Original Article

# Combination Therapy Strategies and Advanced Biomarkers Can Potentially Enhance The Precision-Medicine Treatment of Metastatic Breast Cancer

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## Abstract

**Background:** Breast cancer treatment often involves a combination of different therapeutic techniques to effectively target the disease and overcome resistance mechanisms. This multimodal approach enhances the potency and efficacy of the treatment. **Methods:** The multimodality therapy for breast cancer includes the integration of chemotherapy, targeted therapy, hormone therapy, and immunotherapy. This comprehensive strategy blocks various pathways concurrently, thus circumventing mechanisms responsible for resistance. Chemotherapy combined with targeted medicine, which impedes biochemical processes crucial for cancer progression, is highlighted as a potentially superior approach. **Results:** Oncologists are increasingly employing novel biomarkers to identify specific molecular differences responsible for cancer development. Medications such as PARP inhibitors for breast cancers with BRCA mutations and HER2-targeted therapies for HER2-positive tumors have shown effectiveness. Emerging biomarkers, including circulating tumor DNA (ctDNA) and gene expression profiles, provide real-time insights into tumor status and treatment efficacy. **Conclusion:** The use of multimodality therapy in breast cancer, which leverages various treatment techniques and novel biomarkers, holds promise for more effective and personalized treatment strategies. The incorporation of emerging biomarkers in treatment decision-making processes can significantly improve outcomes by providing current information on tumor characteristics and response to therapy.

**Keywords:** MBC, BRCA, TNBC, Circulating Tumor DNA.

## Introduction

Cancer is a severe disease which has the nature of the orderless growth and division of cells, at the end there are extremely aggressive cell clusters or malignant tumors. The effect is responsible for deaths of millions of people when uncounted. Cancer is a complicated and heterogeneous illness classified by multiple genetic and molecular changes that lead to an uncontrollable propagation of cells in massive quantities. Consequently, harmful tissues develop in the affected parts of the body. Normally, aline cell would receive a command to undergo a programmed cell death and be replaced with a younger and near-normal cell inside of the organism. Cancer cells proliferate in a way that the body's oxygen is used at a rapid pace interrupting the supply of oxygen and nutrients to the normal physiological mechanisms of the cell. These cells can adapt the environment, prepare it and use some other cells functions including the immune system to meet their own requirement. At the moment breast cancer is the leading cancer disease among women in the world in which women are 80 to 113 times likely to get a case per 100,000 women compared to males. The year of 2012 witnessed breast cancer newly diagnosed to the count of 1,608,000 people with breast cancer and around the half of that small group, which unfortunately died of the disease. Meaningful the number of people who have died has constantly dropped in the last years of preceeding decades, but the amount of people who have faced the natural disaster has somewhat increased. There is a growing demand for personalized medicine which involves improving the treatment methods to match the patientâ€™s individual needs and requirements since it

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has been seen to be successful in helping specific cancer patients. The accuracy of medicine brings up different views and declarations based on who is interpreting them. When "personalized medicine" started being mentioned soon in 1995, the term has prevailed in the medical world for years, but lately, the concept of "precision medicine" has been used widely. Precision medicine is a rapidly evolving field with the potential to revolutionize healthcare systems and have a growing impact on patient care.[1]

Discovery of oestrogen receptor (ER) and breast cancer markers such as human epidermal growth factor receptor 2 (HER2) has opened new avenues of targeted treatments. With positive treatment outcomes for patients with ER or HER2 positive or negative strata, the road to precision medicine has become a reality. In addition, the advancement of research of cancer on a genomic scale in several years has strengthened the idea of cancer being a group of diseases that arise as a result of a vast variety of genetic mutations. The genomics of early stage breast cancer have been revealed by subjecting the cells to next-generation sequencing since many projects such as The Cancer Genome Atlas(TCGA) and the International Cancer Genome Consortium(ICGC) have been conducted worldwide. These studies confirmed significant heterogeneity occurring inside a breast tumor where specific molecular changes are the reason of the development of various molecular subtypes. This means, cancers are very unique per each individual and lead to different characteristics and unique characteristics in their molecular level, what tumors have or tumors do. The fact that individualized treatment involves much promise, but only the targeting of ER and HER2 is at the level of molecular changes that have been proven already to have prognostic and predictive significance is known. Of all the targeted drugs on the market, the only ones that have successfully identified predictive biomarkers are drugs like PARP inhibitors, c-MET tyrosine kinase inhibitors, and RAF dimer inhibitors. The most effective drugs in specific subpopulations have not yet discovered any predictive biomarkers, including drugs such as mTOR and CDK4/6 inhibitors.[1,2]

The actionable mutations, unique to breast cancer, have been discovered that makes breast cancer susceptible to pharmacological treatments. A guideline tool called ESCAT (ESMO scale for clinical actionability of molecular targets) is relied on clinicians to select treatment and embrace precision medicine as a part of therapeutic regimen. ESCAT clusters molecules that are targeted in several cancer types and are candidates for clinical translation into six different categories according to their ability to alter the clinical practice in a certain type of cancer. This encourages doctors to be confident in their therapy treatments. To discover the molecule targets associated with the breast cancer, the principle of high potential in ESCAT is followed (Figure 1 and Figure 2).

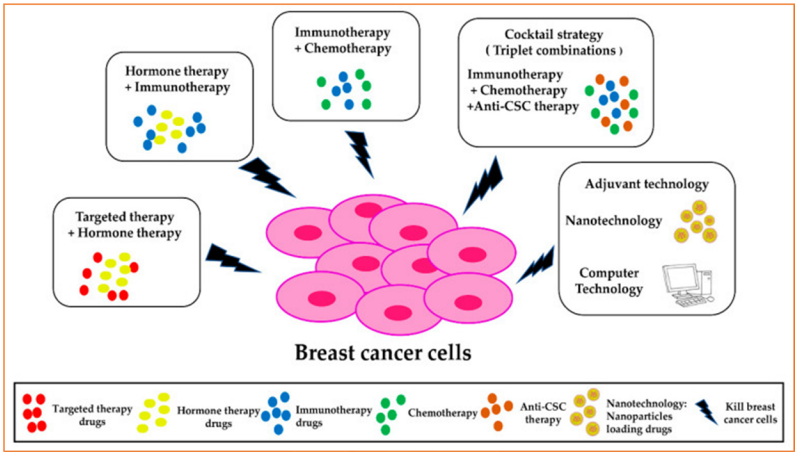


**Figure 1:** Showing Various Therapeutic Routes Used Currently In Treatment of Breast Cancer. Specific Modalities of Therapy Have Been Implemented Based Upon The Cancer Subtype and the Stage of the Disease in Previous Reported Cases. Here in Recent Few Years There Has Been A Choice of Different Types of Therapy Methods Used.[3]

