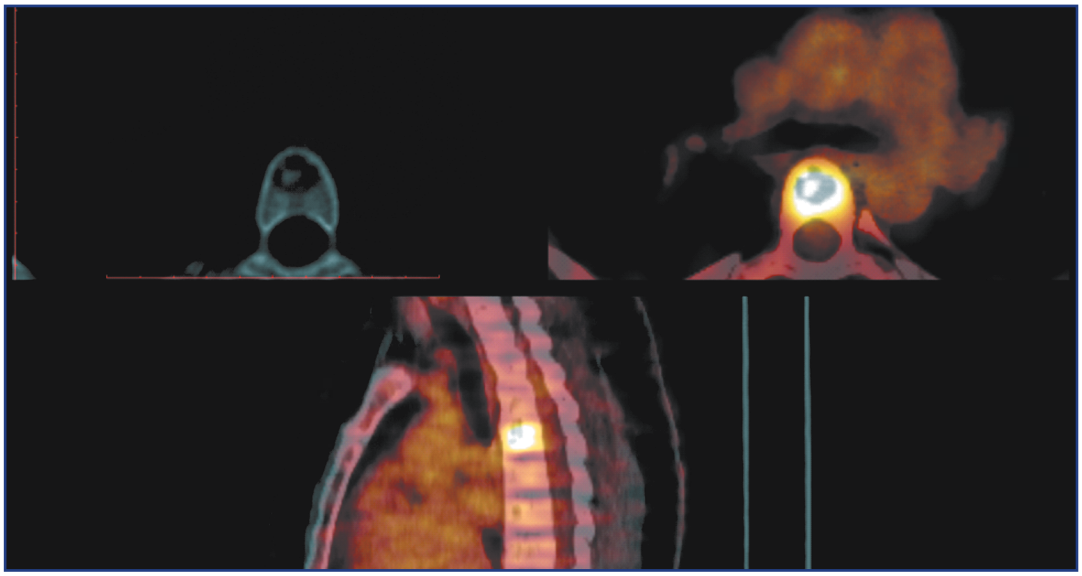

Figure 6 – PET/CT. Metastasis to the body of the Th5 vertebra.

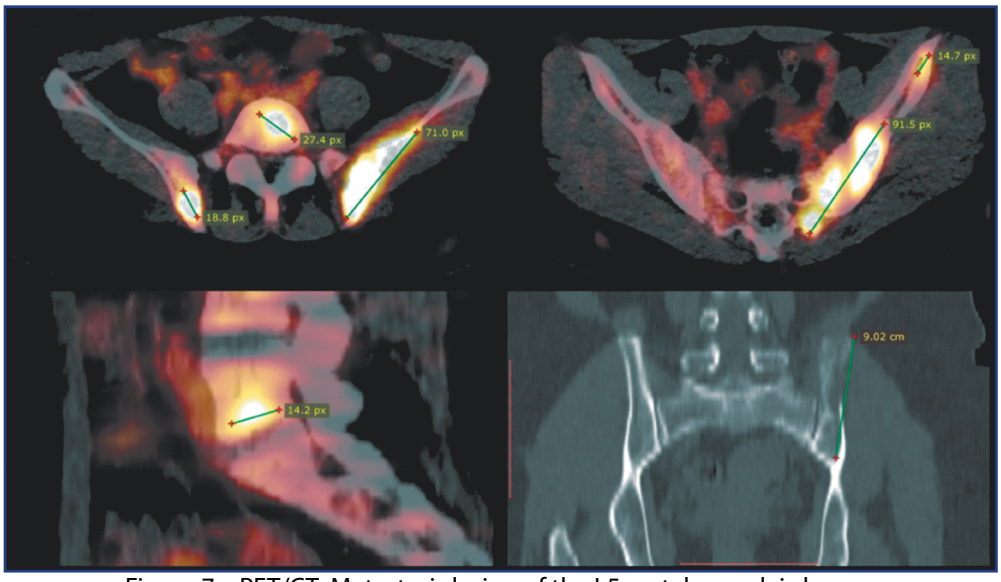

Figure 7 – PET/CT. Metastasis lesion of the L5 vertebra, pelvic bones.

