Current Therapeutic Targets for Breast Cancer Treatment

Betty Matimba Bumba[a], Paranjeet Kaur[b*]

[a]B.Pharmacy, Scholar, School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar- Delhi G.T. Road, Phagwara, Punjab INDIA (144411).

[*b] Assistant Professor, Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar- Delhi G.T. Road, Phagwara, Punjab INDIA (144411).

Abstract:

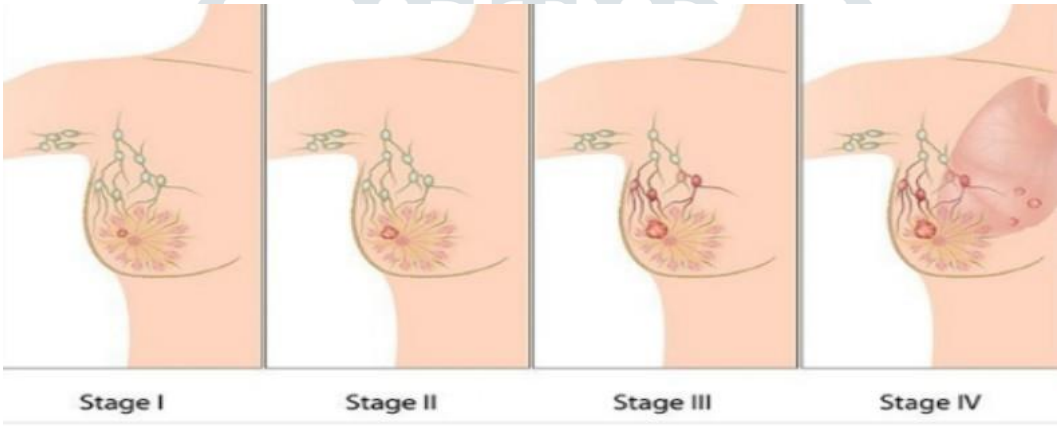


figure 1: Stages of breast cancer

Breast cancer is the most common cancer affecting women world-wide. Because breast cancer is the most common malignancy in women it's for this reason the review provides information on the recent developments of the drug targets in the management of breast cancer. Over the past decades various advancements have been made in the discovery of new drugs for treating breast cancer and this is because of the improved understanding of the biologic heterogeneity of breast cancer which has also allowed the development of more effective approaches to treat breast cancer. Approximately 70% of breast cancers are estrogen receptor positive. Aromatase and Tamoxifen have been used for endocrine therapy and have improved breast cancer survival but a large number of people experience occurrence of the disease either during or near the completion of endocrine therapy.[1] However introduction of new drugs targeting molecular pathway involved in endocrine resistance. The use of combination of endocrine therapy with mammalian target of Rapamycin antagonists with the introduction of cyclin dependent kinase 4/6 inhibitors has significantly improved the response to endocrine therapy.[2] Moving forward HER 2 target immunotherapy consists of monoclonal antibodies such Pertuzumab and Trastuzumab and bispecific antibodies and activated T-cells armed with anti-HER 2 positive metastatic breast cancer.[3] This combined application of the drugs mentioned above plus paclitaxel are a

standard therapy for HER 2 positive breast cancer. Although much needs to be done in improving outcomes for all the patients with breast cancer, especially those who have advanced breast cancer and not forgetting the issue of drug resistance also poses threat to the successful development of targeted therapy in various subtypes of breast cancer. Unfortunately no targeted drug has been approved for the most aggressive subtype triple negative breast cancer.

Key words: Triple Negative Breast Cancer, Breast Cancer, Metastatic Breast Cancer, HER-2, Antibodies

1. Introduction

Breast cancer can be defined as a cancer that forms in the cells of the breasts.It normally occurs in women but rarely in men but according to new research men are prone to it as much now.It can be inherited by a number of mutated genes that can increase the likelihood of breast cancer have been identified. The most well known are breast cancer gene 1(BRCA 1)and breast cancer gene 2(BRCA 2)both of which significantly increase the risk of both breast and ovarian cancer. The following are most likely to causebreast cancer[4];

- Age: The risks increase with age
- Genetics: If a close relative has or had breast cancer the risks are higher
- A history of breast cancer or breast lumps
- Dense breast tissue
- Estrogen exposure and breastfeeding
- Body weight
- Radiation exposure.

