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UNVEILING INNOVATIONS: THE SPECTRUM OF DRUG DEVELOPMENT IN BREAST CANCER SUBTYPES

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Abstract:
Recent years have seen several promising developments in improving our knowledge of molecular pathways of the development of cancer. These advancements have made it possible to identify potential novel objectives for cancer treatment. In Females, breast cancer (BC) is the most prevalent type of cancer. Growing comprehension of the physiological variability of BC has made it possible to create more specific and efficient treatment plans. In this review, we address the different newly developed innovative therapeutics for the main molecular subtypes of BC and provide an update on the current treatment approach. Included is a quick overview of the clinical development of immunological checkpoints, poly (ADP-ribose) polymerase inhibitors, protein kinase B inhibitors, AKT blockers, cyclin-dependent kinases 4 and 6, and, phosphatidylinositol 3-kinase for therapy of BC. Nevertheless, no specific medication has been authorized for the most severe subtype of triple-negative breast cancer. Therefore, we go over TNBC's heterogeneity and how molecular subtyping of TNBC could aid in developing new treatments for this most aggressive cancer of breast. The diagnosis and treatment of metastatic breast cancer are complicated by the heterogeneity of the tumor and a variety of physiological barriers that prevent drugs from reaching the metastatic areas. Few Nano formulated medications have been effectively introduced into clinical practice even though several have been developed and evaluated in preclinical trials as a means of overcoming these constraints. This review shows that, in comparison to traditional chemotherapy, Nano formulated albumin-bound paclitaxel has a better therapeutic index and significantly lower drug toxicity.

Key words: Breast Cancer, Drug Development, Nanoparticles

Introduction:

The most frequent malignancy in women, excluding other malignancies, is the breast cancer. Following the lung cancer, it is the second most prevalent reason of cancer-associated deaths in females overall, but it is the most common among Black and Hispanic women(1). Since 1994,

Pakistan has used cancer registries to routinely gather data on cancer cases. A thorough examination of Pakistan's cancer data from 1994 to 2021 revealed that 109,863 patients were registered, whereas 111,941 patients overall had malignant neoplasms. Khyber Pakhtunkhwa has 20.2 percent according to report and Punjab has 67.6 percent cases accounted for the majority of patients. Among all age groups and sexes, cancer of breast is the most common cancer as 22.2 percent. The most common organ in adults of both sexes is the breast as 24.6 percent. The most prevalent malignancies in adult females were those of the mammary cancer is the most prevalent as 45.9 percent, 4.9 percent is ovary and uterine adnexa cancer, 4.2 percent cancer is cancer of lip and oral cavity, cervix uteri is four percent, and colon cancer is 3.9 percent(2). The primary cause of breast cancer's continued global health concern is metastasis. The proliferation and spreading of cancerous tissues from the original growth to secondary locations is known as metastasis. This multi-step process is frequently explained as a simple sequence of sequential things, including escape from the original malignancy and localized invasion, infiltration and survival in the bloodstream, extravasation, and metastatic seeding. Over ninety percent of tumor-linked deaths are caused by this process, which frequently results in the decrease in fundamental organ function. Breast cancer, the most frequent cancer diagnosed globally. It is the second largest reason of death due cancer among women, presents a serious risk to individuals who have the disease. Even in cases of early diagnosis of breast cancer, 20–30% of patients pass away from metastatic illness. Consistent with clinical findings, specific organ dispersion of breast cancer cells has been primarily documented to the brain, liver, lungs, and bones in addition to lymph nodes(3). Despite significant advancements in conventional chemotherapy, two major issues remain: poor rates of response, particularly in cases of metastatic disease, related to cancer cells' resistance to numerous cytotoxic agents, and serious side effects resulting from these agents' broad-spectrum cytotoxic effects against all proliferating cells. New medications that specifically target cancerous cells and shield healthy tissue from harm are therefore gaining popularity(4). Moreover, creating efficient treatment plans is made extremely difficult by the discovery of substantial genetic variation in human breast cancers.

There have been three primary forms of heterogeneity identified. The three types of heterogeneity are as follows: temporal heterogeneity, which reflects variability over time during tumor development and progression or in reaction to treatment; intratumor heterogeneity, or spatial heterogeneity within a single malignant mass; and population variability, or differences among cancers from different patients(5). Carcinoma heterogeneity poses a significant obstacle to cancer therapy as a result. While genetic variation within cancer cell populations has historically been attributed to heterogeneity, it is now commonly acknowledged that nearly all distinct phenotypic aspects of human malignancies are heterogeneous. Gaining knowledge of the genetic diversity of tumor heterogeneity as well as its non-genetic components will lead to new discoveries regarding how to counteract treatment resistance and enhance cancer treatment(6). The recent therapies involve the use of antibody drug conjugated based treatments or the use of nanoparticles that are highly targeted.