According to the phenotype of the tumor, the patient was administered CDK 4/6 inhibitors (palbociclib 125 mg orally daily for 3 weeks, then a break of 7 days) in combination with aromatase inhibitors (letrozole 2.5 mg daily). The patient began combination therapy in May 2018. Previously, radiation therapy was performed on the Th5 vertebra region - 300cGy, and the left iliac bone - 300cGy. The following adverse events were recorded while taking the drugs: leukopenia, stomatitis, general weakness. However, all of these side effects did not exceed an average degree of toxicity, were stopped when prescribing corrective therapy, and did not lead to a reduction in the dose of palbociclib. During the control examination after three months, the following was revealed:

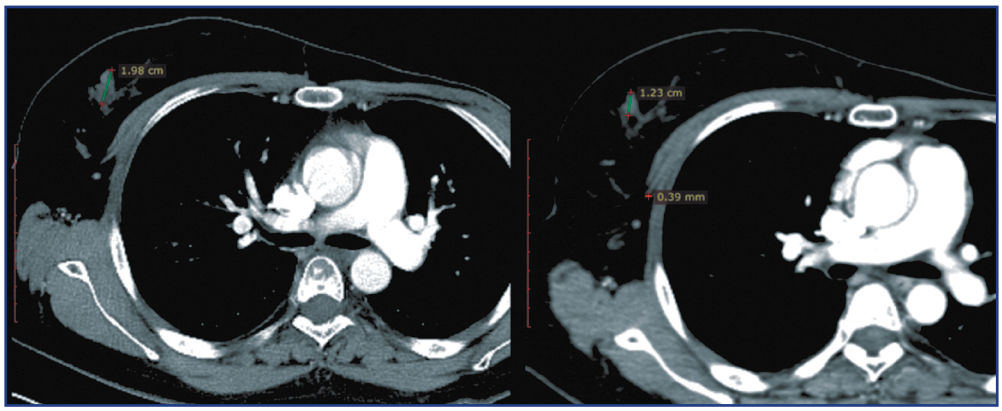

Figure 8 - Thoracic Region CT with bolus contrast from July 2018 compared with data from March 2018. The site of RP (radiopharmaceutical) abnormal uptake in the right mammary gland is determined, partial regression of the process (38%).

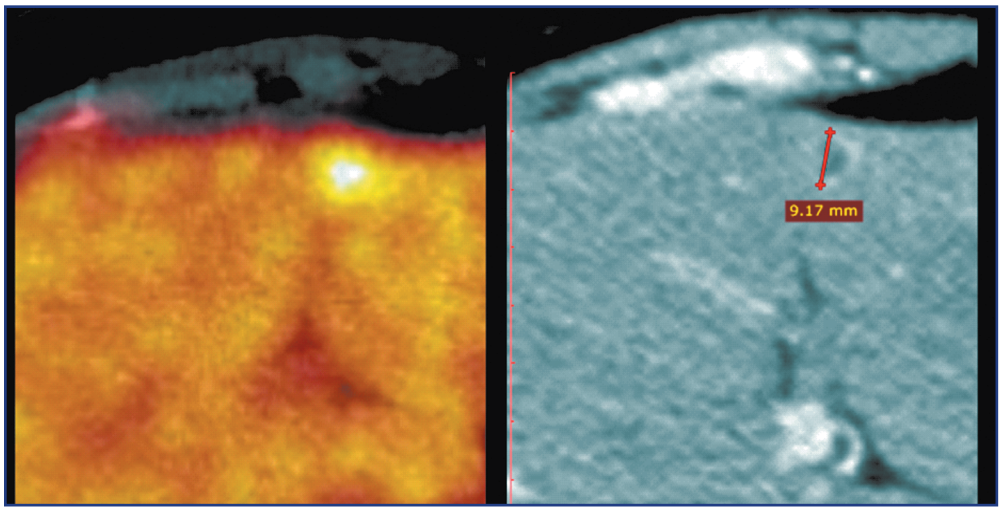

Figure 9 - Thoracic Region CT from July 2018 in comparison with PET CT of March 2018. In the parenchyma S1 of the liver segment - metastatic site, partial regression of the process (40%).