1.1.Types of Cancer

Breast cancer represents a heterogeneous group of tumors with varied morphologic and biological features, behavior and response to therapy.The present routine clinical management of breast cancer relies on the availability of robust prognostic and predictive factors to support decision making. Breast cancer patients are stratified into risk groups based on a combination of classical time-dependent prognostic variables (staging) and biological prognostic and predictive variable.[5]

- Ductal Carcinoma;This begins in the milk duct and is the most common type
- Lobular Carcinoma;This starts in the Lobules

- Invasive Breast Cancer;This occurs when the cancer cells break out from inside the lobules or ducts and invade nearby tissue. This increases the chances of cancer spreading to other parts of the body

- Non-invasive Breast Cancer;This develops when the cancer remains inside it's place of origin and has not yet spread.

1.2.Stages of Cancer

Stages of cancer are according to the size of the humor and whether it has spread to lymph nodes or other parts of the body. There are different ways of staging breast cancer which are 0-4 with subdivided categories at each numbered stage. The specific substage of a cancer may also depend on others specific characteristics of the humor such as HER 2 receptors status. Staging variables include tumor size, lymph node stage, and extent of tumorspread.

- Stage 0: Known as ductal carcinoma insitu (DCIS) the cells are limited to within the ducts and have not invaded surrounding tissues.

- Stages 1: This stage the tumor measures upto 2 centimetres(cm) across.It has not affected any lymph nodes or these are small groups of cancer cells in the lymph nodes

- Stage 2: This stage the tumor is 2 centimetres(cm) across and it has started to spread to the lymph nodes or is 2-5 centimetres(cm) across and has not spread to lymph nodes

- Stage 3: This stage the tumor is upto 5 centimetres(cm) across and it spreads to several lymph node.

