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A Detail Review up on Enhancement of Immunotherapy towards Breast Cancer Treatment

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Abstract: Immunotherapy increases or alters the body's natural defences to target and eliminate dangerous cells, which aids the immune system in fighting diseases, especially cancer. Immunotherapy has completely changed the way that breast cancer is treated by providing advancement as well as adding new features in context of body's own defence mechanism against the illness. Recent developments in this area have greatly enhanced clinical results and increased patient treatment alternatives. Checkpoint inhibitors have been a mainstay of immunotherapy for breast cancer, including inhibitors like-"PD-1", "PD-L1" and "CTLA-4" mainly. By blocking immunological checkpoints, these substances, the immune system get permitted to detect and encounter the malignant cells. Clinical trials have shown impressive effectiveness, especially in HER-2-positive and "triple negative breast cancer". Adoptive cell therapy (ACT) has indicatively shown it's capacity to treat breast cancer that has spread. Uses of nanotechnology in clinical practice, detection, diagnosis, treatment and prevention are now feasible. NeuVax and other cancer vaccines are also being studied for their capacity to elicit specific reactions. In context of cell therapy, the "CAR T-cell therapy" has acquired a promising position. Aside from these developments, research is still being done on combinations therapies, which involve immunotherapy in addition to other treatments including chemotherapy and targeted medicines. All things considered, the field of breast cancer treatment has changed due to recent developments in immunotherapy.

Keyword: Breast cancer, Monoclonal antibodies, PD-L1, CAR T-cell, NeuVax, Chemotherapy.

❖ Introduction

The immune system defends the body against infections and abnormal cells, including potential cancer cells, through a process called immune surveillance. Cancer cells, however, can evade detection, often creating an environment that suppresses immune responses. Immunotherapy leverages this relationship by enhancing immune cells' ability to identify and attack cancer. The modern immunotherapy which has generated new ways, increasing attention on its use in

context of encountering breast cancer. Surgery, chemotherapy, radiation therapy and targeted therapy have historically been used to treat wild breast cancers. Immunotherapy adds a new level of treatment especially for difficult subtypes like triple-negative breast cancer (TNBC). Conventional treatments give patients whose tumours are resistant to conventional medicines hope by directly stimulating the body's immunity mechanism to look out and destroy malignancy more efficiently. Immunocheckpoint inhibitors are among the most promising immunotherapy treatments for breast cancer. These medications prevent tumours from being detected by the immune system by blocking proteins like "PD-1" or "PD-L1".[1]

Now-a-days the nanotechnology is a rising immunotherapy with its improve capacity in generation of immune response, target cancer cells, and minimize side effects for treating breast cancer. In context of immune boost up, nanoparticles can be designed to deliver medications, genetic material, or immunotherapeutic agents straight to cancer cells or the surrounding immunological milieu. Moreover, nanoparticles can be employed to boost immunological responses. As cancer vaccines, they can be coated with tumour antigens to teach the defence system for both identifying and combating breast malignancy. Furthermore, by delivering immunomodulatory chemicals to rewire the region and promote immune activity, nanoparticles can change the tumour microenvironment, which frequently inhibits immune responses.

Monoclonal antibodies, which target particular proteins on cancer cells and boost up the immune system which ultimately leads to upholding the capacity of identification and elimination of cancer cells, denoting as a crucial part of immunotherapy for breast cancer. Targeting the HER2 protein, overexpressed in roughly 15-20% of breast tumours, trastuzumab (Herceptin) is one of the most often used monoclonal antibodies for treating breast cancer.

The following lists some of the main causes of breast cancer that necessitate immunotherapy:

- Immunotherapy offers a more tailored and less toxic approach than traditional treatments like chemotherapy and radiation therapy, which can have multiple side effects that reduce quality of life of an individual.
- Developments in the identification of biomarkers, such as the expression of "PD-L1" in tumours, enable physicians to anticipate which patients would benefit from immunotherapy, offering individualized treatments options for improved results.
- In contrast to conventional treatments, immunotherapy can help the immune system create a long lasting memory of the cancer cell, which lowers the change of recurrence especially in the case of metastatic or high risk breast cancer.[2]

- Considering the complexity and heterogeneity of breast cancer, immunotherapy can be used in conjunction with chemotherapy, radiation therapy and target therapy to improve therapeutic efficacy.
- Checkpoint inhibitors, cytokines, and vaccinations are examples of immunotherapeutic medicines that nanoparticles can deliver straight to tumours, avoiding healthy tissue and reducing adverse effects.
- Nanoparticles can also aid in the activation of ‘‘T-cells’’as well as different immune cells for building up more potent defence against breast cancer cells by targeting certain tumour antigens.
- Transtuzumab attaches itself to HER2 receptors, inhibiting signals that encourage the growth of cancer and designating the cells for immune system destruction.

Immunotherapy is currently in the experimental stage of research, but it has the potential to control disease over the long term and improve patient outcomes. Immunotherapy is a rapidly developing treatment that is not yet common for all forms of breast cancer. Research is still being conducted to find new ways to increase its efficacy, broaden its applicability and provide patients with breast cancer with individualized treatment plans.

❖ Objective

These following could serve as primary motto for immunotherapy in breast cancer: -

- To boost up body’s defence mechanism so that the detection of breast malignant cells as foreign objective more rapidly and launch counter attack.
- To combat the immunosuppressive environment that breast tumours produce, which weakness the immune system.
- To lessen immunotherapy’s toxicity and adverse effects.
- By using immunotherapy, patients are treated according to the molecular and genetic features of their tumours.
- By creating a permanent immunological memory against breast cancer cells can prolong survival and prevent cancer recurrence.
- By developing combination techniques with radiation, chemotherapy and targeted medicines to improve immunotherapy’s overall efficacy in treating breast cancer.

❖ Inhibitors present in cell in context of Breast Cancer

➢ Checkpoint-Inhibitors

Checkpoint-inhibitor includes in a class of immunogenicity that encounters cancerous cell line, thereby revolutionizing the treatment of cancer. They function by blocking particular proteins known as ‘‘checkpoints’’, which cancer cells used to evade immune system attacks. These checkpoints include

"PD-1", "PD-L1" and"CTLA-4", function as immune response brakes in normal circumstances to stop the immunogenic response from attacking healthy cells but these systems are frequently taken over by cancer cells who use them to avoid immune system recognition.