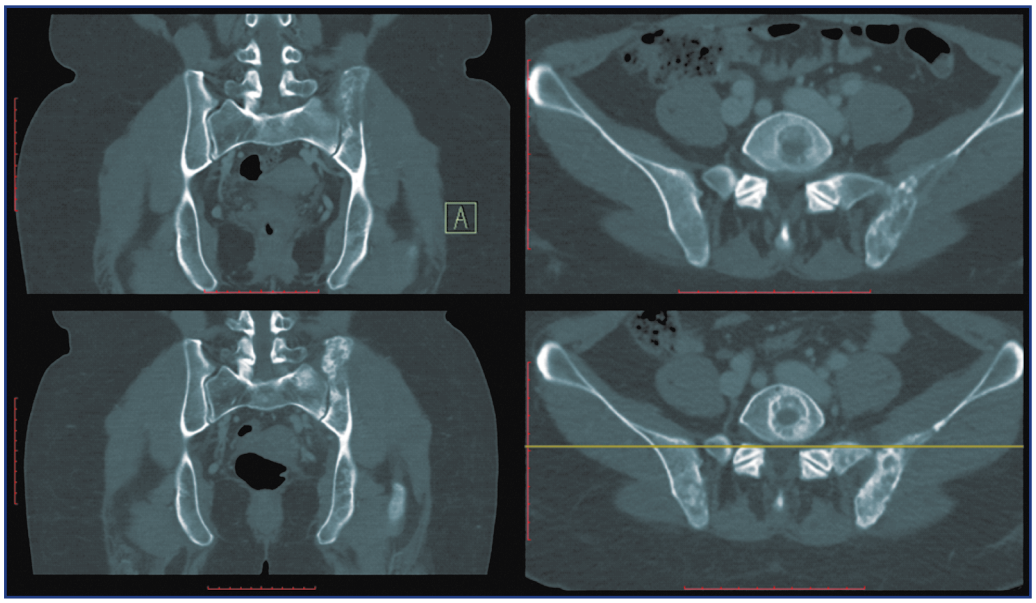

Figure 10 - CT of the skeleton bones from July 2018 in comparison with March 2018. There is a stabilization of the process with positive dynamics in the form of osteosclerosis sites

Given the positive dynamics of the process, it was recommended to continue taking combination therapy: palbociclib in combination with letrozole, as well as recommended to perform bilateral ovariectomy to achieve persistent menopause.

Regression of the process by more than 50% in the mammary gland, liver, and stabilization of the process by metastatic bone damage were recorded during follow-up examinations 6 months after the initiation of therapy.

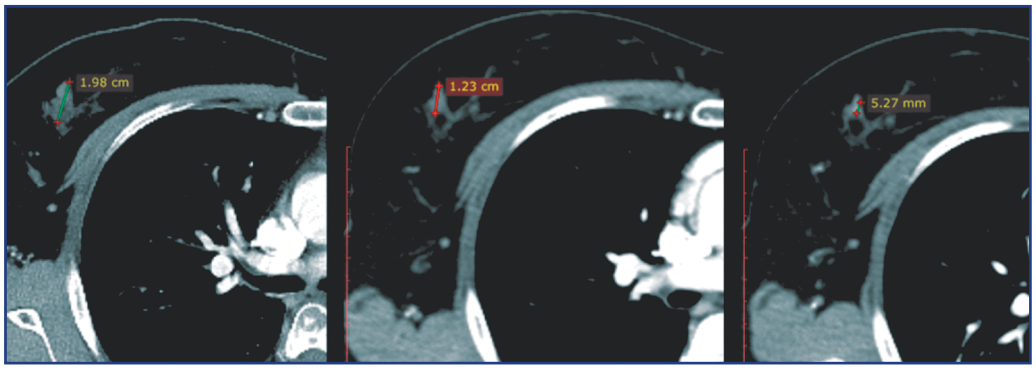

Figure 11 - Thoracic Region CT with bolus contrast from October 2018 compared with data of July and March 2018. Residual mass in the right mammary gland with a diameter in 5 mm.