Antibody Drug Conjugated-based medications bridge the therapeutic efficacy gap between cytotoxic medicines and monoclonal antibodies in the treatment of cancer, especially breast cancer. The targeting antigen, the payload, the linker, and the monoclonal antibody (mAb) are the four essential parts of an ADC. ADCs are made up of an anticancer monoclonal antibody coupled to a cytotoxic payload via a chemical linker that has been developed to allow for both the simultaneous death of tumor cells and effective targeting of tumor cells(7). By combining them with a linker, ADCs have the benefits of both targeted agents and chemotherapeutics. HER2 positive breast cancers, as well as HER2 low and HER2 negative breast cancers, as well as patients with triple negative breast cancer (TNBC), have demonstrated anti-cancer efficacy when treated with ADC medicines(8). Nanoparticles are small crystals that are in the range of 100 nm or smaller, in size, meaning they are limited to the nanoscale in all three dimensions. An integrated surface layer surrounds the nanoparticles, typically consisting of ions or other inorganic or organic molecules. Drug distribution and action are improved with the use of nanoparticles. Because of their particular small size and unique coating, hydrophobic

anticancer medicines are easier to administer to specific body locations with less immune system opsonization. Many different types of nanoparticles have been developed with the express purpose of addressing metastasized breast tumors. These include quantum dots, silica, gold, fullerene, carbon nanotubes, and magnetic nanoparticles(9). Because nanoparticles (NPs) may create chemical interactions with a wide range of medications, they can release these medications in cancer cells instead of normal cells, which makes them a significant tool in cancer therapy. Due to the incredible range and diversity of NPs, particularly their diverse forms and chemical makeup, nanotechnology provides a plethora of options for a range of cancer treatment issues. Additionally, they have great promising effect for the early detection, prevention, diagnosis, and visualization of tumors in addition to their treatment(10).the novelty of this review paper is that as compared to traditional chemotherapy, Nano particles are most targeted and FDA approved albumin bound Nano formulated Paclitaxel is used for treating breast cancer now a days.

Subtypes of Breast Cancer:

Breast cancer is defined as tumor that starts in breast tissue, usually from the lobules that provide milk to the ducts or from the thinner lining of the milk ducts. Cancer that starts in the ducts is named as ductal carcinoma, and tumor that starts in the lobules is known as lobular carcinoma. Breast cancer is caused by aberrant cell proliferation in the breast's normal cells, which changes the firmness of the tissues in the breast.

This abnormality typically appears in the interior lining of the breast lobules or milk ducts(11). According to the availability or lack of genetic markers for human epidermal growth factor 2 (ERBB2; previously HER2), progesterone, or estrogen receptors, breast cancer is divided into three main subtypes: triple-negative (tumors in which all three standard molecular markers are absent; 15%), ERBB2 positive (15–20%), and receptor for hormones positive/ERBB2 negative (known as luminal types, which account for 70% of patients).

At the stage of diagnosis, nearly ninety percent of breast cancers do not have metastases(12). Furthermore, there was a correlation between the clinico-pathologic parameters of both luminal A and luminal B breast cancer, which include age, nodal status, laterality, lesion stage, size, grade, ki67 value, and overall size. In comparison with luminal A, which was more common in older age groups, the incidence of luminal B variant was noticeably greater in a younger age group. Clinically, even with concurrent therapy, luminal B tumors are linked to poor prognoses and aggressive behavior. Breast tumors classified as luminal B or luminal A were determined by ER and/or PR positivity as well as ki67 low (<14%).Estrogen Receptors or Progestrone receptors that are positive with ki67 high greater than fourteen percent or ER and/or PR positive and HER2 positive regardless of ki67 are considered luminal B(13). ERBB2 amplification causes HER2 overexpression in HER2-positive BC, which accounts for 15 percent of all BCs. This subset of malignancies has a worse prognosis and exhibits more aggressive behavior when left untreated. Nonetheless, the creation of several drugs that specifically target HER2 has changed the course of the disease's natural history and offered substantial therapeutic benefits in both early stage and advanced stage situations(14).

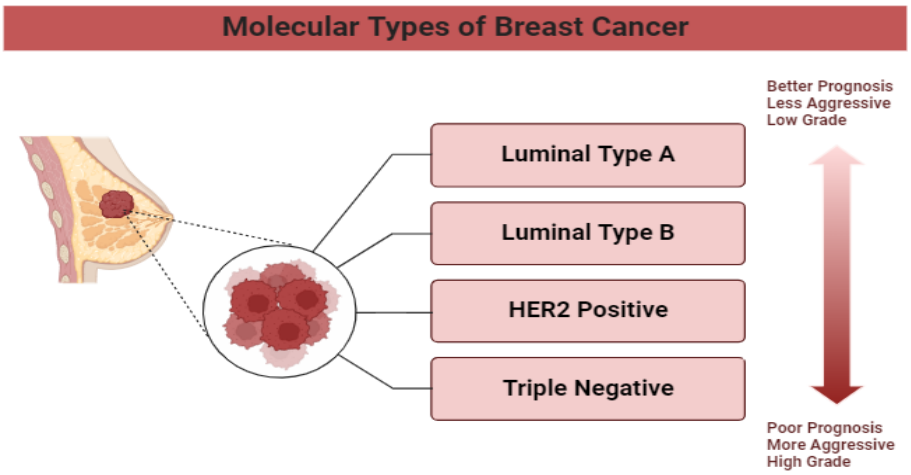

Figure 1 The Molecular Subtypes of Breast Cancer along with their Behavior, Rate of Prognosis and Grading. Triple Negative Breast Cancer has Poor Prognosis, Faster Rate of Proliferation and High Grading as Compared to Hormones Positive Breast Cancer.