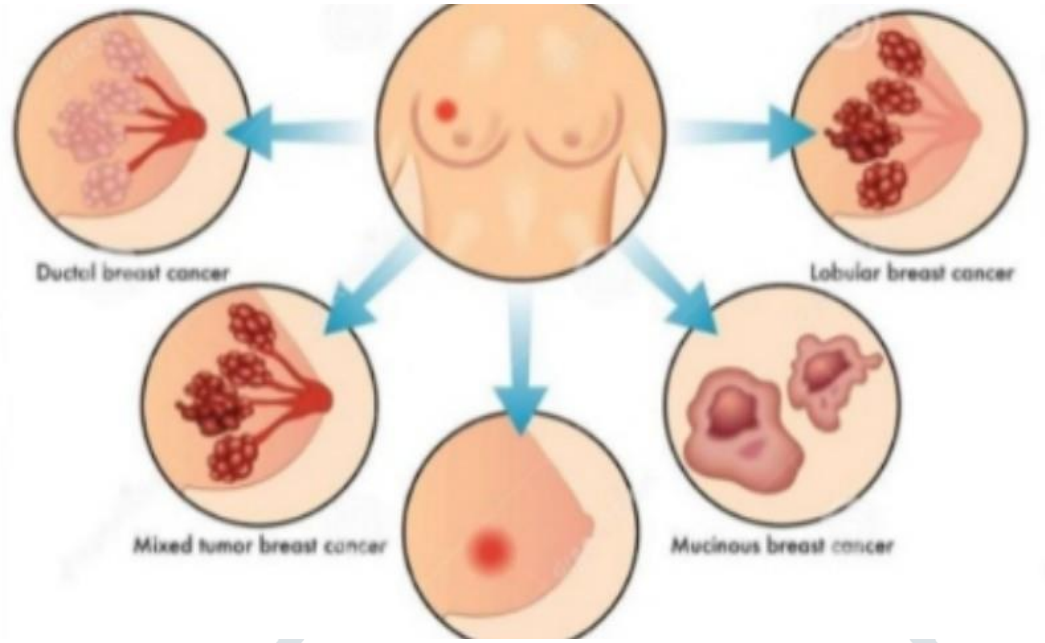


Figure 2: Various types of breast cancer

1.3 Pathophysiology of Breast Cancer

Breast cancer is malignant tumor that starts in the cells of the breast.[6]Like other cancers there are several factors that can raise the risk of getting breast cancer. Damage to the DNA and genetic mutations can lead to breast cancer have been experimentally linked to estrogen exposure. Breast cancer is the most common cancer affecting women. The disease is more common in the affluent world but breast cancer incidence is steadily rising in the developing world. The division of breast tumors into estrogen receptor (ER) positive and estrogen receptor-negative groups was an important step in recognizing heterogeneity and use of antiestrogen therapy in ER- positive disease is the first example of targeted therapy in human cancers. Recent advances in gene expression profiling have further exemplified the heterogeneity of breast cancer. The ER-positive disease is now split into at least 2 groups, one with good prognosis (likely luminal A type tumors) and another with poor prognosis (likely luminal B type tumors).[7] The ER-negative disease is also split into an HER2-enriched category and the so-called basal-like breast cancer category. Although the molecular classes described using gene expression profiling do have morphologic and immune histochemical correlates, there is lack of consensus on a defined morphologic or immune histochemical criteria. Another common but important issue in breast cancer is assessment of HER2 (ERBB2) oncogene.HER2 gene is amplified/overexpressed in approximately 20% of breast cancer and is a marker of aggressive disease. However, with the availability of HER2-targeted therapy, trastuzumab, the natural history of HER2 disease has been significantly altered. Trastuzumab treatment is highly effective in HER2 positive tumor, but it is generally ineffective in HER2-negative disease.[8] Moreover, the treatment is expensive and potentially cardiotoxic, so patient selection is very important. Due to the availability of such an effective treatment, it is very important for pathologists to be aware of all HER2-testing issues. The scope of breast cancer research is quite broad and is difficult to include all topics in one.

Nevertheless ,I have tried to include both common and uncommon topics. Some individuals inherit defects in the DNA and genes like in BRCA1,BRCA2 and P53 among others. Those with a family history of ovarian or breast cancer are at an increased risk of breast cancer.

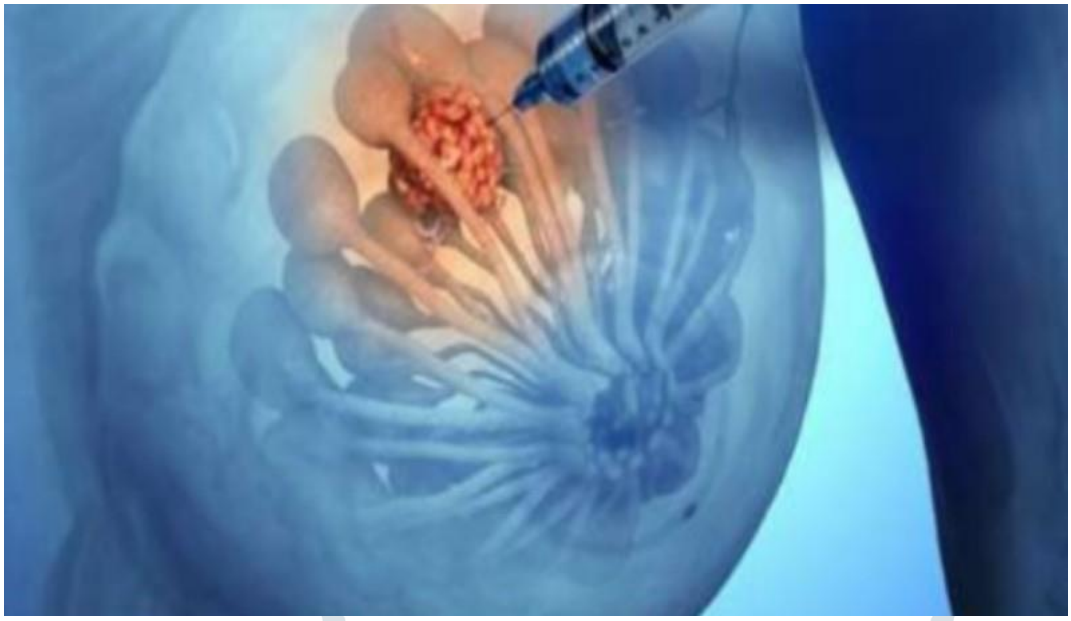


Figure 3: Pathophysiology of breast cancer

1.4.Treatments of Breast Cancer

Understanding of the natural history of breast cancer has evolved alongside technologies to study its genomic, transcriptomic, proteomic and metabolomics. Breast cancer treatments include;