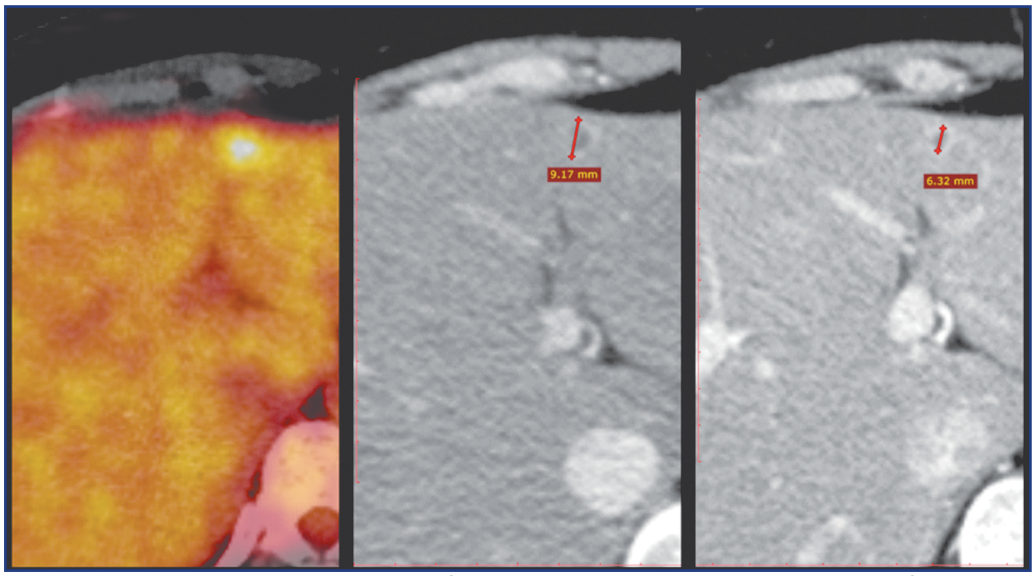

Figure 12 - Thoracic Region CT with bolus contrast from October 2018 compared with data of July 2018 and PET/CT of March 2018. Residual mass in the liver - 0.6 cm.

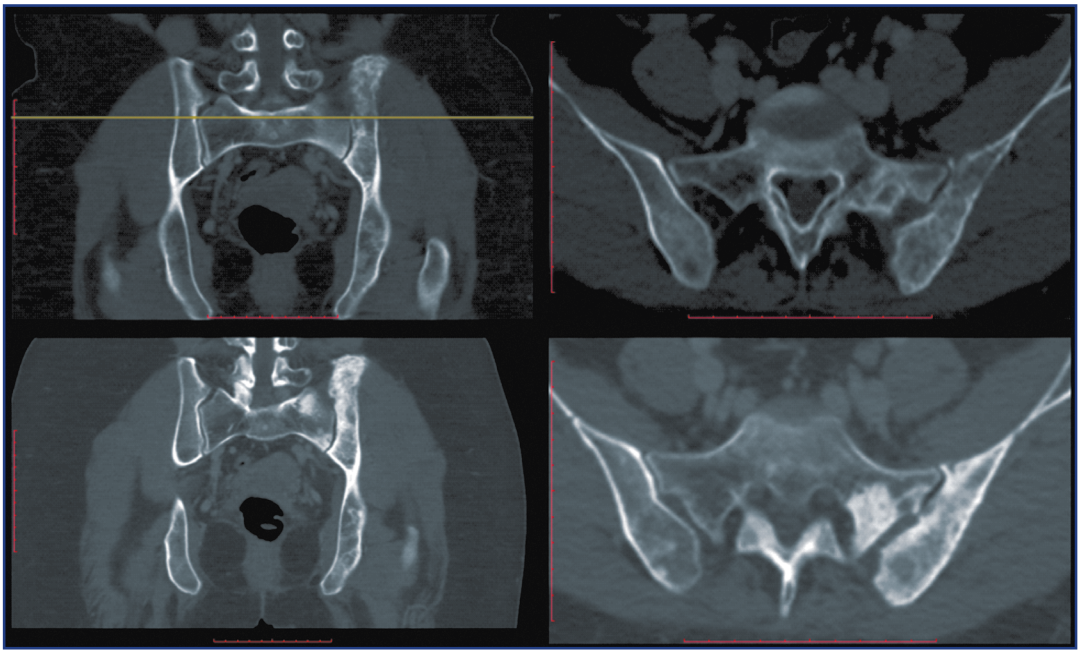

Figure 13 - CT of the skeleton bones from October 2018 in comparison with July 2018. Stabilization of the process with positive dynamics in the form of further sclerotherapy of lytic sites of destruction.

Given the positive dynamics according to control examinations, the patient continued to take targeted therapy in combination with hormone therapy. According to the conclusion of examinations from June 2019, a year after the therapy initiation, complete regression of the metastatic lesion was recorded in the right mammary gland and liver, as well as stabilization of the process and sclerotherapy of lytic sites of destruction in the skeleton bones.