Checkpoint inhibitors such as nivolumab (Opdivo) and Pembrolizumab (Keytruda), prevents checkpoint inhibitors from interacting with their ligands, improving T-cell recognition and anti-cancer cell activity. Triple-negative breast cancer has all responded very well to these medications.[3] Although checkpoints inhibitors show promise not all patients benefit from them and some may have adverse immune-related complications. Through combination medicines and improved biomarkers identification that predicts which patients would respond best to these treatments ongoing research attempts to increase their efficacy.

- **PD-1 Inhibitors**

A vital immunological checkpoint protein called "Programmed Death-1" or "PD-1" is mostly found on the upper surface area of activated T-cells, which are important components of the body's immune response, its main function is to supress the immune system in order to avoid excessive inflammation and autoimmune. The T-cell's capacity to assault is diminished when "PD-1" attaches to its ligands, "PD-L1" or "PD-L2", which are depicted on immune and malignant cells respectively. Many malignancies use this pathway to avoid immune detection, even though it is essential for preserving immulogical balance and avoiding harm to healthy tissues. Overexpression of PD-L1 by tumour cells can active PD-1 on T-cells, so "turning off" the immune response and enabling the disease to spread unchecked.

PD-1 inhibitors have revolutionized cancer treatment in recent years by preventing this interaction, reviving T-cells empowering the defence system to look out and eliminated cancer cells, PD-1 inhibitors like Nivolumab (Opdivo) and Pembrolizumab (Keytruda) have demonstrated notable efficacy in treating malignancies like non-small cell lungs cancer, renal cell carcinoma, melanoma and certain types of breast cancer. These treatments have given patients new hope, especially those whose tumours have progressed or who don't respond to conventional medications.

- **PD-L1 Inhibitors**

Immunotherapy medications known as PD-L1 inhibitors are essential for treating a variety of cancers, especially those that have progressed to an advanced stage, like non-small cell lung cancer, melanoma as well as urothelial carcinoma. These inhibitors target the protein known as PD-L1, which cancer cells frequently use to avoid immune system identification. T-cells' PD-1 receptor is bound by PD-L1, which deactivates these immune cells and permits cancer to spread unabated. The "PD-L1/PD-1 interaction" is blocked by PDL-1 inhibitors therefore restores

the T-cell function. Thus, the immunity system gets help to identify and combat cancer cells by these functions.

Studies and clinical trials have shown that PD-L1 inhibitors can give many patients longer-lasting effects and higher survival rates. For instance, medications such as Durvalumab, Atezolizumab, and Pembrolizumab have demonstrated encouraging outcomes in patients whose tumours display elevated levels of PD-L1. These treatments are not always successful, though, and their efficacy frequently hinges on certain tumour indicators as well as the patient's immune system. PD-L1 inhibitors have potential, but they also come with risks and side effects, such as immune-related adverse events like dermatitis, hepatitis, and colitis. Patients undergoing these treatments therefore need to be closely watched. Research on these treatments is still ongoing with the goal of increasing their effectiveness and expanding their use to include other cancer types.[4]

- **"CTLA-4-Inhibitors"**

The "CTLA-4"or "Cytotoxic T-Lymphocyte-Associated Protein 4" pathway, which mainly controls the immune response, is the target of CTLA-4 inhibitors, a kind of immunotherapy medication used to treat a variety of malignancies. T-cells are vital parts of the body's defence system in charge of recognizing and eliminating aberrant cells, including cancer cells, include the inhibitory checkpoint protein CTLA-4. CTLA-4 typically serves as a brake on T-cells to stop an overreaction that might harm healthy tissue. But cancer cells can take advantage of this system, reducing immune monitoring and enabling tumours to spread unchecked.

Ipilimumab and other CTLA-4 inhibitors function by obstructing this mechanism, which raises the "brake" and promotes T-cell activation and proliferation, this improves the immunity system to identifying and eliminating cancer cells. These inhibitors have demonstrated effectiveness in treating a number of malignancies, such as melanoma, renal cell carcinoma, and non-small cell lung cancer when used in conjunction with other medications. However, CTLA-4 inhibitors can also have serious immunological-related side effects since they activate the immune system. These can include gastrointestinal distress, skin rashes, and other autoimmune disorders that occasionally need to be treated with immunosuppressive medication.

- **Mechanisms of Checkpoint Inhibitors**

Targeting regulatory proteins, or immunological checkpoints, which normally limit immune responses and prevent autoimmunity, checkpoint inhibitors improve immune responses against cancer. These checkpoints are frequently used by cancer cells to evade immune detection and permit unregulated proliferation. These inhibitors primarily targeting these pathways:

(i) "PD-1/PD-L1"

(ii)"CTLA-4".

- **"CTLA-4-Inhibitors"**: T-cell receptor CTLA-4 suppresses immunological activation during the onset of the immune response. CTLA-4 functions as a "brake," restricting T-cell activation to prevent an overreaction by binding to particular ligands. This process is used by cancer cells to avoid immune response. By blocking this receptor, CTLA-4 inhibitors such as ipilimumab enable T-cells to continue to function, proliferate, and target cancer cells, hence boosting anti-tumour immunity.

- **"PD-1/PD-L1Inhibitors"**: PD-1 is another T-cell receptor that binds with PD-L1, a protein often overexpressed by cancer cells. This binding sends an "off" signal to T-cells, dampening their activity and helping cancer cells escape immune destruction. PD-1/PD-L1 inhibitors, such as "PD-1" or"Pembrolizumab" and "PD-L1" or "Atezolizumab", block this interaction, preventing T-cell deactivation. Thus, it allows T-cells to recognize and encountertumour cells.[5]

Although the"immune-related adverse effects" is observed for these inhibitors due to their elevated activity yet these have transformed cancer treatment and can provide some patients with long-lasting results.