The St. Gallen Consensus categorizes breast cancer into four clinically significant subtypes: A (Table 1, 2) lists the following as subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, and TNBC. The main grouping is generally based on IHC markers – the most common are just genetic – ER, PR, ERBB2/HER2, and Ki-67. These aims, which have been demonstrated as high lean muscular mass in treatment situations, are tangible and in accordance with the subtypes. They still versatile resource in the procedure of taking or deciding on the various treatment options available. Although, with the development of the whole-genome sequencing, single-cell analysis, and proteomics, novel targets that are capable of providing more specific decision making or better outcomes were revealed (Figure 3).[4]

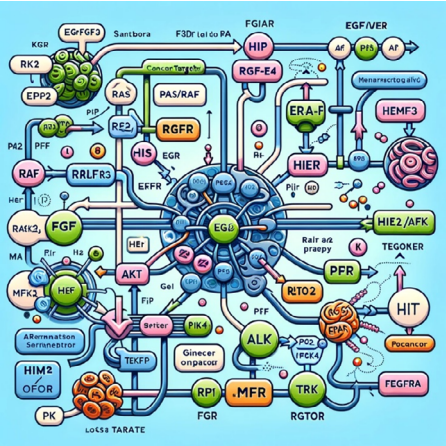


**Figure 2:** Genetic Modifications That are Responsible For the Advancement of Precision Oncology.

**Table 1: ESCAT Ranking of Molecular Alterations in A Specific Cancer Type.**

| Tier IV | ARID1A/B CDH1 Igf1R |
|---|---|
| Tier III b | HRD non BRCA1/2<br>ERBB3 |
| Tier III a | TMB<br>BRAF |
| Tier II b | ERBB2 mut |
| Tier II a | ESR1<br>PTEN |
| Tier I c | MSI<br>NTRK |
| Tier I a | PIK3CA<br>ERBB2 amp<br>gBRAC1/2 |

**Table 2: Sub-type Classification of Breast Cancer According to St. Gallen Consensus.**

| Subtype | ER | PR | Ki-67 | ERBB2/HER2 |
|---|---|---|---|---|
| Triple negative | negative | negative | High | Negative |
| HER2-enriched | +/- | +/- | Both | Overexpressed |
| Luminal B | positive | positive | > 15% (high) | Negative |
| Luminal A | positive | positive | < 15% (low) | Negative |

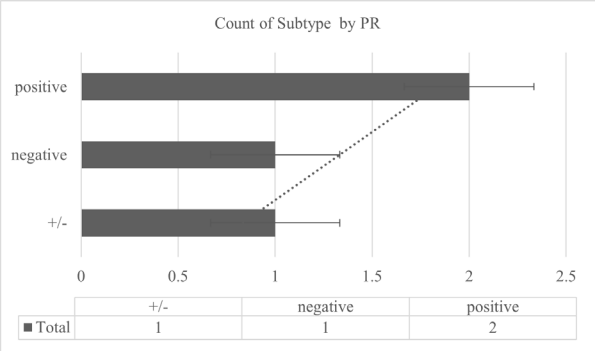


**Figure 3:** Sub-type Classification of Breast Cancer According to St. Gallen Consensus

Normally, the systemic treatment with a neoadjuvant targeted agent is prescribed prior to surgery for HER2-positive and TNBC disease. The chronic ingestion of immune checkpoint inhibitors along with standard chemotherapy seems to correlate with a higher proportion of pathological complete response (pCR) observed in patients with TNBC. Concurrent administration of trastuzumab and pertuzumab with chemotherapy in HER2-positive cancer cases caused a higher incidence od pCR (pathological complete response) and it provided a better event-free survival. Addition of trastuzumab emtansine to the treatment cluster is an adjuvant of individuals with HER2-positive tumors who have not completely response (pCR) after the initial surgery. Approximately 25% of the patients with cancer, luminal A/B, go through chemotherapy after primary operation. Such genetic markers, as Oncotype DXR, MammaPrintR, EndoPredictR, Predictor of Microarray 50 (PAM50), and other similar tests allow to differentiate those cancers that may provide an extra benefit from additional intervention. For the time being, the regimens based on anthracycline and taxanes are the main ones used.

A recent meta-analysis has shown breast cancer expressing androgen receptor, progesterone receptor and human epidermal growth factor receptor 2 in the whole range of the expression levels according to 4000 human samples analyzed. The variance between the samples which are from +++ to -+++ and the sample which comes from ++ - was 24% and 14% ($p=0.0183$) for ER, %46 and 15% ($p<0.0001$) for PR, and 13% and 5% ($p=0.0004$) for HER2. Breast cancer altering expression profile tends to have substantial implications on the therapy selection; and therefore, it is highly recommended to do a biopsy from metastatic location may be practiced in the situations of metastatic recurrent breast cancer.

Moreover, a part of deaths of cancer could be caused by adverse effects of treatment utilization. Notice the use of “might” and “could” to indicate uncertainty, and the substitution of “consequences” with “effects” for better readability. The study conducted in United Kingdom confirms that the mortality rate of 2%- 3% was incurred 30 days after the patients had the comprehensive treatment for breast cancer. For example, studies for a population demonstrated that for those who undergo radiation on the 30 days of differing kinds of cancer the death rate equals 12.3%. In the same token, the massive budget allocated on this drugs mostly filled with the use of expensive treatment is also one the disadvantage economically. Due to this detail in mind, it is of utmost priority to start to develop other alternative methods which will improve the efficiency of cancer treatment.[5]

The microarray was invented by means of chip technology, which is why this tool helped the initial gene expression profiling that later developed into genome-wide association studies of millions of single nucleotide polymorphisms (SNPs). Nevertheless, for the most part NGS, which was used as a high-throughput method of next-generation sequencing (NGS) of genomic DNA and cDNA derived from RNA, was employed later.3 Eventually, these technology-driven developments have created reliable

base where genomic medicine has been established. Precision medicine, as defined by NIH, is a developing method of customizing treatment and prevention of disease, making use of known individual differences in genes, environment, and lifestyle, for which genomic medicine offers significant contribution. Therefore, such people are archived in special clusters of vulnerable ones that relate to a particular plan or protocol of treatment.