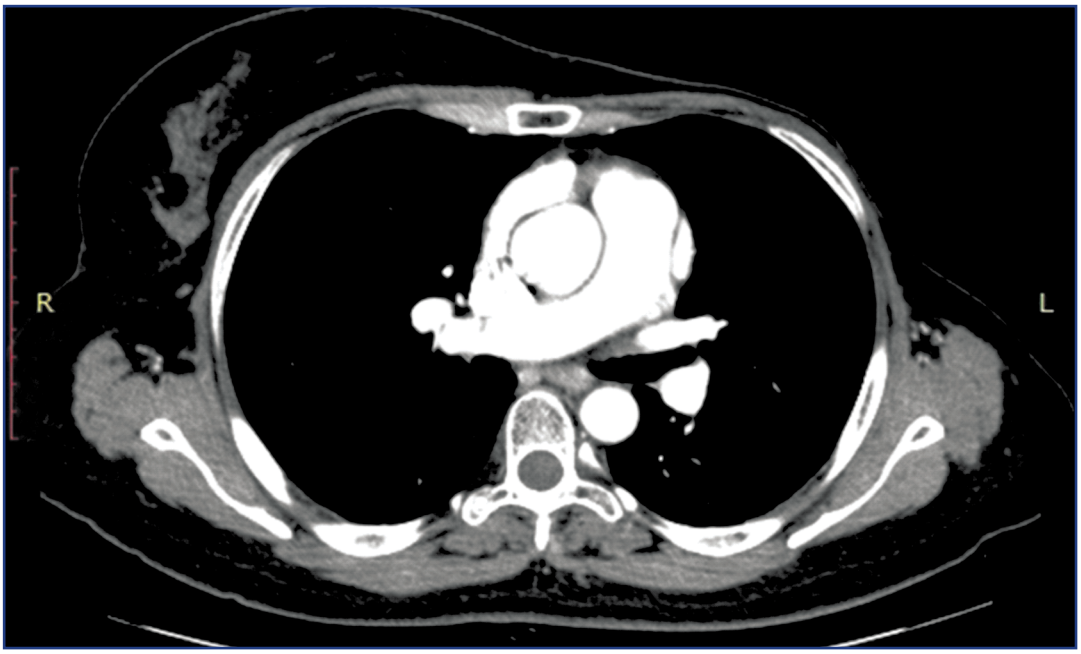

Figure 14 - Thoracic Region CT with bolus contrast from June 2019. Complete regression of the metastatic lesion of the right breast.

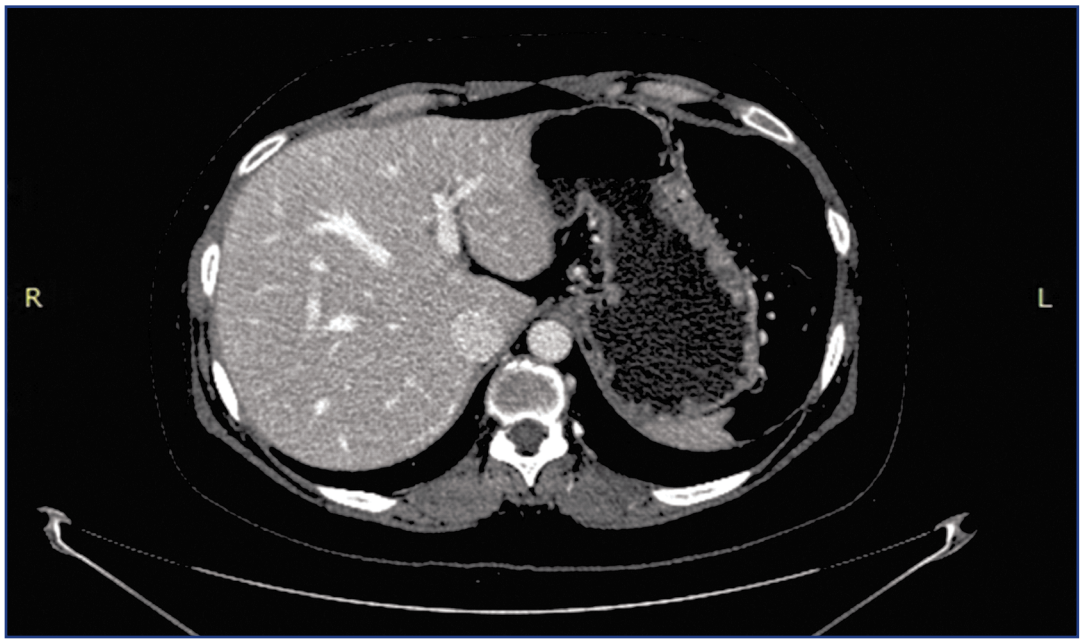

Figure 15 - Thoracic Region CT with bolus contrast from June 2019. Complete regression of liver metastasis.