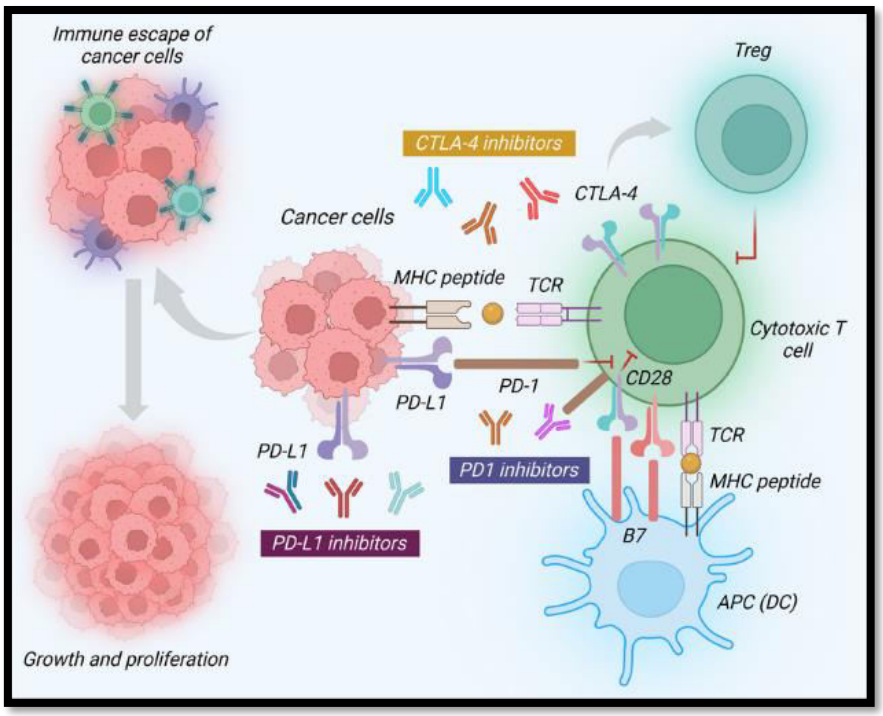

Fig1- Mechanism of Checkpoint Inhibitors[6]

❖ **Monoclonal Antibodies (mAbs)**

Laboratory prepared immunogenic molecules known as "Monoclonal antibodies"mimic the capacity of the defence system to target orient infections or aberrant cells, such as cancer cells. A distinct antigen, or a particular protein on the surface of target cells, is what each monoclonal antibody is made to attach to. By identifying dangerous cells for elimination, obstructing disease processes, or administering medications directly, mAbs' focused approach makes them useful for treating illnesses.

Cloning a single B-cell yields monoclonal antibodies, which guarantee that all produced antibodies are identical and target the same antigen. mAbs come in a variety of forms, such as conjugated, bispecific, and bare antibodies. Often employed in immune checkpoint treatments for cancer, naked monoclonal antibodies (mAbs) bind directly to antigens to disrupt cell growth or function. When conjugated monoclonal antibodies (mAbs) are mixed with poisons, chemotherapeutic medications, or radioactive materials, the effects on healthy cells are reduced and the treatments are delivered precisely to the targeted cells. In order to stimulate immunological responses, bispecific monoclonal antibodies (mAbs) frequently form a bridge between immune cells and cancer cells by binding to two distinct antigens at the same time.

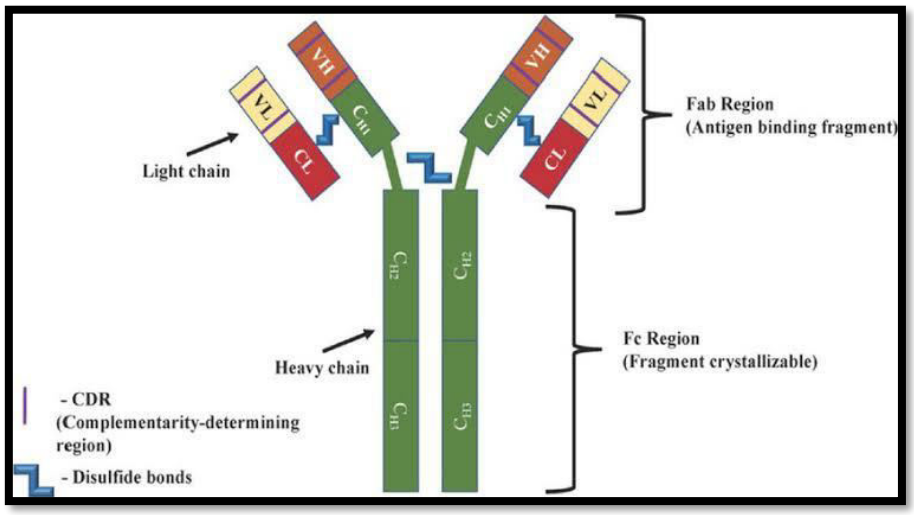

Fig 2 – Monoclonal Antibodies[7]

- **HER2-Targeted Therapies**

The management of "HER2-positive breast cancer", a subtype identified by accumulation of the HER2 protein, which speeds up the aggressiveness and proliferation of cancer cells, has been completely changed by HER2-targeted medicines. HER2-positive breast cancer frequently advances quickly and is more likely to return in the absence of specific therapies. But the advent of HER2-targeted medications, starting with Trastuzumab (Herceptin), has greatly enhanced results by raising survival rates and lowering recurrence.

"Trastuzumab" which is a monoclonal antibody, binds HER2 protein selectively. The reaction held on the cancer cells surface, obstructing the signalling cascades that propel tumour growth and enhancing immune system's ability of both identification and elimination of these cancer cells. Chemotherapy and Trastuzumab are frequently used together to increase efficacy, especially in early and metastatic HER2-positive breast malignancies.

In addition to trastuzumab, patients now have more effective alternatives because of additional HER2-targeted treatments. Another monoclonal antibody called Pertuzumab (Perjeta) binds to a different location on HER2 and is frequently used in conjunction with Trastuzumab to provide a dual blockade that inhibits HER2-driven cell proliferation more efficiently than either medication alone. With a upholding progression-free as well as survival rates, this combination has emerged as the gold standard for treating advanced and metastatic "HER2-positive breast cancer".