## Progress and Challenges of Precision-Medicine Therapy of Breast Cancer

The words, 'Precision', 'Customized', 'Stratified', and 'Individualized' Medicine are closely connected and used by different disciplines. On the one hand, it has to be mentioned that at present there is no consensus between different disciplines on the essence of these sets of terms. In essence, precision medicine is a comprehensive term that incorporates the use of genetic analysis, biomarker utilization as well as algorithms that are used for varied objectives which include but are not limited to illness risk as well as treatment evaluation, mapping screenings, forecasting prognosis, diagnosis and treatment selection, and surveillance or monitoring. Precision medicine is generally speared of mechanisms such as pharmacogenomics that in conjunction give more accurate results related to specific individual traits (Table3). Through this application of precision medicine it can be possible to be able to figure out the reliable biomarkers which can help in predicting the response of the customized medication in the group of the specific patients. Past the last 10 years a lot of observations were made by the experts in oncological therapies that are now in favor of the use targeted therapies.[4]

There are two primary methods for implementing personalized medicine in the treatment of advanced-stage breast cancer.

**Table 3: Development of MBC Precision Medicine.**

| | A Stratified Medicine Approach | A Personalized Medicine Approach |
|---|---|---|
| **Goal** | Pharmaceutical substances are assessed in every genetic region.<br>In order to identify the particular molecular change in a tumor tissue (that was removed before screening) during a screening session, certain methods are employed. This drug is only administered to the tumors that have too mutations that the same gene is usually targeting. The abnormal change in the structure of molecules could uncover potential side effects, which in turn could enable the correction of further aberrations that could be used to guide more targeted medicines to be introduced. As such molecular screening that uses high-throughput methods to simultaneously register several molecular changes may also be employed, and they should receive much more attention. | The methodology for assigning therapy is assessed in the whole population.<br>Here a medicine is tested to prove in a group of patients sharing a common genetic alteration how effective it is. Through this approach, we can determine whether tailoring patient therapy with DNA sequencing methods such as high throughput genomic medicine leads to better outcomes than treating everyone the same way. |
| **Limitation** | The prevalence of these genetic abnormalities is characterized by a low frequency. | In order to establish the standard arm, it is necessary to consider targeted treatment without selection or the standard of care. |

Information technology employments in breast cancer research are stratified medecine today, but long term their liquidity cannot be guaranteed. As technology is becoming more developed and biological breakthroughs are made in the oncoming future, it is inevitable that more unusual genetic variations will be discovered. This will continue to represent a major obstacle to investigator recruitment and thus stratified trials will become extremely complex for clinical trials. In addition, personalized cancer treatment or granularized treatment could be a lieu compared to categorized drugs or stratified treatment.

The hormone therapies in the endocrine treatment target estrogen and progesterone receptors. Therefore, these endocrine treatments are appropriate in dealing with the receptor positive HER2-neu breast cancers. In addition, given that both drugs have shown tremendous improvements in the outcomes of breast cancer treatment, apart from being widely used to target hormonal receptors on the breast cancer cells, they are famously referred to as 'targeted drugs' or 'targeted cancer drugs'. To increase the intensity of cytotoxic cancer treatment delivered safely, there are one of the strategies which are reducing the intervals between chemotherapy cycles or giving medicines in steps at optimum doses. With dosage-intesive approach coming to the fore, especially in the treatment of very high-risk cancers, this is crucial, for instance, in patients having high-grade, extensive lymph nodes or harboring a rapid cell division. These methods such as medication treatments have even improved patients' oncological outcomes. In the last twenty years, there were two gene panel: Oncotype DX and MammaPrint and were successfully applied among the early breast cancer patients with positive oestrogen-receptor and negative HER2 in breast cancer patients, and it is proven beneficial for them. This remained unproven in carefully planned, randomized studies, implicitly it helped in predicting the risk of metastatic recurrence and response to adjuvant therapy.

## Accommodate Precision Targeting of Multiple Biomarkers/Pathways

Targeted therapies tailored to the specific characteristics of the disease becomes a promising approach and the possibility to treat multiple indications using a single therapy is gaining momentum. Medicine of this kind utilizes DNA, RNA, and synthetic peptides as its basis and may, in the end, substitute drugs or the ones used in their combinations. Additionally, the technologies used on these therapies will become more sophisticated and use them help to quantify the state of the disease in a very specific and personalized way to the point of developing and optimizing a truly personalized treatment for the patient. HTA authorities will have to adapt to the new circumstances by developing more flexible procedures for decision-making. The multitarget treatments can be beyond doubt become more effective by different means and result in complete elimination or at least reduction of diseases. The chance of altering several different entities at once has some uncertainty on the effectiveness of precision medicine, which carry alongside some points that need to be addressed Yes, those treatments are still under development, though these are, in fact, the best factors for further research in order to foresee the expected evaluation parameters related to them. It is required to involve critical components from current general frameworks and other frameworks applicable to the particular precisions, or, in the case of diagnostic tests, in the decision-making frameworks that will be created to tackle precision medicine. The value evaluation framework should go the extra mile to educate the people about the the potential negative impacts of using different tools in reaching the aim precision of precision medicine and the issue of opportunity cost. An essential feature of value-based framework is incorporating the opinions of key stakeholders like drugmakers, payers, patients, providers and the entire beneficial medicine mechanism. The member of HER (HER2) family is over expressed in 20% of all the cases of breast cancer. Monoclonal antibodies directed at HER2 and other molecular targets that were previously out-of-range for therapy tremendously improved the prognosis for patients in this group. Multiple new monoclonal antibodies in the form of HER2-directed been developed. Through the HER2 in monoclonal antibodies leads to the identification of some candidates with antagonistic activity. However, the secondary and tertiary antibodies possess the higher level of specificity concerning HER2 receptor than trastuzumab. This is where some of these antibodies can be shown to bind not only to one of the epitopes, but to other epitopes as well, which can even increase the effectiveness of the immune response. Margetuximab (MGA) is a chimeric human-mouse monoclonal antibody, engineered through targeted modification of trastuzumab (TDM-1), an existing FDA-approved drug, which specifically targets the HER2 receptor. It keeps an Fc domain. Create your own unique essay by following these simple steps: 1. Prepare a list of topic ideas that interest you. 2. Select the most engaging subject for your paper topic. 3. Write an outline describing the structure and key points of your essay. 4. research and gather information related to your chosen topic. 5. Incorporate supportive details and real-life Cue to this sort of mechanism cancer cells are killed by CD 16a antibody-dependent cellular cytotoxicity which showed a modest but significant efficacy in the termination of HER2-positive metastatic breast cancer progression in the SOPHIA trial.