Compared to the other BC subtypes, TNBC has a faster rate of proliferation, a higher frequency of brain, liver, and lung metastases(15) and a higher tendency to afflict younger individuals(16). Because of its aggression and the lack of targeted treatments, TNBC continues to be an unmet clinical challenge. Because of their transcriptional heterogeneity, TNBCs can be classified into subgroups that differ greatly in their biology and how they react to targeted and chemotherapeutic treatments. Six molecular TNBC subtypes were previously discovered, and they all showed distinct ontologies and varied responses to chemotherapy administered as part of conventional care. Six molecular TNBC subtypes were previously discovered, and they all showed distinct ontologies and varied responses to chemotherapy administered as part of conventional care. There are six subtypes of TNBC: mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), two basal-like (BL1 and BL2), and luminal androgen receptor (LAR). Increased expression of DNA damage response and cell cycle genes characterize the BL1 subtype, but myoepithelial markers and growth factor signaling are more abundant in the BL2 subtype. The genes that encode immune antigens, cytokines, and fundamental immunological signal transduction pathways make up the IM subtype, which most likely reflects the expression of genes from both infiltrating lymphocytes and tumor cells Genes related to growth factor and epithelial-mesenchymal-transition pathways are expressed more highly in M and MSL subtypes than in M, but genes related to proliferation are expressed less frequently in MSL subtypes. The androgen receptor (AR) is the primary driver of luminal gene expression, which is a characteristic of the LAR subtype(17).

Additionally, TNBC tumors found four stable groups with different prognoses utilizing copy number variations (CNVs) and proposed potential subtype-specific targets. Mesenchymal (MES), basal-like immune-activated (BLIA), basal-like immune-suppressed (BLIS), and LAR were the names given to these subtypes. In comparison to the other groups, BLIS displayed the lowest survival rate and BLIA the highest. Using the fuzzy clustering technique, transcriptome profiling was also used to identify three distinct TNBC subtypes (C1, C2, and C3).

TNBC tumors with a molecular apocrine phenotype that indicated a better prognosis were included in the C1 cluster, while C2 and C3 were enriched in basal-like characteristics. C3 described the adaptive immune response and immune checkpoint upregulation, while C2 demonstrated biological aggression and an immunological-suppressive phenotype(15, 17). Shao's group identified immunohistochemistry (IHC) biomarkers in 2020, including androgen receptor (AR), CD8, FOXC1, and DCLK1. IHC staining results show that TNBC can be classified into five subtypes: IHC-based

basal-like immunosuppression (IHC-BLIS; AR−CD8−FOXC1+), IHC Based IM (IHC-IM; AR−CD8+), immune factor-based mesenchymal (IHC-MES; AR−CD8−FOXC1−DCLK1+), IHC-based LAR (IHC-LAR; AR+), and IHC-based unclassifiable (AR−CD8−FOXC1−DCLK1−).

The IHC-IM subtype has an immunoinflammatory phenotype, which is defined by the infiltration of CD8+ T lymphocytes into the cancer parenchyma, while the IHC-LAR subtype shows the activation of the HER2 signaling pathway(18). Furthermore, vascular endothelial growth factor (VEGF) overexpression is a characteristic of the IHC-BLIS subgroup. The JAK/STAT3 (signal transducer and activator of transcription 3) signaling pathway is stimulated by the IHC-MES subtype. Additional information is provided for the prognostic evaluation of patients with TNBC using IHC-based subclassification. This facilitates the subtyping of TNBC patients in clinical trials and the assessment of targeted therapy efficacy for distinct subtypes, hence encouraging subtype-specific treatment of TNBC patients(19).

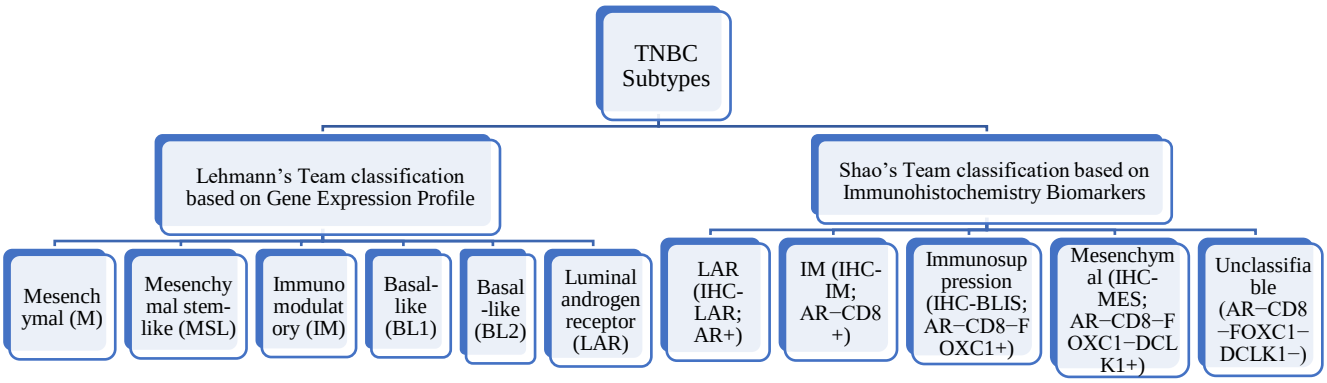

Figure 2 The Molecular Subtypes of TNBC Based on Gene Expression Profile and Immunohistochemistry Biomarkers

Novel approach to subtypes of breast cancer:

Luminal Breast Cancer:

Every breast cancer treatment guideline suggests analysis of the expression of the steroid hormone receptors (HR) for progesterone and estrogen. In luminal BC, HR expression is correlated with tumor grade; low-grade tumors have higher levels of ER and PR expression, while intermediate- and high-grade tumors may have lower ER and/or no PR expression. The presence of both receptors is required for the diagnosis and classification of breast cancer subtypes, and can be found using immunohistochemistry (IHC) procedures(20). Endocrine therapy, which functions by inhibiting the effects of hormones or lowering hormone levels, is the cornerstone of treatment for HR+ BC. The first medication on the market right now is tamoxifen, a prodrug that prevents the ER from absorbing estrogen; the second is an aromatase inhibitor (exemestane, letrozole and anastrozole), which inhibits the conversion of androgens to estrogens and causes estrogen depletion; the third is an analogue of luteinizing hormone-releasing hormone (leuprolide and goserelin), which inhibits the ovary's production of hormone and forth is fulvestrant, a selective degrader of estrogen receptors that is appropriate for BC patients who have not responded to prior hormonal therapy. Chemotherapy is

appropriate only when a speedy response is required or there is indication of clinical resistance. Until then, sequential administration of endocrine therapies is advised(21).

CDK4/6 Inhibitors:

Cancer is caused by unchecked cell division, which is brought on by a dysregulation of the cell cycle's four phases: M (mitosis), G2 (Gap phase 2), S (DNA synthesis), and G1 (Gap phase 1). Many pathways track the cell cycle, one of which is the retinoblastoma (RB)-E2F signaling pathway. Renowned tumor suppressor RB alternates between jobs in the cell cycle. The transcription factor family E2F, which has been conserved throughout evolution, regulates the cell cycle and has a role in the growth of tumors. Cell cycle entry depends on the CDKsRB axis.

When CDK4/6 and cyclin D work together, RB is phosphorylated and rendered inactive(22). It then releases E2F, which causes the G1-S block that follows, the induction of transcriptional activating agents, and altered transcription of genes involved in the cell cycle process. The three most important of these new waves are oral inhibitors called palbociclib, ribociclib, and abemaciclib. The FDA has approved the combination of palbociclib and ribociclib with an aromatase inhibitor as the initial therapy for HR+/HER2− aggressive breast cancer(23).

Inhibitors of histone deacetylases:

Epigenetic mechanisms play a role in carcinogenesis and cannot be solely attributed to genetic changes. A crucial aspect of the epigenetic control of the expression of genes is the alterations of histones by acetylation, which is governed by the equilibrium among histone deacetylases with histone acetyltransferases. HDAC inhibitors suppress angiogenesis, alter the immune system, and cause malignant cell cycle stop, differentiation, and cell death.

The curative properties of HDAC inhibitors have diverse mechanisms that vary depending on the kind of cancer, HDAC inhibitors used dosages, and other factors. HDAC inhibitors appear to be effective anti-cancer medications, especially when used in conjunction with radiation therapy or other anti-cancer medications. The three most commonly used HDAC inhibitors are belinostat, romidepsin, and vorinostat (24). When used in conjunction with exemestane and tamoxifen, respectively, as a second-line therapy for HR positive progressive breast cancer, entinostat and vorinostat had greater anticancer efficacy than exemestane or tamoxifen alone(25).

Inhibitor of PI3K/Akt/mTOR:

Lipid kinases called phosphatidylinositol-3 kinases (PI3Ks) phosphorylate the signaling lipid PIP2 to PIP3.In the PI3K/ Akt /mTOR signaling pathway, PIP3 molecules attract proteins with PIP3-binding pleckstrin homology (PH) domains, like Akt, to the plasma membrane. With a significant influence on about 50% of human tumors, the PI3K pathway is one of the most commonly activated pathways in cancer. PI3Kα, β, and δ class IA isoforms have a particularly strong correlation with cancer. The second and third most common mutations in cancer are activating mutations in the PIK3CA gene, which encodes the p110α catalytic subunit of PI3Kα, and suppressing mutations of the tumor suppressor PTEN (a lipid phosphatase that dephosphorylates PIP3, thus opposing PI3Kα action).

As a result, PI3Kα is an extremely important target for drug discovery(26). PI3K over-activation in immunological dysregulation and cancer has led to a great deal of work in the development of therapeutic PI3K inhibitors. The PI3Kα isoform-selective blocking alpelisib for the curative use of breast cancer and agents primarily targeted at the leukocyte enriched PI3Kδ in B cell carcinomas have both received regulatory approval, despite obstacles including poor drug tolerance and drug resistance impeding progress.

Emerging data emphasizes the possibility of PI3K inhibitors in cancer immunotherapy, in along with their ability to target intrinsic PI3K activity in cancer cells(22). Despite its enormous significance, the FDA just authorized the first medication for breast cancer in May 2019 (novartis' alelisib) (27).