- Hormonal therapy
- Surgery
- Immuno-Therapy
- Radiation
- Targeted Therapy
- Chemo-Therapy

Some of these treatments may be further divided as follows;

- Surgery
- Mammaplasty: Plastic to increase or reduce the size of the breast to reconstruct a breast.
- Tissue Explanation: Inserting a balloon under the skin and then gradually expanding it to stretch and grow the skin and surrounding tissue
- Lumpectomy: Surgical removal of a lump(tumor)in tge breast
- Lymph node dissection: Surgical removal of a lymph node
- Mastectomy: Surgical removal of some or all of the breast
- Medical Procedure
- Teletherapy: Radiation therapy that uses x-rays or other high energy beams to destroy cancer cells and shrink tumors.
- Radiation: Treatment that uses x-rays and other high energy rays to kill abnormal cells.
- Medications
- Estrogen Modulator: Mimics the effects of estrogen on various tissues including the breast, bones and reproductive organs.
- Chemotherapy: Kills cells that are growing or multiplying too quickly
- Bone Health: Helps to strengthen and build bones

1.5. Commonly used drugs for the treatment of Breast Cancer.

- **For Risk Reducation**
- Abraxane
- Adriamycin
- Aranesp
- Aredia
- Aromasin

- Carboplatin
- Daunonibicin
- **For Prevention**
- Evistsa
- Raloxifene
- Tamoxifen
- **For Treatment**
- Abemaciclib
- Vinblastin
- Thiotepa
- 5-Fluorouracil Injection
- Docetaxel
- **For Target Therapy**
- Lapatinib
- Pertuzumab
- Trastuzumb

All these medications prompt the body's immune system to destroy cancer. They target breast cancer cells that have high levels of protein HER2.

1.6. *Current Therapeutic Targets for Breast Cancer Intervention A new approach in Radiotherapy*

Short-course radiotherapy using hypo fractionation has been found to result in a similar outcome to standard radiotherapy in terms of local recurrence and survival, without increasing long-term toxicities and because of this it is therefore now accepted as a standard of care for early-stage breast cancer. Whole-breast radiation following breast- conserving surgery aims to create a uniform dose distribution to target tissues with minimal toxicity to normal tissue.[9]Post-mastectomy radiotherapy is conventionally given to patients with four or more nodes to reduce locoregional failure and breast cancer mortality. For patients with one to three nodes, factors

such as adverse tumour biology or tumor size of more than 5 cm may shift the decision to recommend radiotherapy after considering the benefits and toxicities. Breast cancer care is now a tool used with the appropriate therapy to target the tumor characteristics of individual cancers, to achieve an improved survival outcome for breast cancer patients. Targeted cancer treatment is proliferating. More scientific work is required to further our understanding of the unknown subtypes, especially in triple-negative cancers and problems dealing with development of tumor resistance to drug therapy.

A new approach in Immunotherapy

Recent advances and future challenges in cancer immunotherapy, for example the identification of neoantigens for the development of individualized immunotherapies, the development of new CAR-T cell therapies, which include the so-called armored CAR- T cells that can induce greater clinical effects and thereby achieve longer survival, the development of off-the-shelf treatment regimens using non-self cells or cell lines, and effective cancer immunotherapy combinations.