## Triple-negative Breast Cancer (TNBC)

Triple-negative breast cancer (TNBC) is a specific form of breast cancer characterized by the absence of three receptors often present in other kinds of breast cancer: ER, PR, and HER2 as these are the main ones that takes part in breast cancer. A reason for this could be due to the fact that TNBC cells lack these receptors, which in turn makes conventional therapies such as hormone therapy and medications that target HER2 ineffective. This results in the difficulty encountering TNBC rather than other types of breast cancer due to treatment. Unlike other kinds of breast cancer, TNBC (Triple-negative breast cancer) is more aggressive and has a worse outcome. It is linked to poorer survival rates. On the presence of that, however, emerging therapies come to the light as the investigations in the area of science shows satisfaction in the development of highly precise treatments and immunotherapies that may work in a contingent manner (TNBC) in the human body. For triple-negative breast cancer (TNBC) the standard treatment is multimodal and may consist of a combination of surgical removal, chemotherapy and radiotherapy. The development of the clinical studies now has been amended to encompass newly affecting treatment approaches, alongside immunotherapy and targeted drugs that operate one specific biological pathway.

TNBC is a very aggressive and diverse medical condition that is poorly understood. TNBC is the subtype of breast cancer which comprises 11-20% of all the breast cancers and in most cases affects premenopausal women, particularly young and women of color (mostly Negro Americans). TNBC is associated with the highest rate of annual deaths and metastasis in the five-year period after diagnosis among patients with all types of breast cancer. The present reality draws a line between the narrow selection of uniquely-targeted TNBC drugs and others. Though chemotherapy is the principal therapeutic option, immunotherapy has eventually provided a considerable counterpart by setting its way. Strict adherence to perfection in therapy by incorporating epidemiologic and maybe immunological characteristics would be a great step. In the context of TNBC, comorbidities are of great importance, as they affect the risk and the outcome, particularly through their influence on tumor biology.[6] It has been reported that obesity is more likely to be associated with triple-negative breast cancer, this cancer is also more aggressive and more difficult

to treat is more difficult to treat. It is suggested that obesity manifests in the development of MMe-phenotype macrophages in conjunction with the key obesity-associated biological characteristics of TNBC. M2-type macrophage is commonly found in the adipose tissue of humans and animals during obesity. Tumorigenicity of these cells is mainly attributed to aberrant increases of IL6 having a dependency on the presence of arginase-1 (ARG-1), NOX2. IL-6 (Interleukin-6) is proved to trigger a consequent activations of glycoprotein-130, which in return can stimulate characteristics of stem-like cells in TNBC. Another research suggested that obesity involved appointment of an inflammatory pathway with the release of reactive oxygen species, which, in turn, triggered a specific form of a gene control protein MBD22. This upregulation, to the extent it occurs, leads to acquisition of the stem cell-like attributes of TNBC. 4 Obesity gives rise to the bloom of additional adipose tissue then consequently leptin hormone levels are elevated. This hormone promotes the activation of genes associated with stem cell-like characteristics and the transformation of cells from epithelial to mesenchymal. Another hypothesis is that hyperinsulinemia, which is caused by insulin resistance, enhances the activation of the AKT/mTOR pathway. This, in turn, stimulates the growth and survival of triple-negative breast cancer (TNBC) cells. In addition, the AKT/mTOR pathway enhances glucose absorption and facilitates the Warburg effect, a metabolic change from aerobic oxidation in the mitochondria to anaerobic glycolysis. This metabolic alteration enables fast cellular growth and resistance to programmed cell death.FourWhen developing targeted therapeutics for TNBC, it is crucial to take into account the interplay between adipose tissue, metabolism, and tumor biology.[5]

## Current Status of Precision-Medicine Therapy for TNBC

In 2020, statistics show that more than 2.3 million new cases of breast cancer in women were diagnosed, which makes more than 87 percent of the total cases of freshly diagnosed cancers. TNBC is the second common kind of breast cancer which is resulted in about 10% to 20% of the patients around the world. TNBC is a kind of vernenous cancer that is, fails the receptor affinity test of hormones (estrogen or progesterone) and also of human epidermal growth factor receptor 2 (HER2). Both of the hydrocarbons compel the therapeutic drugs into their specific. The result is that TBNC fails to have a response to hormone therapy anymore, or to the HER2-targeted therapy either. Therefore, besides these cost EU governments should focus available resources on investments on new medical technologies and an active promotion of physical activities and a healthy lifestyle.[7,8]

The key downstream signaling events in the TNBC signaling axis are driven by RTKs through two major pathways, including RAS/MAPK and PI3K/AKT/mTOR. RTKs in the acini of TNBC cells generally set signals in motion following their activation by EGFR, PDEGFR, VEGFR, IGFR, FGFR, and TGF-_. Correlation of EGFR with histologic subtype also existed in TNBC, of which more aggressive variants have higher EGFR expression. About 60-80 percent of tumors that are brought about by TNB have traits which result in the conspicuous expression of EGFR. PI3K/AKT/mTOR pathways are usually misregulated in TNBC-associated tumors. AKT and mTOR being overactivated is the one which is associated with TNBC of a worse characteristic in the patients. Therefore, the concurrent blockade of AKT and mTOR holds the promise to serve as a new potentially effective therapeutic target against TNBC. AKT inhibitors like ipatasertib and capivasertib were promising candidates against aggressive TNBC as face to face survival rate improved.© Another mechanism of resistance emerging in these tumors is through hyperactivation of AKT nanoediting improved the sensitivity of resistant cells to cis-platin-induced apoptosis.[9] Everolimus in combination with carboplatin may serve as effective.

Tumor dimensions and stage at diagnosis and the onset or not of systemic adjuvant and neoadjuvant chemotherapy are potential radiations of risk factors, regarding TNBC recurrence and survival rate. Surgical treatment of TNBC is definitely indicated. The choice of the operation will depend upon the condition factors such as the situation and placement of the tumor mass, the type of cancer stage, and the general condition of a patient. There are two primary surgical procedures for treating breast cancer: lumpectomy which consists in removing only the cancerous tissue together with a small adjacent healthy tissue and mastectomy which is a procedure of removing all of an abnormal breast tissue (the tumor and the healthy tissue around it). The patients undergo neoadjuvant or adjuvant therapy incline the utilization of radiotherapy, chemotherapy or even their combination. A triple negative breast cancer (TNBC) in high grade/high risk patients should be evaluated for advanced stages. Both surgery and in particular chemo therapy are the main treatment modalities which are used in pre- operative, post- operative and metastatic triple negative breast cancer (TNBC). Chemotherapy regimens using toxic drugs like anthracyclines (doxorubicin and epirubicin), taxane-based drugs (paclitaxel and docetaxel), alkylating drugs (cyclophosphamide), antimetabolites (capecitabine) and platinum-based drugs (carboplatin and cisplatin) are the most.