Table 1 : Drugs for Hormone Receptors, Estrogen or Progesterone Receptor, with respect to mode of action, phase and combination therapy as administration with other drugs

Series Number	Drug	Therapy(mono/combination)	Mode of action	Population Targeted	Phase
For Hormone Positive Breast Cancer (ER+/PR+)					
01	Palbociclib (Ibrance)	Combine with Letrozole	Cyclin Dependent Inhibitor	Advanced Stage	Approved by US FDA
02	Palbociclib (Ibrance)	Combine with Fulvestrant	Cyclin Dependent Inhibitor	Advanced Stage	Phase 3
03	Ribociclib (Kisqali)	Combine with Letrozole	Cyclin Dependent Inhibitor	Advanced Stage	Approved by US FDA
04	Ribociclib (Kisqali)	Combine with Fulvestrant	Cyclin Dependent Inhibitor	Advanced Stage	Phase 3
05	Abemaciclib (LY2835219)	Combine with Letrozole	Cyclin Dependent Inhibitor	Advanced Stage	Phase 3
06	Abemaciclib (LY2835219)	Combine with Fulvestrant	Cyclin Dependent Inhibitor	Advanced Stage	Phase 3
07	Everolimus (Afintor)	Combine with exemestane	mTOR Inhibitor	Advanced Stage	Approved by US FDA
08	Voxtalisib (SAR245409)	Combine with letrozole	mTOR Inhibitor	Advanced Stage	Phase 1
09	Temsirolimus (Torisel)	Combine with letrozole	mTOR Inhibitor	Advanced Stage	Phase 3
10	Temsirolimus (Torisel)	Monotherapy	mTOR Inhibitor	Advanced Stage	Phase 2
11	Pictilisib (GDC-0941)	Combine with Fulvestrant	PI3K inhibitor	Advanced Stage	Phase 2
12	Buparlisb (BKM120)	Combine with Fulvestrant	PI3K inhibitor	Advanced Stage	Phase 3
13	Buparlisb (BKM120)	Combine with Letrozole	PI3K inhibitor	Advanced Stage	Phase 2
14	Pilaralisib (SAR245408)	Combine with Letrozole	PI3K inhibitor	Advanced Stage	Phase 1
15	Taselisib (GDC-0032	Combine with Fulvestrant	PI3K inhibitor	Advanced Stage	Phase 2
16	Alpeisib (BYL719)	Combine with Fulvestrant	PI3K inhibitor	Advanced Stage	Phase 3
17	Alpeisib (BYL719)	Combine with Letrozole	PI3K inhibitor	Advanced Stage	Phase 2

18	Entinostat	Combine with exemestane	Histone deacetylase (HDAC) inhibitor	Advanced Stage	Phase 3
19	Vorinostat	Combine with tamoxifen	Histone deacetylase (HDAC) inhibitor	Advanced Stage	Phase 2

HER2-positive breast cancer:

HER2-positive breast cancer was linked to worse outcomes and greater death rates than other subtypes of the disease for many years. Twenty percent of original invasive breast tumors are positive for the HER2 (human epidermal growth factor receptor 2) oncogene. It is commonly established that higher levels of disease relapse and fatality are linked to HER2 overexpression. Furthermore, there is an increased likelihood of brain metastases for breast tumors that are HER2+. Neoadjuvant HER2-based therapy is commonly utilized (as in other subtypes) in patients with an early stage of HER2+ illness who wish to preserve their breasts, have limited axillary nodes affected (N1), or have locally progressing breast cancer (Stage IIb with T3 illness, or Stage III).

Nonetheless, the therapy paradigm for patients with HER2-positive cancers of the breast has undergone a substantial shift since the introduction of trastuzumab (Herceptin). The arsenal of treatments for HER2-positive breast tumors has been significantly expanded by the development of more recent HER2-targeted medications such as pertuzumab (Perjeta). When it came to aggressive HER2+ invasive breast cancer, trastuzumab (Herceptin) was the first anti-HER2 focused medication to be approved in 1998. Small-molecule HER1 and HER2 tyrosine kinase inhibitors are inhibited by lapatinib(28). According to a different study, HER2 positive indicates whether subsequent chemotherapy with doxorubicin plus cyclophosphamide, the addition of paclitaxel following adjuvant chemotherapy, or both, will be beneficial. Doxorubicin doses of more than 60 milligrams per square meter did not show any advantage, although paclitaxel supplementation increased overall and survival without disease(29).

The FDA has approved two anti-HER2 ADCs, each with a different indication for treating HER2-positive breast cancer. In 2013, trastuzumab and a taxane were approved for metastatic patients. In 2019, the label was expanded to include adjuvant treatment of high-risk patients with residual disease following neoadjuvant taxane and trastuzumab-based therapy. Ado-trastuzumab emtansine (T-DM1) was the first-in-class HER2-targeting ADC. The second approved ADC for patients who have undergone at least two lines of anti-HER2-based therapy in a metastatic context was trastuzumab deruxtecan (T-DXd) in 2020. The development of ADCs has been revitalized, and the treatment of HER2-positive breast cancer has changed as a result of these two medicines' success(30).