"Ado-trastuzumab Emtansine" and "Trastuzumab Deruxtecan" are two examples of "ADCs" that provide new options for affected individuals who has"HER2-positive tumours" that haven't responded to previous therapies. To lessen harm to healthy tissues and increase tolerance, T-DM1 delivers trastuzumab straight into HER2-positive cells in combination with a chemotherapeutic agent. Patients whose malignancies show lower amounts of HER2 or who have been resistant to prior HER2 therapies benefit most with trastuzumab deruxtecan, a next-generation ADC. This medication maximizes efficacy while preserving healthy cells by releasing its cytotoxic payload only inside HER2-expressing cells.[8]

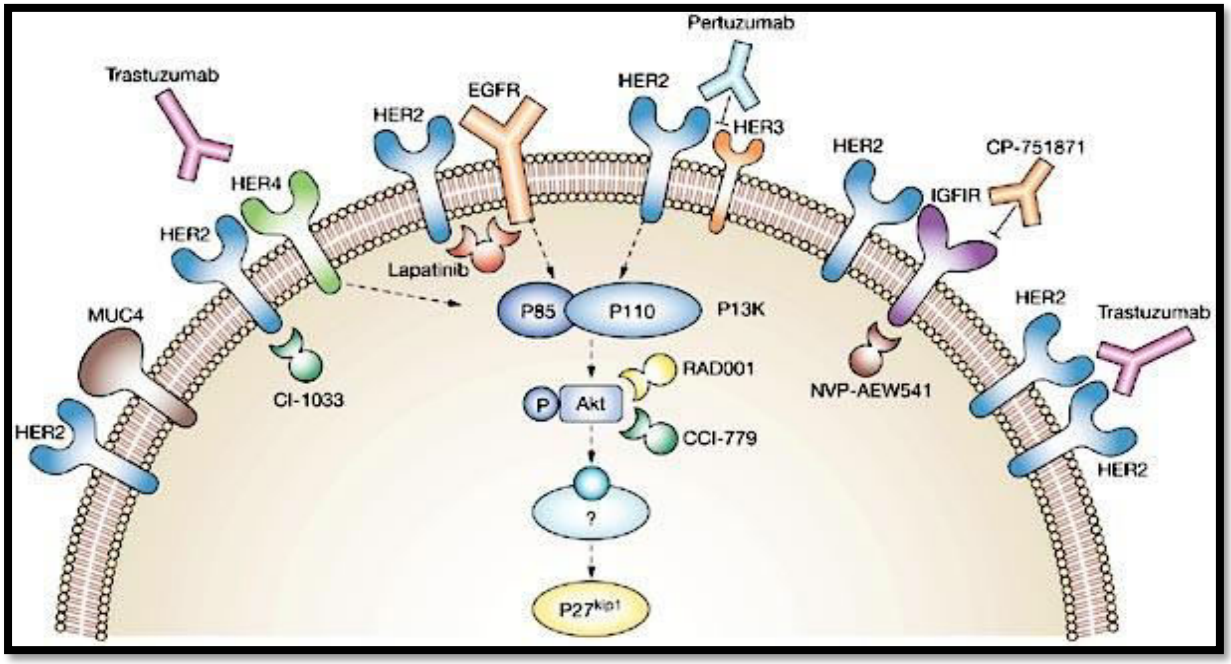

Fig 3 – HER2 Targeted Therapy[9]

❖ Application of Nanotechnology as Immunotherapy in Breast Cancers

The use of nanotechnology in immunotherapy for breast cancer is novel since it offers a number of ways to boost the immune system and precisely target cancer cells. The problems with conventional cancer treatments, such as toxicity to healthy tissues, limited effectiveness in tumours, and immune resistance, are lessened by the use of nanoparticles and nanomaterials in immunotherapy. Here's an overview of how nanotechnology is applied as immunotherapy in breast cancer:

➢ Nanoparticles as Immune-Activating Carriers in Breast cancer

Nanoparticles as immune-activating carriers helps the body's immune system in looking out the cancer cells and thereby eliminate these, opening up a promising novel path for breast cancer immunotherapy. These highly designed nanoparticles have the ability to transport immune-stimulating substances and cancer antigens, delivering them directly to the tumour microenvironment or exactly to immune cells. Through targeted delivery, dendritic cells—which are essential for triggering T-cells, the body's main defence against cancer—can be exposed to breast cancer antigens by nanoparticles. Activated T-cells identify and eliminate cancer cells, resulting in a long-lasting immune response that prevents breast cancer from recurring.

➢ Immune Checkpoint Blockade using Nanoparticle

Nanoparticle-based immune checkpoint blockage is one of the most promising novel therapy strategy for ''breast cancer'' that aiming to improvement ofidentification and combatingcapacity of defence system against cancerous cells. Proteins on immune cells called ''immune checkpoints'', like wise''PD-1'' and ''CTLA-4'', typically stop the response generated by immune system from becoming overactive, shielding healthy tissues from immunological assault. However, in order to avoid immune detection, breast cancer cells frequently take advantage of these checkpoints, allowing tumours to proliferate unchecked.Although these proteins can be effectively blocked by conventional checkpoint inhibitors, systemic treatment of these drugs frequently results in adverse consequences, including inflammation of healthy organs. By facilitating the targeted distribution of checkpoint inhibitors straight to the tumour microenvironment (TME), nanoparticles provide an answer. In order to ensure that immune checkpoint inhibitors reach the tumour site precisely, reduce off-target effects, and enhance safety, these nanoparticles are designed to release their therapeutic payload in response to particular triggers in the TME.