Results: Currently, the patient continues the combination therapy with CDK 4/6 inhibitor and palbociclib in combination with an aromatase inhibitor – letrozole. The presented clinical case demonstrates a long period of objective response to the targeted therapy in a patient with metastatic lesions of the skeleton bones, liver, and contralateral mammary gland. The combined use of an inhibitor of cyclin-dependent kinases - palbociclib in combination with an aromatase inhibitor - letrozole, led to a pronounced effect with complete step-by-step regression of the metastatic lesion in the liver and right mammary gland. Supportive therapy with palbociclib provides a long, relapse-free period with minimal side effects with a high quality of life for the patient. The convenience of taking this therapy makes it the option of choice for patients with advanced hormone-sensitive BC.

Discussion: Today, metastatic BC continues to be an incurable disease and is regarded as a chronic process that requires quite a long treatment with a periodic change of one type of therapy to another. Thus, the drug treatment of metastatic BC is the main option when choosing a treatment strategy for a doctor. However, currently available chemotherapy often leads to the development of resistance of tumor cells to cytostatic drugs and a decrease in the functional reserves of the liver, cardiovascular system, and bone marrow hematopoiesis. The presented clinical case, as well as the data of randomized clinical trials, demonstrate the possibility of using targeted therapy to overcome hormonal resistance in patients with luminal type of BC with the progression of the process. In the described clinical case, it is possible to increase the duration of remission, survival and improve the quality of life of patients through a combination of antitumor treatment methods. The main goal of modern research remains the desire for personification of therapy, the basis of which is a deeper understanding of the molecular biological mechanisms of carcinogenesis and the application of the latest scientific achievements.

References:

1. International Agency for Research on Cancer, https://gco.iarc.fr/databases.php.; 25/09/19.

2. Bray F., Ferlay J., Soerjomataram I., Siegel R.L., Torre L.A., Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries // CA Cancer J Clin. – 2018. – Vol. 68(6). – P. 394-424;

3. Kononenko I.B., Snegovoy A.V., Sel'chuk V.YU. Ingibitory tsiklin-zavisimykh kinaz: effektivnost' i bezopasnost' (Cyclin-dependent kinase inhibitors: efficacy and safety) // Meditsinskiy Sovet (Medical Council). – 2019. – №10. – P. 42-55 [in Russian];

4. Cardoso F., Spence D., Mertz S. et al. Global analysis of advanced/metastatic breast cancer: decade report (2005–2015) // Breast. – 2018. – Vol. 39. – P. 131–138;

5. SEER Cancer Statistics Review, 1975– 2013 // seer.cancer.gov/csr/1975_2013. April 2016;

6. Are the cells in the G0 phase of mitosis really suspended? Erin Cram, Grad student, Molecular and Cellular Biology, University of CA, Berkeley. 1999. MadScience Network;

7. Pan H., Gray R.G., Davies C. et al. Predictors of recurrence during years 5–14 in 46,138 women with ER+ breast cancer allocated 5 years only of endocrine therapy (ET). ASCO 2016 // J Clin Oncol. – 2016. – Vol. 34(suppl). – Abstr. 505;

8. Saad E., Katz A., Machado K., Buyse M. Post-Progression Survival (PPS) and Overall Survival (OS) According to Treatment Type in Contemporary Phase III Trials in Advanced Breast Cancer (ABC) // SABCS 2009. – Abstr 5116;

9. Dawood S., Broglio K., Gonzalez-Angulo A.M. et al. Trends in survival over the past two decades among white and black patients with newly diagnosed stage IV breast cancer // J Clin Oncol. – 2008. – Vol. 26. – P. 4891–4898;

10. DeVita V., Lawrence T., Rosenberg S. et al. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of oncology. 8th ed. – Philadelphia: J.B. Lippincott, 2008. – P.1634.