Table 2: Drugs for Human Epidermal Growth Receptor, with respect to mode of action, phase and combination therapy as administration with other drugs

For HER2+ Breast Cancer					
Series Number	**Drug**	**Therapy(mono/combination)**	**Mode of action**	**Population Targeted**	**Phase**
01	Pilaralisib (SAR245408)	Combine with trastuzumab and paclitaxel	PI3K inhibitor	Advanced stage	Phase 2
02	Pilaralisib (SAR245408)	Combine with lapatinib	PI3K inhibitor	Advanced stage	Phase 1b
03	Buparlisb (BKM120)	Combine with trastuzumab and paclitaxel	PI3K inhibitor	Advanced stage	Phase ½

04	MK-2206	Combine with trastuzumab	PI3K inhibitor	Advanced stage	Phase 1
05	Sirolimus	Combine with trastuzumab	mTOR Inhibitor	Advanced stage	Phase 3
06	Ridaforolimus (MK-8669)	Combine with trastuzumab	mTOR Inhibitor	Advanced stage	Phase 2b
07	Everolimus (Afintor)	Combine with trastuzumab and vinorelbine	mTOR Inhibitor	Advanced stage	Phase 3
08	Neratinib (HKI-272	Monotherapy	Irreversible binder of HER	Early Stage	Phase 3
09	Lonafarnib (SCH66336)	Combine with trastuzumab and paclitaxel	Farnesyl transferase Blockers	Advanced stage	Phase 1
10	Patritumab (AMG 888, U3-1287	Combine with trastuzumab and paclitaxel	Monoclonal antibody	Advanced stage	Phase 1b
11	Margetuximab (MGAH22)	Monotherapy	Monoclonal antibody	Advanced stage	Phase 1
12	Nelipepimut-S (E75)	Combine with trastuzumab	Vaccine (Peptide)	Early Stage	Phase 2
13	Recombinant HER2 protein (dHER2)	Combine with lapatinib	Vaccine (Peptide)	Advanced stage	Phase 1
14	Recombinant HER2 protein (dHER2)	Monotherapy	Vaccine (Peptide)	Early Stage	Phase 1
15	Recombinant HER2 protein (dHER2)	Monotherapy	Vaccine (Peptide)	Advanced stage	Phase ½
16	Ado-trastuzumab emtansine (T-DM1)	Trastuzumab linked to mertansine	ADC-Based	Advanced stage	FDA approved
17	Trastuzumab deruxtecan (T-DXd)	Trastuzumab linked to deruxtecan	ADC-Based	Advanced stage	FDA approved

Triple Negative Breast Cancer:

Fifteen to twenty percent of all breast cancers are triple negative (TNBC), meaning they do not express the progesterone or estrogen receptors, nor do they have human epidermal growth factor receptor 2 (HER2) amplification or overexpression. Because there is no specific targeted treatment and a strong propensity for metastatic progression, these tumors have a more aggressive character and a worse prognosis(31). Based on their gene expression profiles, TNBCs can be divided into 6 different subtypes. The subtypes that have been found are luminal androgen receptor (LAR), mesenchymal (M), immunomodulatory (IM), mesenchymal stem-like (MSL) and basal-like 1 and 2 (BL1 and BL2). Their prognosis and key biological mechanisms are different. For instance, BL1 and BL2 exhibited increased expression of genes linked to the cell cycle and damage to DNA response in addition to their high proliferative capacity. The epithelial-to-mesenchymal transition (EMT) pathway genes were more abundant in the M and MSL groups, while immune cell signaling characteristics were more

prevalent in the IM subtype. The LAR cell lines were responsive to the AR antagonist bicalutamide, and the LAR subtype was ER-negative but AR-positive(32).

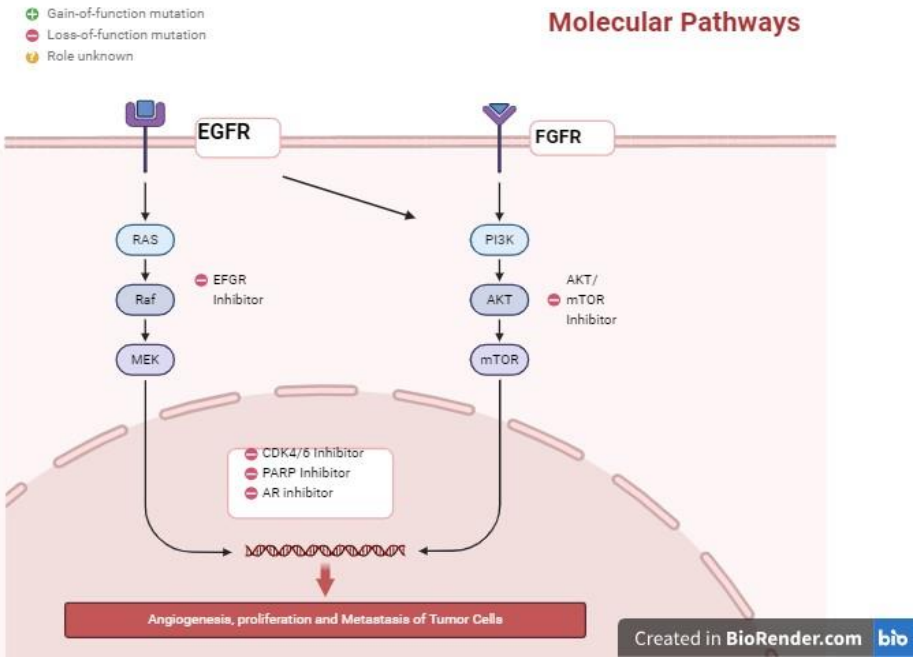

Figure 3: Molecular Pathways involve in Breast Cancer Mechanism

PARP Inhibitors:

Poly ADP Ribose Polymerase Inhibitors (PARPi) are a class of targeted therapeutic medicines newly licensed by the FDA for use in ten to fifteen percent of TNBC patients with genetic mutations in BRCA1 or BRCA2. In two separate phase 3 randomized controlled investigations, the effectiveness of two PARP inhibitor, olaparib and talazoparib, as single agents were shown in patients with metastatic HER2-negative BRCA1/2 mutations who had gone through a maximum of three sessions of chemotherapy. Comparing the PARP inhibitor to the doctor's recommended single-agent chemotherapy, these trials showed similar outcomes, with the PARP inhibitor linked to a reduction in progression-free survival of roughly 3 months and a measurable response rate close to sixty percent(33). Twenty-six patients with breast cancer who had received extensive pretreatment with a maximum of seven sessions of chemotherapy were assessed for olaparib, and neither BRCA-mutant nor BRCA wild type patients showed any objective response. Veliparib was examined in conjunction with four treatments; regardless of the presence of a BRCA mutation, there was no further advantage of this PARP inhibitor responsiveness to olaparib in several breast cancer cell lines. It has also been discovered that BRCA wild-type tumors are responsive to olaparib and talazoparib in vivo in two different cohorts of xenografts produced from breast cancer patients(34).

AR Inhibitors:

In breast cancer, the androgen receptor (AR) has gained attention as a possible treatment approach. Up to 50% of TNBCs and over eighty percent of all types of breast cancer excessively express AR. By controlling the cell cycle, AR activation also enhances the survival of cells. The removal of androgen causes the G1 phase to stop. For more than ten years, anti-androgens have been extensively studied about breast cancer. Bicalutamide is one of the first-generation anti-androgens that works as an antagonist to stop AR transcriptional function. In comparison to first-generation anti-androgens, enzalutamide, a second-generation anti-androgen, exhibits minimal partial agonist effect since it is a competitive inhibitor that prevents AR from being nuclear localized. Both of these AR antagonists have demonstrated positive clinical results in TNBC and are well-tolerated by patients, with certain patient subgroups exhibiting long-term stable illness(35).

EGFR Pathway Blockers:

Nearly fifty percent of TNBC cases have overexpressed EGFR, and this overexpression is associated with a bad prognosis. Tyrosine kinase receptor EGFR plays an important role in the proliferation as well as survival of cells. It is a member of the membrane-anchored receptor tyrosine kinase ERBB/HER family. When cancer cells have uncontrolled activation of EGFR due to point mutations, protein overproduction, or gene copy number amplification, the outcome is uncontrolled proliferation, spreading, metastasis, and resistance to apoptosis. A poor prognosis and decreased estrogen response are associated with EGFR overexpression(36). Afatinib, a second-generation treatment, effectively inhibits the kinase function of EGFR and its erlotinib-resistant variants. In a xenograft model of acquired cetuximab resistance, afatinib can also reverse the resistance to cetuximab, a monoclonal antibody targeting EGFR. In vitro and in clinical trials, afatinib demonstrated strong anti-tumor activity in HER2-positive breast cancer. Furthermore, afatinib has shown antiproliferative efficacy in vitro in the TNBC cell line SUM-149. Additionally, after receiving afatinib therapy for at least 110 days, three patients in a clinical trial comprising 29 TNBC patients demonstrated stable illness. Afatinib may therefore be a cutting-edge therapeutic approach for TNBC patients. Moreover, Dasatinib and afatinib may have therapeutic benefit in TNBC(37).

Table 3: Drugs for Triple Negative Breast Cancer, with respect to mode of action, phase and combination therapy as administration with another drug.

For Triple Negative Breast Cancer					
Series Number	**Drug**	**Therapy(mono/combination)**	**Mode of action**	**Population Targeted**	**Phase**
01	Talazoparib (BMN 673	Monotherapy	PARP inhibitor	Advanced stage	Phase 3
02	Olaparib (Lynparza)	Monotherapy	PARP inhibitor	Advanced stage	Phase 3
03	Rucaparib (Rubraca)	Monotherapy	PARP inhibitor	Advanced stage	Phase 2
04	Rucaparib (Rubraca)	Combine with cisplatin	PARP inhibitor	Advanced stage	Phase 2
05	Niraparib (Zejula)	Monotherapy	PARP inhibitor	Advanced stage	Phase 3
06	Niraparib (Zejula)	Combine with pembrolizumab	PARP inhibitor	Advanced stage	Phase ½
07	Veliparib (ABT-888)	Combine with carboplatin and paclitaxel	PARP inhibitor	Advanced stage	Phase 3
08	Pembrolizumab (Keytruda)	Monotherapy	monoclonal antibody	Advanced stage	Phase 2
09	Bicalutamide (Casodex)	Monotherapy	Androgen-receptor inhibitor	Advanced stage	Phase 2
10	Enzalutamide (Xtandi)	Monotherapy	Androgen-receptor inhibitor	Advanced stage	Phase 2
11	Glembatumumab vedotin	Monotherapy	ADC	Advanced stage	Phase 2
12	Gilotrif (Afatinib)	Monotherapy	EGFR Inhibitor	Advanced stage	Phase 2
13	Gilotrif (Afatinib)	Combine with Dasatinib	EGFR Inhibitor	Advanced stage	Phase 2

Advanced Strategies in Drug Development:

One of the leading causes of suffering and death for women is breast cancer. Due to shortcomings in the present therapeutic and diagnostic methodologies, new approaches have been developed to improve the standard of life and prognosis rates for patients with breast cancer. Nanotechnology presents a genuine chance to reduce the death rate from breast cancer through earlier detection of the disease, more accurate assessment, and more potent therapies with fewer adverse effects. The authorized nanoplatforms for breast cancer therapies currently in use depend on passive tumor targeting with organic nanoparticles, and they have not produced the anticipated significant developments in clinical practice(38).