Pembrolizumab (Keytruda®) received FDA's breakthrough therapy application, which is one of the tools being used to improve TNBC treatment outcomes. Twice, when given with another medicine called chemotherapy, this medicine is an immunotherapy drug for the treatment of locally recurrent unresectable or metastatic TNBC with expression of PD-L1. Standalone pembrolizumab was effective neither in (OS) progression-free survival (PFS) compared to single-agent chemotherapy.[9] Conversely,

grade 3-4 adverse events such as leucopenia were less frequent among patients receiving immunotherapy compared to those in the chemotherapy Arm 14% vs. 16%. The data of the Keynote-355 clinical trial also showed that the efficacy of pembrolizumab was improved with chemotherapy (10%). The pembrolizumab combination with chemotherapy examination was prompted by this information. During this experiment, a total of 847 patients were randomly assigned to one of two groups: nab-paclitaxel, paclitaxel, gemcitabine + carboplatin, or pembrolizumab–continuation underplacebo–chemotherapy. The study was conducted on both the patients and the researchers not to reveal the assigned grouping to anyone, which is called double-blind study. In 2021, it was the first and only ICI (immune checkpoint inhibitor) to receive accelerated approval and commonly be considered a routine therapy used to treat multiple advanced stage cancer types. Furthermore, fares the FDA approval for pembrolizumab as neoadjuvant treatment for high-risk from those without the presence of metastatic TNBC when used together with chemotherapy. Besides, pembrolizumab was also approved as a monotherapy for this phase in the case Keynote-522 trial having the completion of neoadjuvant treatment patients received either pembrolizumab or a placebo in association with carboplatin and paclitaxel during four cycles. In the interval, doxorubicin (or epirubicin) + cyclophosphamide chemotherapy was administered. In the adjuvant stage, the endpoints were in-situ failure/disease-free survival (FSDFS) at nine cycles or until unacceptable toxicity. Permission of pembrolizumab for the hit in the early stages triple-negative breast cancer (TNBC) is a remarkable fact since it is the first case of immunotherapy introduction. The latest findings from the US Food and Drug Administration (US-FDA) panel that allowed treatment of triple-negative breast cancer (TNBC) was therapeutic antibody-drug conjugates ADCs. ADCs combine the one-of-a-kind nature of monoclonal antibodies with the power of cytotoxic (poisonous) small compounds. Tropelitiy (is now available to patients with metastatic disease that has demonstrated progression on at least two previous treatment lines, as IMMU-132-01 clinical trial demonstrated). Sacituzumab govitecan has been on a standard commercialization route, one year after achieving a fast-track approvals which is a very good step for a drug that is still in clinical trials. The indication focuses on the use topped in such additional following systemic treatment of the advanced stage of non-invasive breast cancer, including those for metastatic disease. The conditionally s approved because of the current ASCENT study.[10]

## *Recently FDA-Approved Therapies for TNBC (Table 4)*

**Table 4: Timeline for FDA Approved Therapy.**

| Time line | Approved | Withdraw |
|---|---|---|
| January 2018 | Olaparib | |
| October 2018 | Talazoparib | |
| March 2019 | Atezolizumab and Albumin bounded paclitaxel | |
| April 2020 | Sacituzumab | |
| November 2020 | Pembrolizumab | |
| October 2021 | | Atezolizumab and Albumin bounded paclitaxel |

Though Gagliato et al. reported about success or failures they had encountered in using the PD-1/PD-L1 as immunotherapy for triple-negative breast cancer (TNBC), the information was quite comprehensive and unambiguous. It is also worth noting that TNBC's clinical studies are looking into several blockers of immune checkpoints, such as CTLA-4, LAG-3, and several blockers of PD-1 such as its ligand TIM-3.[11] Ipilimumab, a molecule that blocks CTLA-4, is at the moment with nivolumab being tested in a phase 2 clinical A neo-adjuvant chemotherapy regiment utilizing a "PD-1 blocking" antibody and "taxane-based" treatment.

In the initial half of 2019, the FDA granted manner speedy clearance to atezolizumab (Tecentriq®) when used in combination with an albumin-bound paclitaxel (nab-paclitaxel), which led to the introduction of immunotherapy into the current treatment of triple-negative breast cancer (TNBC).[12] Atezolizumab is the first totally humanized monoclonal antibody that recognizes only PD-L1 at a molecular level and was approved on the obtained initial data from the IMpassion130 study (NCT02425891), which is a placebo-controlled, phase III clinical trial in inoperable locally advanced or metastatic TNBC.

The development of cancer is largely attributed to the transformation of cellular metabolism. Through detailed analysis of the circulating metabolites in Triple-Negative Breast Cancer (TNBC) system we could acquire knowledge that may provide a foundation for targeted interventions on TNBC. Possible drug targets with the aim to inhibit tumor malignancy may be identified by the exploration of metabolites promoting tumor growth.[13] Carrying out extensive research on polar metabolome and lipidome in involved samples of triple negative breasts cancer (TNBC) and normal breast tissues (330 and 149 samples respectively), researchers concluded that the potential therapeutic targets forming the backbone of The aim was to construct an atlas of metabolomic profile of TNBC patients. The study first analyzed the metabolomes of the

patients with triple negative breast cancer (TNBC) from a single group of individuals that were linked to their genome. This analysis resulted in the classification of TNBCs into three unique metabolomic subgroups, namely C1 to C3. C1 exhibited an increase in ceramides and fatty acids, while C2 displayed metabolites associated with oxidation processes and glycosyl transfer. C3, on the other hand, showed the least amount of metabolic reprogramming. The research used a comprehensive collection of metabolites and optimized previous subtypes based on gene expression to identify particular metabolites that might serve as possible treatment targets for individuals with triple-negative breast cancer (TNBC).