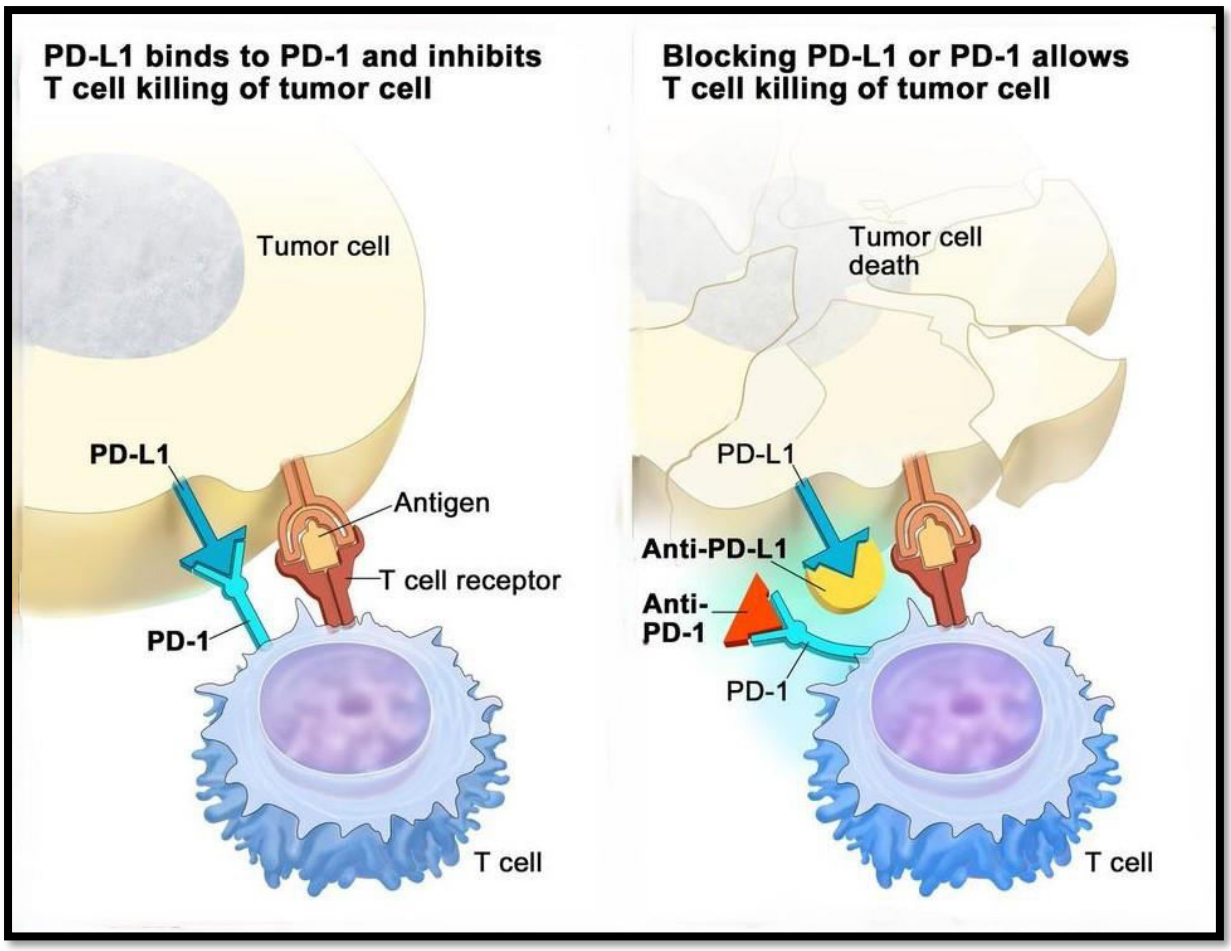

Fig 4- Immune Checkpoint Blockade using Nanoparticle[10]

- **Nanoparticle-Based "Breast Cancer Vaccines"**

"Breast cancer vaccines"which is based on nanoparticles, are a new immunotherapy approach that aims to stimulate the defence system for identification and combating breast cancer. The durability of the antigen, targeted administration, and adequate immune activation are problems with conventional cancer vaccines. By encapsulating cancer-specific antigens within nanoparticles, improving stability, and guaranteeing efficient delivery to critical immune cells, such as dendritic cells, which are necessary for triggering targeted immune responses, nanoparticle-based vaccines overcome these drawbacks. To effectively teach "T-cells" for identification and elimination breast cancer cells that possess certain antigens, these nanoparticles can be designed to release their antigen payloads only after they have reached particular immune cells. By creating immunological memory, this method offers a preventative approach that may help stop cancer from returning.[11]

Nanoparticle-based breast cancer vaccines work by using nanoparticles to prime the defence system for identification and combating breast cancer cells by delivering tumour-specific antigens directly to the immune system. First, breast

cancer antigens, like proteins specific to cancer cells, are encapsulated in nanoparticles to prevent their degradation and guarantee efficient distribution to dendritic cells, which are crucial for triggering immune responses. When the nanoparticles get to these cells, they carefully release the antigens. Dendritic cells successfully trained the defence mechanism in recognition of breast cancer cells as targets by processing these antigens before the"T-cells" on their surface.

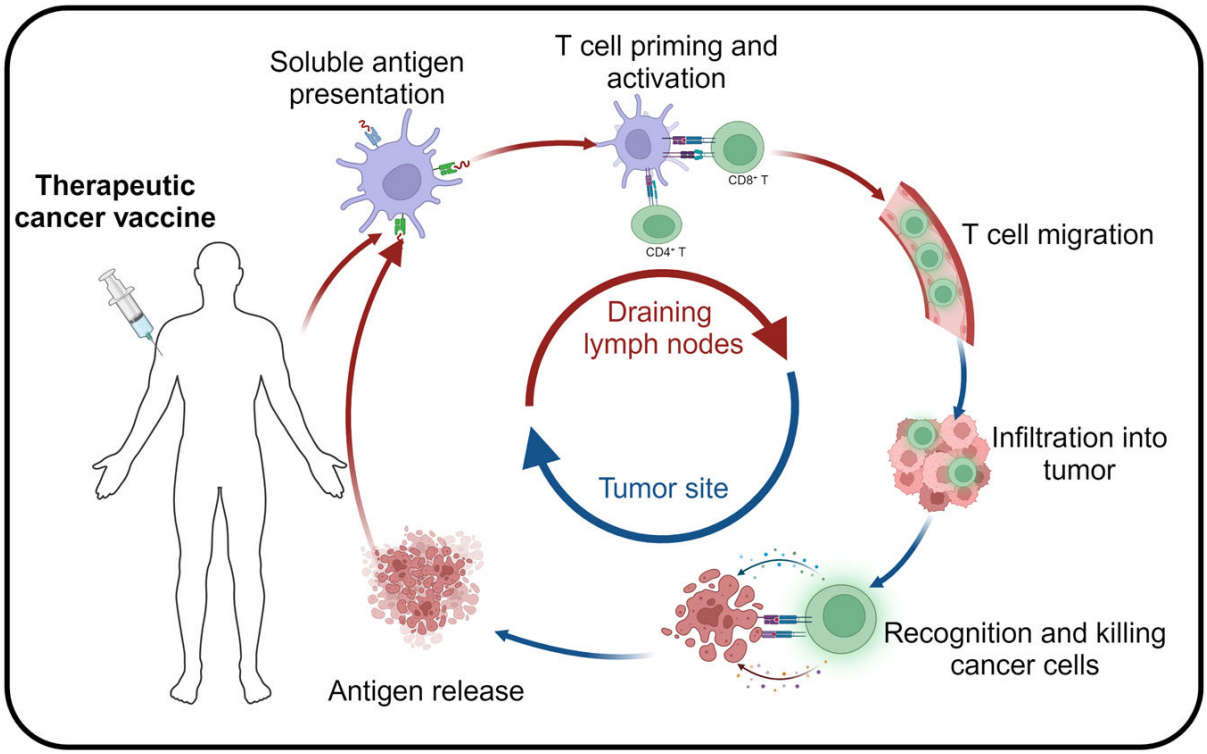

Fig 5- Nanoparticle Based Breast Cancer Vaccines[12]