To maximize the amount of active medication delivered to the tumor while minimizing adverse effects, the nano drug exhibits the highest selectivity towards cancer cells. created and later approved by the FDA, a 130 nm-sized Nano formulated albumin-bound paclitaxel (Nab-paclitaxel, Abraxane) is currently being used in clinical practice for a variety of solid tumors, including MBC. Following the procedure, albumin-mediated increased active transport helps Nab-paclitaxel particles aggregate inside the tumor(39). To maximize the amount of active medication delivered to the tumor while minimizing adverse effects, the nano drug exhibits the highest selectivity towards cancer cells.

created and later approved by the FDA, a 130 nm-sized Nano formulated albumin-bound paclitaxel (Nab-paclitaxel, Abraxane) is currently being used in clinical practice for a variety of solid tumors, including MBC. Following the procedure, albumin-mediated increased active transport helps Nab-paclitaxel particles aggregate inside the tumor(40). Since only Y2 receptors are overexpressed in healthy breast tissue, the neuropeptide Y1 receptor has been identified as an unusual target for breast cancer cells. To effectively deliver the nano drug to breast cancer cells, albumin nanoparticles modified with PNBL-NPY, a ligand of Y1 receptors, and loaded with doxorubicin have been employed. The administration and release of doxorubicin in HER2-positive cancer cells has been extensively studied using HER2-targeted nanocarriers, which exhibit superior anticancer activity than nontargeted nanoparticles(41).

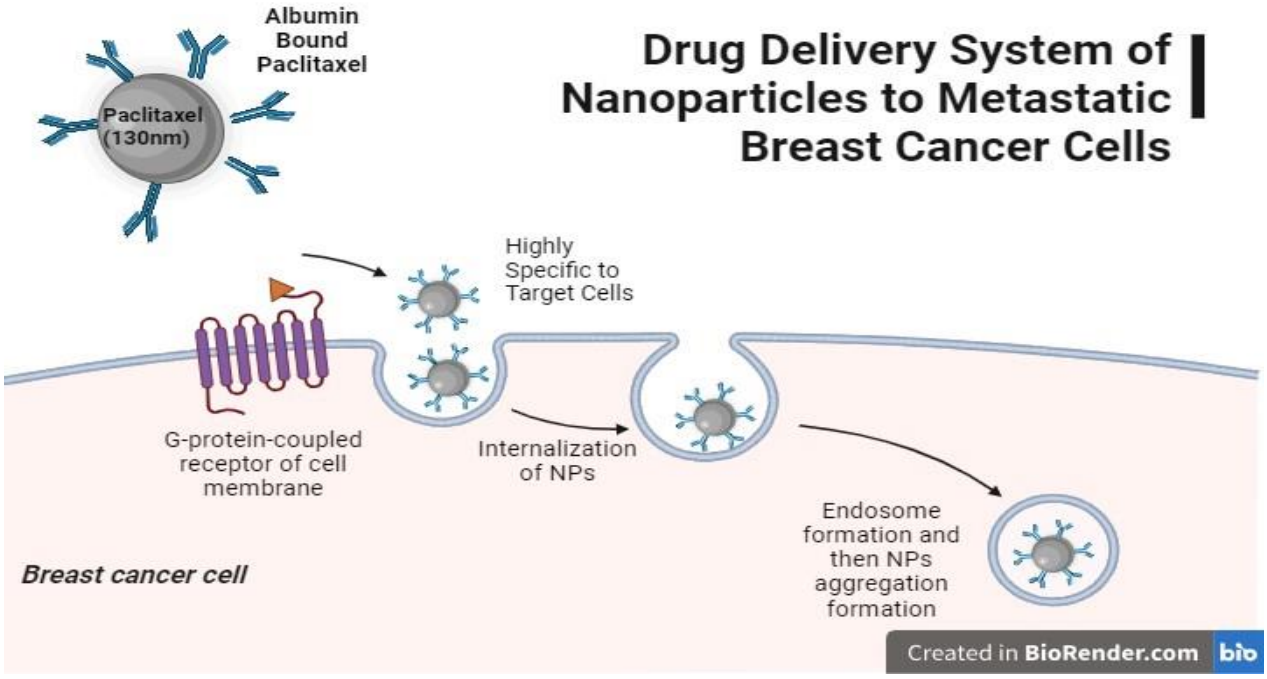

Figure 4: Mechanism of NPs Drug Delivery to Cancer Cells

Table 4: Nano DDS (Drug Delivery System) in Breast Cancer

Series Number	Nano Particle	Size	Target	Toxicity
01	Metal nanoparticles	185nm	HER2 Receptor	Not Found
02	Composite nanoparticles	67nm	HER2 Receptor	Toxicity Found
03	Composite nanoparticles	112-165nm	Transferrin Receptors	Not Found
04	Silicon nanoparticles	175nm	CD105	Not Found
05	Albumin Bound Paclitaxel (Abraxane)	130nm	Metastatic Breast Cancer, P32	Found Grade3-4
06	Liposomes Bound (Doxorubicin)	180nm	Estrogen Receptor	Found

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