Through the targeted Notch regulation method the useful remedy technique may come out. The conjugation of PF-03084014 GSI on the advanced clinical stage with either AKT inhibitor MK-2206 or NF-kB inhibitor Bay11-7082, succeeded in curing PTEN WT and Notch mutation suspected triple-negative breast cancer cells.[14] On the other hand, another research discovered a relation between Notchs.[15]

An antibody-drug conjugate (ADC) is a drug which could bring about a feasible and a precise approach for both breast cancer and TNBC. In the year 2020, the FDA-US issued an expedited approval of cytiricab govitecan for treating metastatic triple-negative breast cancer (TNBC) that previously has been treated with at least two other metastatic treatment clinic. In 2021, the FDA of the USA approved fully, with marketing Trodelvy (produced by Immunomedics Inc.) as a way to cure patients with unresectable locally advanced or metastatic TNBC (Triple-negative breast cancer) who failed two or more previous systemic treatments, of which at least one was used in diseases of the metastases. The targeted therapy is a prospective and appealing strategy owed to an antibody-drug conjugate (ADC), where the latter can be loaded with potent cytotoxic drugs, in patients with triple-negative breast cancer (TNBC). The technology in the amount of the utilized loading, the linkage chemistry, and the delivery mechanism of the drug will boost the treatment of triple-negative breast cancer (TNBC) with the goal of increased patients survival rates. Oncolytic viruses disseminate throughout tumors and enhance antitumor responses via two distinct mechanisms: curbing the multiplication of the movement of cells of cancer and promoting body immune system to fight against it. Oncolytic infections by virus do not only release the antigen, cell debris when given it to the tumor cell, but also stimulates the intrinsic defense solution of the body.

Impassion130 study had a favorable response to patients treated with the combination of atezolizumab and Abraxane®, revealing a statistically significant 40% reduction in chance of disease progression or death in terms of overall survival compared to patients who received placebo after reviewing the data, subsequently the FDA granted approval to the first immunotherapy drug in anti-PD-L1 checkpoint Unlike chemotherapy, these drugs target specific abnormalities in the biology of these cancers. They can now be used in patients with metastatic disease in triple negative breast cancer patients who have tested positive for PDL1 protein expression. The median overall survival of the patients participating in phase 3 of the IMpassion130 trial has been found to be different from their counterparts who received placebo as the pre-specified second interim analysis showcased no remarkable difference. Atezolizumab and nab-paclitaxel in the medical setting have revealed that patients with metastatic TNBC who have PD-L1 positive immune cells will gain a significant increase in their overall surviving time.[12] This improvement was demonstrated while comparing the group of nab-paclitanel + atezolizumab patients to the control group. However, the lack of significant disparity in overall survival (OS) across the treatment groups does not include their appearance of immunotherapy combination toxic death only in two patients and the present of other side effects including neutropenia, endocrinopathies, and so on continues to challenge the eff Such a finding, therefore, stresses on the need of more research and explanation of the demand for the practice of new **combination therapy** approaches.

## Antibody-Drug Conjugates (ADC)

Following the granting of the FDA clearance for Trodelvy in 2020, more pharmaceutical companies remained enthusiastic to explore possibilities of approximation of ADC for the treatment of TNBC. Besides, the phase I trial reported a satisfactory effectiveness and tolerability if using ladiratuzumab vedotin.[16] Also latest reviews of literature have unveiled other antibody-drug conjugates (ADCs) that are now being examined in clinical trials. ZW49, the only well-tested bispecific antibody-drug combinations, consists of ZW25 and monomethyl auristatin E. Unlike other trastuzumab-ADCs which only attach HER2 cell membrane, ZW49 is found to be selectively uptaken by the cells that expresses HER2. The efficacy of ATXD in the preventing of tumor growth as observed in patient-derived xenograft models was reported across the cell lines with high and low expression of HER2.[17] The FDA approves the medication fam-trastuzumab deruxtecan-nxki (Enhertu), an ADC, on August 5, 2022. This approval includes HER2-low breast cancer patients with either unresectable or metastatic tumors that are resistant or restagized after losing response to neoadjuvant/metastatic disease etiopathogenesis or disease recurrence within six months after adjuvant therapy was completed.[18] Point treatment at a genetically-synthesized mutation that has enabled the tumor to flourish will propel the same treatment to inhibit the growth of the tumor. Though, the unpredictability of intratumour heterogeneity may now be the reason of some cases for initial response to therapy. The theory proposes that multiple mutations in cancer genes that pertain to treatment resistance have been observed both in benchmarking and clinical research. In a recent study carried out by Ganesan *et al*.[19], it was demonstrated that almost two-thirds (67%) of the samples with breast

cancer showed two or more genetic changes. Various contexts of this problem have been noticed, i.e. breast cancer. Where as the corroborations that exist among the resistance making for substitution for trastuzumab and lapatinib shows when there are concurrently PI3KCA mutations and ERBB2 amplification. Data obtained from this research have resulted in selection of this combination for the further clinical testing. Furthermore, the resistance mediated through the inhibiting of HER2 when dual HER2 blockade of with two monoclonal antibodies is applied. So far, a similar kind of resistance has not been observed in patients administered with PIK3CA/HER2 monoclonal antibodies in the early stages where PIK3CA mutations are already present. In the three-part BOLERO-2 study, the combination of the mTOR inhibitor everolimus and the aromatase inhibitor exemestane was explored for patients who already go through advanced-stage disease or earlier breast cancer where estrogen receptors were positive and HER2 was negative. The protocol demonstrated that a suppressive mTOR inhibitory function was observed in the presence of alterations presented in numerous pathways such as FGFR1/2, CCDN1, PTEN, and PIK3CA (Table 5, Figure 4).

**Table 5: Treatment Protocols for Various Stages of HER2-positive Breast Cancer.**

| Breast Cancer Description | Treatment Protocol |
|---|---|
| First-line therapy | Taxane, trastuzumab, Pertuzumab |
| Second-line therapy | Trastuzumab emtansine |
| | Capecitabine, lapatinib |
| | Aromatase inhibitor |
| Third-line therapy | Trastuzumab/lapatinib |
| | Chemotherapy, trastuzumab |
| | Lapatinib, trastuzumab |
| | Vinorelbine, trastuzumab |