- **"Nanoparticle based drug delivery in breast cancer"**

The method of drug delivery in "breast cancer" using nanoparticles is intended to minimize adverse effects on disease free tissue system while optimizing treatment effectivity and precisely targeting cancer cells. Anti-cancer medications are encapsulated in nanoparticles, which improves their absorption and prevents premature breakdown. Because of this encapsulation, the medications are guaranteed to stay stable in the bloodstream and reach the tumour location at higher quantities. Nanoparticles are frequently modified with ligands or antibodies that identify and bind to receptors that are highly expressed or unique on breast cancer cells, such as the HER2 or folate receptors, in order to enable targeted delivery. By facilitating selective binding and uptake by breast cancer cells, this surface alteration reduces off-target effects.

The "EPR" effect knows as characteristic of tumours with leaky blood arteries and inadequate lymphatic drainage, is exploited by nanoparticles once they reach the tumour. This mechanism enables nanoparticles to aggregate in the tumour tissue. Once inside the tumour microenvironment, nanoparticles have designed for meet up the reaction for a specific stimuli including acidic pH, enzymes, or redox conditions that are frequently seen in tumours. The nanoparticles' regulated, localized release of their therapeutic payload is made possible by their stimulus-sensitive architecture, which raises the drug's concentration only in cancer cells.

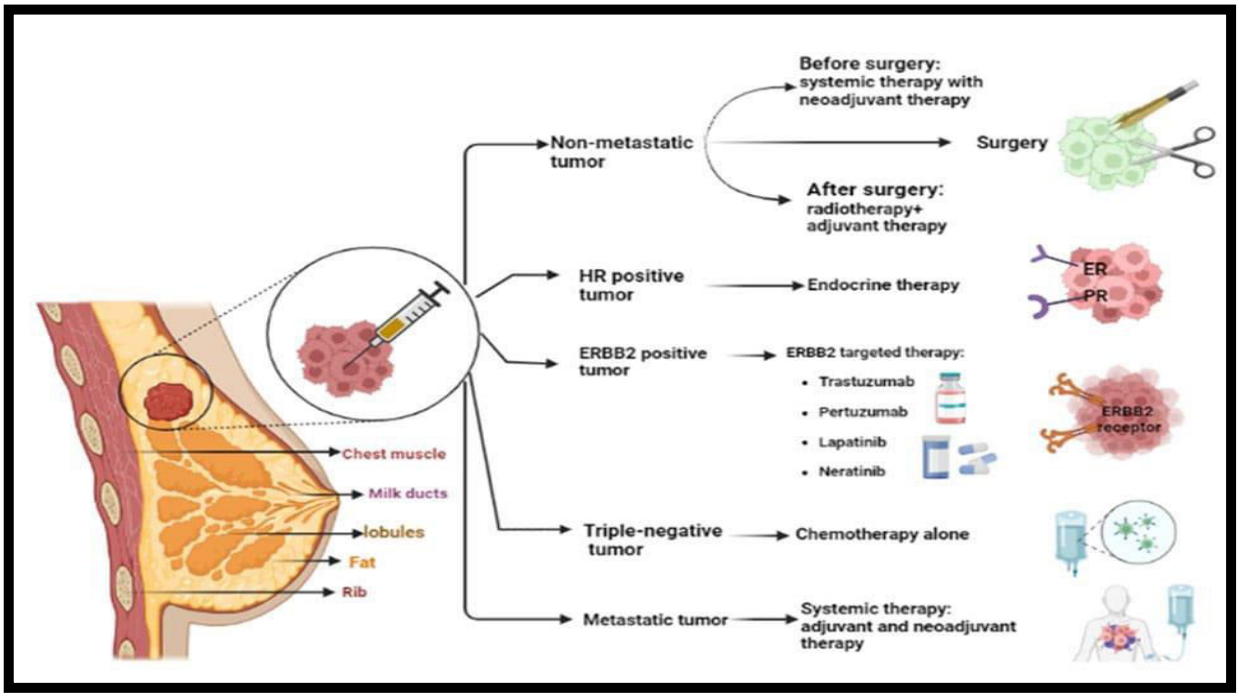

Fig6–"Nanoparticle-based drug delivery in breast cancer"[13]

- **Nanoparticles for Immunoimaging & Real-Time Monitoring**

Nanoparticles are transforming real-time monitoring and immunoimaging in breast cancer, improving diagnostic capacities and enabling individualized treatment plans. It is possible to construct these nanoscale particles to carry imaging agents, such as magnetic nanoparticles, radionuclides, or fluorescent dyes, which would enable the highly sensitive early identification of malignancies. Nanoparticles can selectively bind to breast cancer cells when functionalized with antibodies or ligands that target tumour-associated antigens. This enhances the contrast between malignant and healthy tissues during imaging operations. Clinicians can see the tumour's size, location, and even heterogeneity because to this specificity, which is essential for precise diagnosis and therapy planning.

Nanoparticles can be used not just for imaging but also for real-time tracking of the tumour's reaction to treatment. Nanoparticles provide simultaneous therapy and monitoring by combining medicinal and imaging agents. For example, imaging techniques such as ''MRI'' and ''PET'' can monitor the distribution and build-up of drug-loaded nanoparticles within the tumour, offering important information about how well the treatment is working. Clinicians can use this capability to measure the tumour's response over time without intrusive procedures, which is especially helpful when assessing the efficacy of new medicines.