Also promising results of immunotherapy in treating non—small-cell lung cancer and other cancers have led to clinical trials in breast cancer. An improved clinical activity has been observed in treating triple-negative breast cancer and those expressing PD- L1.Furthermore Pembrolizumab is a human monoclonal IgG4-κ antibody against the programmed cell death 1 receptor (PD-1).[10] It's showed clinical efficacy and safety in patients with advanced TNBC. PD-1 prevents autoimmunity by suppressing T cells and thus preventing the immune system from killing cancer cells. While patients with PD-L1 (a ligand of PD-1)-positive advanced TNBC were selected for investigation in a phase Ib study and the antitumor activity of pembrolizumab appeared to be independent of PD- L1 expression according to another ongoing phase II study, most importantly pembrolizumab also showed durable antitumor activity in patients with heavily pretreated metastatic TNBC.

A new approach in Chemo-therapy

Chemotherapy is the utilization of pharmacologic products that hinder the advancement of intrusive disease either by obstructing the DNA harm that starts carcinogenesis or by capturing or switching the development of premalignant cells in which such harm has just happened. Chemoprevention is a recently introduced and quickly developing region of oncology that is distinguishing agents with a potentially preventive part in malignancy.[11]Since the disclosure and further restorative utilization of Tamoxifen, a particular estrogen receptor modulator, bosom disease treatment has turned to the advancement and accomplishment of custom fitted restorative.

Cyclin-Dependent Kinases as Targets and Biomarkers for Cancer Therapy

[12] Drugs targeting cell cycle-regulatory cyclin-dependent kinase (CDK) 4 and 6 have been approved for the treatment of hormone receptor-positive breast cancer, and inhibitors targeting other cell-cycle CDKs are currently in clinical trials. Another class of CDKs, the transcription-associated CDKs, including CDK7, CDK8, CDK9,

CDK12 and CDK13, are critical regulators of gene expression. Recent evidence suggests several novel functions of these CDKs, including regulation of epigenetic modifications, intronic polyadenylation, DNA-damage responses, and genomic stability

Targeting the Unfolded Protein Response in Hormone-Regulated Cancers.

[13]Cancer cells exploit many of the cellular adaptive responses to support their survival needs. One of these is the unfolded protein response (UPR), a highly conserved signaling pathway that is mounted in response to endoplasmic reticulum (ER) stress. Recent work showed that steroid hormones, in particular estrogens and androgens, regulate the canonical UPR pathways in breast cancer (BCa) and prostate cancer (PCa).

Andrographolide inhibits osteopontin expression and breast tumor growth through down regulation of PI3 kinase/Akt signaling pathway.

[14] Breast cancer is one of the most common cancers among women in India and around the world. Despite recent advancement in the treatment of breast cancer, the results of chemotherapy to date remain unsatisfactory,Andrographolide (Andro) is one such molecule which has been shown to possess inhibitory effect on cancer cell growth.Andro, a natural diterpenoid lactone isolated from Andrographis paniculata has been shown to inhibit breast cancer cell proliferation, migration and arrest cell cycle at G2/M phase and induces apoptosis through caspase independent pathway.

Hormonal treatment combined with targeted therapies in endocrine-responsive and HER2-positive metastatic breastcancer

[15]Approximately 50% of HER2-positive breast cancers are also estrogen receptor (ER)- positive, dividing HER2 positive patients into two main subgroups (ER-negative plus HER2-positive, and ER-positive and HER2-positive) with different patterns of growth and response to treatmen.

For the nonendocrine-responsive and HER2-positive disease, the treatment strategy includes the use of chemotherapy combined with anti-HER2 drugs. In the subgroup of HER2- and ER-positive metastatic breast cancer (MBC), different strategies are being investigated.Several lines of data support a role for close crosstalk between the ER and HER2 signaling pathways