Carcinoma cells, including TNBC, regularly suffer overexpression of CDKs, namely CDK4/ CDK6. CDK4/ CDK6 tend to be expressed in abnormal cyclin D1-centered kinase activity associated with malignancies. That is primarily: they can be either disrupted or increased. CDK4/ CDK6 works as a central hub that plays a role for many pathways of signaling, which activate cell cycle Cf. the author's understanding of humanize the given sentence. The CDK4/CDK6 proteins can add phosphate groups to the RB, the p107, and the p130, which are closely related to them. The RB proteins contribute to the maintenance of the cell cycle. List of key points to address in the given essay: 1. Accommodate a host of functions: Plants serve as the foundation of the global food system, providing sustenance and nourishment to billions of individuals and communities worldwide. 2. Limited genetic diversity: Due to the narrow genetic pool available for selection, genetic diversity can As this pathway is the trigger for cell cycle, most of cancers mutate to go on cycling for cell proliferation. The abolishment of the CDK4/CDK6-RB axis hugely paves the path for the activation of CDK4/ CDK6 activity function, which is subsequently perceived as oncogenic. CDK4/CDK6 are CDK proteins that belongs to the regulatory kinases. Hence, they can exist in the form of phosphorylation. Instability and emphasized shuttling are traits of cyclin D1 that dictate shuttling between the cytoplasm and the nucleus. Cancer types may often have changed ways of increasing cyclin D1 protein gene expression, translocation and duplication. Cyclin D1 deregulation serves as a characteristic feature in breast cancer arising in 25% of cases. Owing to this, CDK inhibitors have become a valuable treatment tool in TNDC clinics with highly favorable results. Dinaciclib, a CDK inhibitor, is currently the subject of phase I clinical trials that may yield promising results as a treatment option for patients with metastatic or advanced breast cancer as well as those affected by triple-negative breast cancer (TNBC). Trilaciclib, a CDK4/6 inhibitor, is now being tested in a phase I clinical study in conjunction with gemcitabine for the treatment of metastatic triple-negative breast cancer (mTNBC).[20] Ribociclib, a different CDK4/6 inhibitor, is now being tested in phase I/II clinical studies for patients with advanced AR-positive TNBC. It is being used in conjunction with bicalutamide, which is an androgen receptor inhibitor (ARi). At present, the FDA has authorized three CDK4/6 inhibitors: palbociclib, ribociclib, and abemaciclib. The clearances were granted based on data obtained from extensive phase III trials, including the MONALEESA study for ribociclib, the PALOMA study for palbociclib, and the MONARCH study for abemaciclib. Alpelisib, a selective inhibitor of the alpha form of PIK3CA, was recently authorized for the treatment of metastatic breast cancer with ER+ and PIK3CA mutations.[21] The SOLAR-1 research showed that patients who received alpelisib in addition to fulvestrant had a significantly longer progression-free survival (PFS) compared to individuals who received placebo along with fulvestrant (11.0 months versus 5.7 months).[22] The medicine is very tolerable, with the most prevalent adverse effects being elevated blood sugar levels, gastrointestinal toxicity, and skin toxicity.

## Future of TNBC

TNBC as being its treatment advancement depends on more accurate, biomarkers-driven trials, and ADCTs (that stand for adaptive clinical trial). The present FUTURE trial is one of the best illustrations (3). This is a research combined germane to phases I and II assisting physicians to accurately classify the cases of breast cancer of mixed genotype by using molecular subtyping and genomic profiling. This will help in making precise determination of the patients' response to different treatment modalities. Patient's categorization in this experiment rests on an integrated approach that incorporates somatic mutations, copy number abberations(CNAs), gene expression pattern and validated immunohistochemical surrogates. TNBC patients are categorized into four subtypes based on these criteria: luminal androgen receptor (LAR), an immunomodulatory (IM), and basal-like immune-suppressed (BLIS), but then sees a shift to mesenchymal-like (MES).