- **CAR T-Cell Therapy**

A novel immunotherapy called ''CAR T-cell therapy'' is depicted potential on medical management of breast cancer, all those it is still primarily in the experimental stage,by altering a patient T-cell this therapy can enhances they are ability to identify and combat cancer cell however, because breast cancer are solid tumours CAR T-cell therapy poses specific challenges the intricate micro environment surrounding breast cancer may hamper CAR T-cells' ability to travel and function making it more difficult for them to target the malignancy.Additionally,it is challenging to identify appropriate to antigen target in breast cancerbecause many of the surface protein found on health cells. This raises the possibilityof off-target consequences, in which normal tissue is inadvertently attack by CAR T-cell.

To increase the effectivityof ''CAR T-cell therapy'', researchersare researching a number of approaches. A long with MUC1 and ROR1, which have been identified in different sub types of breast cancer, potential targets including ''HER2'' that is overexpressedin some more violentforms of ''breast cancer'', are also being studied. Dual- targeting CAR T-cell are one of the most sophisticated strategist being research to improved specificity by requiring the recognitions of two antigens, which lowers the possibility off-target effect. ArmouredCAR T-cell are an additional strategy that can assist combatthe immunosuppressiveenvironment of solid tumoursby secreting cytokines. These modified ''CAR T-cell'' are currently undergoing in a number of clinical phases detection for individual with metastatic or resistant to treatment breast cancer. Despite the fat ''CAR T-cell therapy for breast cancer''is still in its infancy, these developments give patients with advance breast cancer hope for better outcome and a wider range of applications for the treatment.[14]

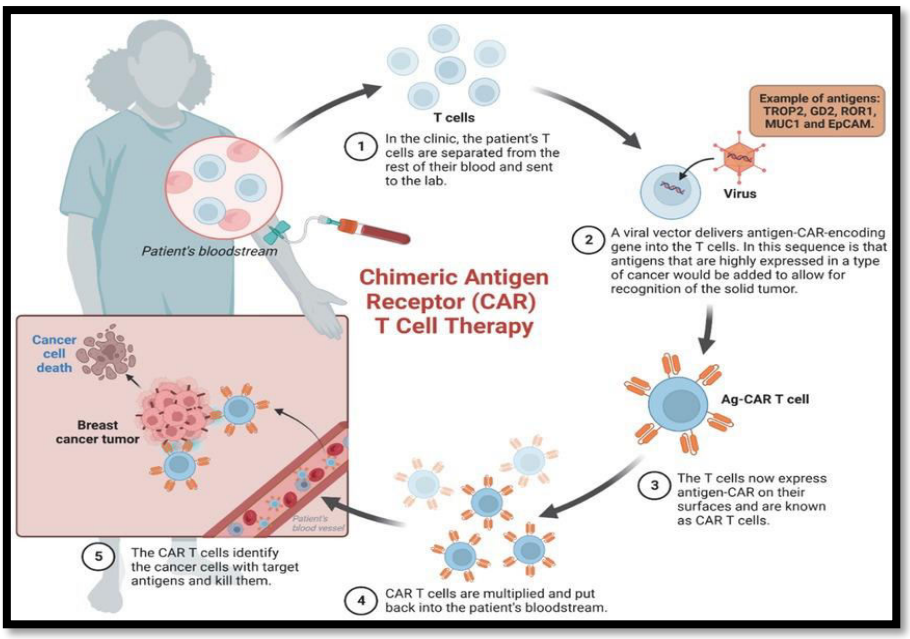

Fig 7 – Application of CAR T-cell therapy[15]

- **Combination Therapy**

Several treatment modalities are imploding in combination therapy for breast cancer in order to increase effectiveness and decrease resistance. These approaches are design to target particular subtype of breast cancer as well as TNBC, HER2-positive and hormone receptor- breast cancer. Combination therapies enable a multi-targeted tactics, increasing the effectiveness of therapy and lowering the probability of resistance that single that agent therapies frequently generate.[16] Hormone therapy and CDK4/6 inhibitors work well together to treat hormone-positive breast cancer, that relies on hormones like estrogen and progesterone to thrive, while the CDK4/6 inhibitor purveyance cancer cell from moving through the cell cycle and stope there are both.

Chemotherapy is frequently employed in conjunction with HER2-targeted medication. These approach tackles the cancer by killing dividing cells directly and also by inhibiting HER2 signalling, which encourages cell development. Combination therapy are even more crucial for TMBC since its therapeutic option and more limited dew to its lack of both hormonal receptor and HER2. Combining immune checkpoint inhibitors, which aid the defence mechanism in identification and elimination of cancer cells, with chemotherapy is a promising treatment for TMBC.[17]

❖ **Neoantigen vaccines to improve cancer personalized immunotherapy**

Neoantigen vaccines, which offer highly targeted, customized therapies that target specific mutations within a patient's tumour, are transforming personalized immunotherapy. Neoantigen vaccines target solely neoantigens, which are modified proteins found only in cancer cells, in contrast to traditional treatments which frequently target both healthy and diseased cells. These neoantigens are identified by mapping the distinct mutational makeup of a patient's tumour through sequencing. The neoantigens that are most likely to trigger a robust immune response are then predicted using sophisticated bioinformatics methods. The selected neoantigens are then manufactured and combined to create a customized vaccine that, when given, stimulates the immune-defence system, especially ‘‘T-cells’’, for identification and combating of malignant cells that exhibit these distinct indicators.[18]

Neoantigen vaccines are frequently used in clinical trials in conjunction with ‘‘immune-checkpoint inhibitors’’, such as ‘‘PD-1’’ or ‘‘CTLA-4’’ blockers, which improves defence system's capacity for identification and reaction with cancer cells. The efficacy of these vaccines can also be enhanced by combining them with therapies like radiation or chemotherapy, which can make tumours more visible to the immune system.[19] Neoantigen vaccines are still in the experimental stage, but preliminary results indicate that they may have fewer adverse effects, enhance immune responses, and increase therapeutic precision.Neoantigen vaccines have the potential to revolutionize cancer care as part of the growing field of personalized medicine by providing patient-specific, long-lasting medicines that precisely match the unique mutational landscape of each malignancy.