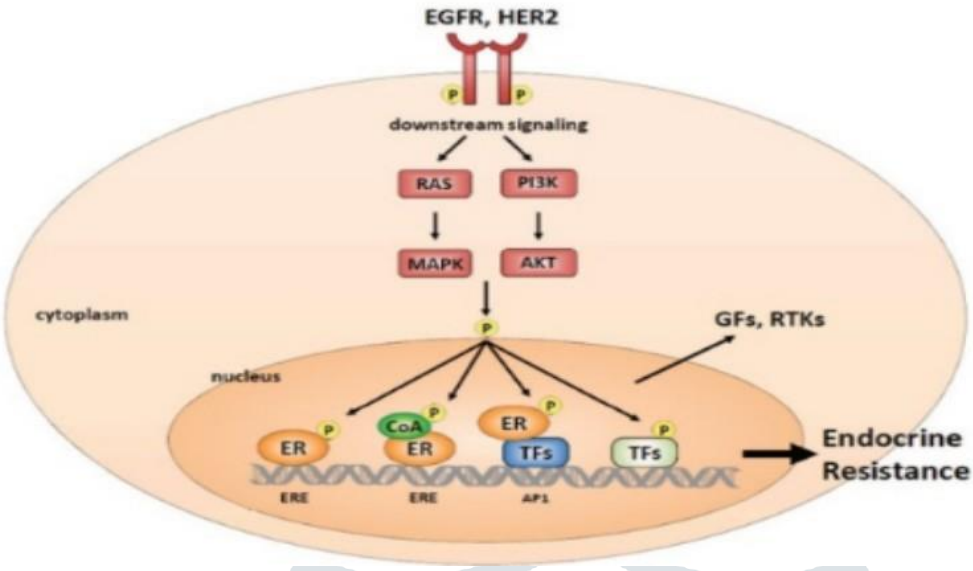
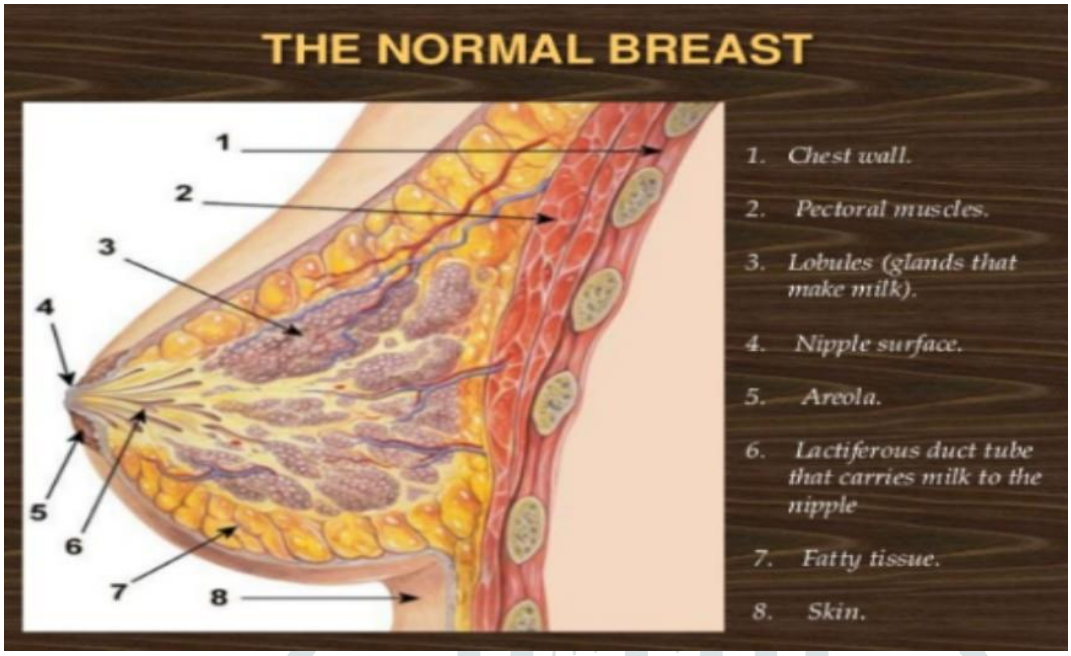


Figure 4: Hormonal treatment of breast cancer

1.7. Conclusion

Breast Cancer is the most common malignancy in women, for example Triple Negative Breast Cancer remains a deadly disease with limited treatment options. Over the past decade, the molecular mechanisms driving the heterogeneous treatment response in Breast Cancer are better elucidated. This has fueled the development of novel targeted agents, including inhibitors of PARP, CDK4/6, PI3K/AKT/mTOR, multiple kinases, or immune checkpoint, for the treatment of specific molecular subtypes of Breast Cancer and treatment options should be tailored to individual patient accordingly.