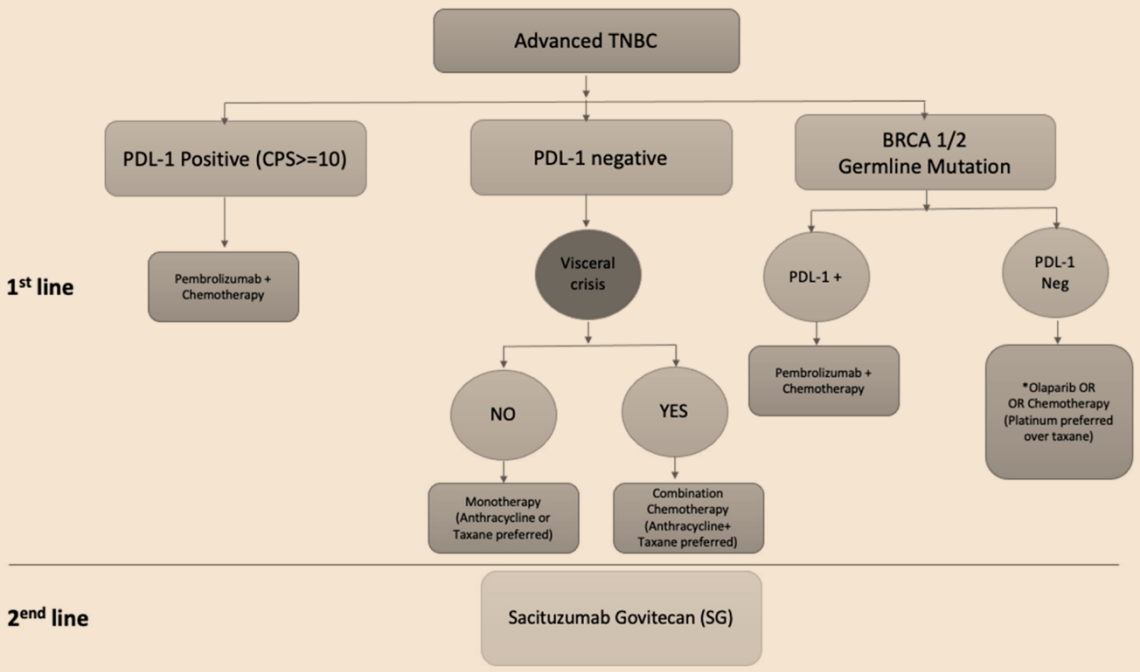


**Figure 4:** Treatment Protocols for Various Stages of HER2-positive Breast Cancer.

## Clinical Trials Status in Metastatic BC and TNBC

Through a phase II study, lotus, the efficacy of Ipatasertib which is AKT (a protein) inhibitor was evaluated. The study was to look at if Ipatasertib plus paclitaxel A couple treated well or not that well with placebo. Chief FPS was 6.2 and 4.9, respectively, in Ipatasertib and placebo groups. The study was conducted on a 124-patient sample group; the patients had TNBC tumors that were locally advanced or metastatic and 48 patients had PTEN-low tumors. In the PTEN-low group, the 6.2-month median PFS were noted in the Ipatasertib group and 3.7 months PFS were observed in the placebo group. In addition, AZD5363, an inhibitor of AKT, was analyzed in the patients with AKT1 E17K-mutant ER+ breast cancer, and MK-2206 drug, which inactivates PIK3CA, was performed in the patients with ER+ and HER2– breast cancers, those both carry PIK3CA mutation. These trials, which involved studying the use of neoadjuvant therapy for individuals with unique cancer profiles, evaluated the effectiveness of jeopardize. An AKT1 E17K investigation has been conducted which aims to determine the usefulness of this target in treating of residual ER-positive breast cancer. AZD5363 is an orally administered inhibitor of AKT kinase which competes with ATP. The clinical trial has revealed a signal of activity, as the study reported a median PFS of 5.5 months for AZD5363. Despite that, it is actually possible to employ medication combination, but it is only through such combination, the potential of this drug can be fully exploited. To illustrate, apoptosis was initiated in cell culture with hormone therapy containing AKT inhibitors. The fact that when MK-2206, a compound which blocks AKT, inhibited the growth of different cancer cell lines, including those of humans, and it even showed tolerability and AKT inhibition clearly where further investigation was needed in patients in neoadjuvant types of PIK3CA-mutant ER+ and HER2-negative breast cancers with an objective of generating a personalized treatment. The absence of a pathologic complete response was noted, indicating that the combination of anastrozole and MK-2206 in phase II trials was not significantly more successful than either drug used alone. This finding has led to a restriction on future investigations.

## Angiogenesis and TNBC Role

Angiogenesis is a vital process that cancer cells must undergo in order to become large tumors. VEGF-A is the primary pro-angiogenic agent secreted by solid tumors. Increased VEGF expression in TNGC is associated with a worse prognosis regardless of tumor size, histological grade, or nodal status. Combining chemotherapy with the anti-VEGF antibody, bevacizumab, was shown to enhance PFS in triple-negative breast cancer (TNBC). However, it did not result in statistically significant increases in OS when compared to chemotherapy alone. Currently, researchers are investigating the simultaneous suppression of VEGF and Notch ligand DLL4, which are both necessary for angiogenesis, using bispecific monoclonal antibodies.

## Limitation of Precision Medicine

The use of precision medicine in clinical setups has attained a large extent of growth, but there are certain challenges that delay the uptake of precision medicine in the clinical setting. This massive amount of variation in the human genome which is still uncovered is a big

hurdle to clinical application of genomic data. Also, you must gather sufficiently large groups of samples to study their functions. Objective number two shows that discovering risk factors is a really complex process. Its relationship with genetics is more complicated than we thought. Different individual may have the same kind of disease even though there passion comes from different risk factors (Table 6).[23] Interestingly, likewise, it is also as difficult to realize the average constituents of polymorphisms among ancestors' populations. Such case will be African genome which differs from the European because of the higher levels of genetic variation with correlations between single nucleotide polymorphisms. Not only is the development of infra and education in health care clinics one of the barriers to the further expansion of personalized medicine, but there also is the lack of these essential elements in this medical field. For precision medicine to be woven into regular practice, therefore, it is imperative that records be kept which comprise of clinical, lifestyle and genetic characteristics of the patients. On the other hand, the hospitals at present a paucity of genetics staff. Before thorough genetic information could be implemented and adopted by the therapeutic process, the issue on costs and reimbursement must be resolved.

**Table 6: Limitations and Solutions for Precision Medicine in MBC.**

| Steps | Limitation | Solutions |
|---|---|---|
| Patients with MBC | Biopsies not feasible in some patients | circulating tumour DNA) |
| Tumour specimen | High-throughput analysis not feasible in some patients | • Deep sequencing,<br>• circulating tumour DNA<br>• Develop cancer-related gene catalogues |
| Molecular profilling | Driver identification | • Deep sequencing<br>• circulating tumour DNA |
| Target identification | Availability of optimal treatment | • Develop precision medicine only in the context of drug access programs |
| Targeted therapy | Drug development in cohorts defined by a genomic alteration | • Scale up number of patients screened for the alteration<br>• Develop personalized medicine trials |

## Conclusion

Precision medicine is future-oriented strategy consisting of tools, approaches, and models designed to lower the toxicities of the chemotherapeutic drugs and to enhance the clinical results for patients. This approach is important for effective breast management of cancer. 3D tumor organotypic spheroids for phenotypic screening could become another way of doing home screenings or adding them to the present ones to give better results as long as the screening was carried out within the short period of time and the treatment could be adjusted based on the tumor progression by several screening tyres. The proposed future treatment approaches for breast cancer (BC) and the triple-negative breast cancer (TNBC) are in the nature of targeted approaches, making use of the inhibitory techniques, namely the immune checkpoint inhibitors (ICIs), targeting the EGFR receptor (EGFRi), poly (ADP-ribose) polymerase inhibitors (PARPi), antibody-drug conjugates, Besides, possibly intended towards the blocking of signaling pathways would be among the approaches for the treatment of breast cancer. Using union therapy methods along with the best single modalities can however further improve the accuracy of the medicine used for treating the patients with metastatic breast cancers and TNBC. The idea of precision medicine for MBC based on genomic data would indeed be tempting; however, to date, there is no data that supports the use of women's genotype to predict their individual response to therapy.

This disaster is the result of both scientific and practical problems. This difficulty can thus be characterized as multidimensional. Indeed, the greatest problem in the area of mammography is the high prevalence of non-specific genes that do not have well defined causative factors like ER, ERBB2, PIK3CA, and AKT1. The combination of morphological/biomarker staging with machine learning systems that use deep learning algorithms and cancer genomic studies can precisely predict prognostic effects for individual patients and give an adverse outcome, as well as the most effective treatment options. Advanced technologies like as microarray and next generation sequencing, combined with machine learning methods, have the potential to bridge the divide between clinical and research-based subtyping of breast cancer. This might greatly contribute to the progress of breast cancer care. The potential of precision medicine in treating TNBC and other solid cancers is unquestionable. The integration of more sensitive "omics" and phenotypic screening techniques has the potential to greatly expedite the discovery of new therapies. The most favorable routes identified were the cyclic independent kinase pathway, the PIK3CA/mTOR/AKT pathway, the BRCA pathway, or the overexpression of PD-L1 in individuals with TNBC. Additional research is required to provide a uniform and consistent diagnosis and treatment strategy for individuals with breast cancer. In the future, each individual diagnosed with breast cancer will have a comprehensive analysis of their tumor at the molecular level. This will enable personalized treatment strategies to be developed, leading to enhanced treatment outcomes and reduced side effects.

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