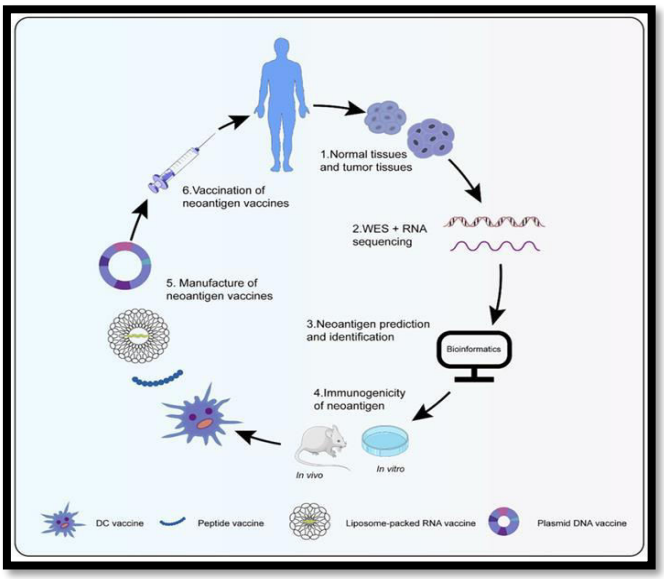

Fig 8 – Preparation of Neoantigen vaccines[20]

❖ **Challenges in Immunotherapy for Breast Cancer**

- In comparison to other tumours, immunotherapy for breast cancer is limited by a number of serious issues. The very low mutation burden in breast cancer, which results in fewer neoantigens available for immune detection, is a prime obstacle.
- Breast-cancer is less visible to the immune system than melanoma or lung cancer, which have high mutation rates and hence a lot of neoantigens. As a result, it is more difficult to trigger a robust immunological response.[21]
- The immunosuppressive tumour microenvironment (TME) that breast cancer frequently produces is made up of cells such as ''myeloid-derived suppressor cells'', ''regulatory T-cells'', as well as''immunosuppressive cytokines'' that actively suppress immune function, enabling the tumour to avoid detection.

- Immunotherapy techniques are further complicated by the fact that different breast cancer subtypes respond differently to immunotherapy, including ''HER2-positive'' ''hormone receptor-positive'', as well as''triple-negative breast tumours''. [22]
- Given its marginally increased immunogenicity, TNBC exhibits the greatest promise for immunotherapy; yet, response rates are still low. Patient diversity needs highly customized methods, which complicates the use of broad, standardized immunotherapy.
- Because immunotherapy activates the immune system, it may damage healthy tissues, resulting in immunological-related side effects.
- Due to high cost and potential inaccessibility to certain individuals the broad spectrum application of immunotherapy is quite low till now.[23]

❖ **Recent Clinical Trials**

✓ **KEYNOTE-355**- Pembrolizumab, an immune checkpoint inhibitor, plus chemotherapy were tested in the ground-breaking KEYNOTE-355 trial to treat ''mTNBC'' or ''metastatic triple-negative breast cancer'', which is a difficult and aggressive subtype. Introducing this combination to the patients who has PD-L1 positive tumours was specially investigated in this trial, which revealed that patients with high PD-L1 affection had considerably better ''PFS'' or''Progression-free survival''.[24]The FDA approved ''Pembrolizumab plus Chemotherapy'' for PD-L1 positive mTNBC thanks in large part to KEYNOTE-355's findings, opening up a new treatment option. In order to improve outcomes for aggressive breast cancer subtypes, this trial emphasizes the importance of tailored immunotherapy and biomarker-guided treatment.

- ✓ **DESTINY-Breast01-** In these phenomena, patients with ‘‘HER2-positive’’ metastatic breast cancer who had received intensive treatment before were evaluated for the safety and effectiveness of ‘‘Trastuzumab Deruxtecan’’ or‘‘T-DXd’’, a new antibody-drug combination.[25] In contrast to conventional treatments, this trial showed that T-DXd considerably increased overall response rates and ‘‘PFS’’ or ‘‘Progression-free Survival’’, especially in patients with extremely resistant illness. Notably, the drug's special architecture enables precise delivery to cancer cells by combining a strong chemotherapeutic payload with HER2-targeting capabilities. The results of DESTINY-Breast01 led to the regulatory approval of T-DXd, demonstrating improvements in targeted therapy and providing a potent new alternative for advanced ‘‘HER2-positive’’ breast cancer.[26]

- ✓ **SWOG S1314-** In these SWOG S1314-trial, patients having‘‘high-risk, early-stage breast cancer’’ were evaluated using a gene expression-based test known as ‘‘RCB’’or ‘‘Residual Cancer Burden’’, score to forecast their reactions to preoperative chemotherapy.[27] The experiment sought to determine if the RCB score could accurately predict treatment results by comparing changes in tumour biology before and after neoadjuvant (pre-surgical) chemotherapy. The study was noteworthy since it assessed common chemotherapy regimens and covered a broad spectrum of breast cancer subtypes.[28] By identifying patients, most likely to beneficiary by Neoadjuvant treatment and directing individualized treatment methods, the findings from SWOG S1314 have improved our understanding of prognostic indicators in breast malignancy.

- ✓ **Vaccine-Trials** - Vaccine trials for breast malignancy aim to target particular tumour-associated antigens to activate the defence system for identification and defence cancer cells. These vaccinations, which were frequently created for individual patients with advanced or high-risk breast-cancer, are intended to increase survival rates and decrease recurrence.[29] HER2, MUC1, and other antigens commonly expressed in breast cancers are being targeted by vaccinations in key trials. By stimulating T cells to fight cancer cells, promising candidates such as the NeuVax vaccination are shown the ability to stop recurrence. In addition to evaluating safety and efficacy, these trials aid in the improvement of tailored immunotherapy strategies, raising the prospect of long-term cancer immunity.[30]

❖ Conclusion

New developments in immunotherapy for breast cancer are revolutionizing therapeutic strategies, particularly for aggressive subtypes such as HER2-positive and triple-negative tumours. Significant improvements in patient outcomes have

been shown by breakthroughs like immune checkpoint inhibitors and tailored therapy like trastuzumab deruxtecan. Further increasing the likelihood of successful treatments are ongoing studies on cancer vaccinations and the application of biomarkers for individualized care. In addition to raising survival rates, these advances seek to enhance people's quality of life. Although there are still obstacles to overcome, the developing field of immunotherapy has enormous potential for highly individualized, efficient breast cancer treatments.

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