Cancer prevention is currently playing a significant role in the fight against the disease. It is because of the modifications of therapies and as well as greater awareness among women regarding breast cancer, may significantly contribute towards reducing the incidence of this cancer. Another important aspect is the number of women undergoing diagnostic tests, although it still remains at an unsatisfactory level.



1.8. References

1. Reinert, T.; Barrios, C.H. Optimal management of hormone receptor positive metastatic breast cancer in 2016. *Therapeutic Advances Medical Oncology* **2015,** 7, 304—20.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies, C.; Godwin, J.; Gray R. et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*, **2011**, 378, 771-84.
3. Swain, SM.; Baselga, J.; Kim, SB. et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *The New England journal of Medicine*, **2015,** 372, 724-34.
4. Washbrook Elinor. Risk factors and epidemiology of breast cancer. *Women's Health Medicine*, **2006**, 3, 8—14.
5. Eccles, SA.; Aboagye, EO.; Ali, S.; Anderson, AS.; Armes, J.; Berditchevski, F.; Blaydes, JP.; Brennan, K.; Brown, NJ.; Bryant, HE.; Bundred, NJ.; Burchell, JM.; Campbell, AM.; Carroll, JS.; Clarke, RB.; Coles, CE.; Cook, GJ.; Cox, A.; Curtin, NJ.; Dekker, LV.; Silva, Idos, S.; Duffy, SW.; Easton, DF.; Eccles, DM.; Edwards, DR.; Edwards, J.; Evans, D.; Fenlon, DF.; Flanagan, JM. Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer. *Breast Cancer Research* . **2013,**15-92.
6. Sledge, G.; Mamounas, E.; Hortobagyi, G.; Burstein, HJ.; Goodwin, PJ.; Wolff, AC. Past, present and future challenges in breast cancer treatment. *J Clin Oncol*, **2014**, 32:1979—86
7. de, Melo, Gagliato, D1.; Jardim, DL1.; Marchesi, MS2.; Hortobagyi, GN3. Mechanisms of resistance and sensitivity to anti-HER2 therapies in HER2+ breast cancer, **2016**, Sep, 27;7, 39, 64431-64446.
8. Kümler I1, Tuxen MK, Nielsen DL. A systematic review of dual targeting in HER2- positive breast

cancer. **2014,** 259-70.

9. Whelan, TJ.; Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med, **2010**,362:513-20.

10. Swain, SM.; Kim, SB.; Cortés, J.; Ro, J.; Semiglazov, V.; Campone, M.; et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double- blind, placebo-controlled, phase 3 study. *Lancet Oncol*, **2013**;14, 6, :461—471.

11. Suzuki, M.; Hori,K.; Abe, I.; Saito,S.; Sato, H.; A new approach to cancer chemotherapy: selective enhancement of tumor blood flow with angiotensin II. *J Natl Cancer Inst.* **1981** Sep, 67, 3, 663-9.

12. Hettman, T.; Schneider, M.; Blum, S.; Hartmann, S.; Hendrich, M.; Moor, R.; et al. Abstract B161: U3-1287 (AMG 888), a fully human anti-HER3 mAb, demonstrates preclinical efficacy in HER2+ and HER2- breast cancer models. *Mol.Cancer Ther*. **2009**, 8:B161—161

13. Cristofanilli, M.; Turner, NC.; Bondarenko, I.; Ro, J.; Im, SA.; Masuda, N.; 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 3 randomised controlled trial. *Lancet Oncol*, **2016**, 17:425—39

14. EA. Treatment strategies for advanced hormone receptor-positive and human epidermal growth factor 2-negative breast cancer: the role of treatment order. *Drug Resist Updat* , **2016**, 24:13—22

15. Xu, H.; Yu, S.; Liu, Q.; Yuan, X.; Mani, S.; Pestell, R, G.; et,al. Recent advances of highly selective CDK4/6 inhibitors in breast cancer. *J Hematol Oncol* , **2017,** 10:97.