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Review Article

# Advancing Breast Cancer: Strategies to Counteract Taxane Resistance in Her2-Positive and Triple-Negative Breast Cancer

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## ABSTRACT

Resistance is one of the major problems in chemotherapy during Breast Cancer (BC) treatment. Earlier treatments, such as radiation, surgery, and chemotherapy including taxane-based therapies like paclitaxel and docetaxel, play a crucial role in managing BC, particularly in aggressive subtypes like Human Epidermal Growth Factor Receptor-2 (HER-2) positive and Triple-Negative Breast Cancer (TNBC). Taxanes disrupt cell division by stabilizing microtubules, inducing apoptosis in rapidly dividing cancer cells. However, challenges arise due to drug resistance mechanisms, including alterations in microtubule dynamics, drug efflux, mutations in tubulin, Autophagy and survival pathway activation. Recent advancements in nanotechnology, such as nanoparticle-based drug delivery systems, have shown effect result in improving solubility, stability, and tumor selectivity, enhancing their therapeutic efficacy. By enabling targeted therapy, combination therapy and overcoming multidrug resistance, nanomedicine offers a promising approach to improve outcomes in resistant BC cases. This review examines the mechanisms of action of taxanes and resistance caused and discusses the role of various therapeutic strategies to overcoming treatment barriers in BC.

**Keywords:** Paclitaxel (PTX), Docetaxel (DTX), Multidrug Resistance (MDR), Nanotechnology, HER2-positive, Triple-negative Breast Cancer (TNBC).

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## INTRODUCTION

Breast Cancer (BC) continues to be the most frequently identified malignancy among females and serves as a significant factor in cancer-associated mortality on a global scale.[1] According to WHO in 2022, globally there were 2.3 million women identified with BC and 670000 deaths. BCs occur 99% in women and 0.5-1% occur in men.[2,3] BC initiates from the unchecked proliferation of cells within the breast parenchyma, predominantly occurring in the mammary ducts or lobular structures, and exhibits considerable heterogeneity for its molecular subtypes, which encompass luminal A and B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC).[4,5] These subtypes are classified based on the presence or absence of hormone receptors, specifically Progesterone Receptor (PR), Estrogen Receptor (ER) and Human Epidermal Growth Factor Receptor 2 (HER2), each linked with different clinical scenarios and variable therapeutic response.[6]

The classification of BC progresses from non-invasive (stage 0) to metastatic (stage IV) malignancy, wherein early-stage neoplasms (stages I and II) are frequently managed with a curative intent. In contrast, advanced stages (III and IV) need more rigorous and multifaceted therapeutic interventions.[7] Standard treatments involve surgery, chemotherapy, immunotherapy, radiation therapy combination and targeted therapies. Surgery is typically the basis for early-stage disease often followed by radiation to reduce the risk of local recurrence.[8,9] Chemotherapy is critical in addressing aggressive or high-risk cases and is especially valuable for treating advanced or metastatic BC.[10] BC is a heterogeneous and multifaceted disease amongst all, HER-2 and TNBC stand out as two aggressive subtypes with unique biological and clinical features.[11,12] HER2-positive BC, accounting for approximately 15-20% of cases, is characterized by overexpression or amplification of the HER2 gene, which drives rapid tumor growth and metastasis.[13] On the other hand, TNBC representing 10-15% of BC cases, is defined by the absence of estrogen, progesterone and HER2 receptors. This receptor-negative profile limits treatment options and is associated with a highly proliferative and invasive tumor phenotype.

Taxanes involving Paclitaxel (PTX) and Docetaxel (DTX), have become pivotal agents in managing both HER2-positive and TNBC subtypes due to their effective mechanism of action.[14] Taxanes

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induce cell cycle arrest and apoptosis by stabilizing microtubules and disrupting the mitotic process, effectively targeting the rapid proliferation characteristic of these cancers.[15,16] In HER2-positive BC, the integration of taxanes with HER2-targeted therapies has revolutionized treatment, offering synergistic effects that significantly enhance survival outcomes.[17,18] For TNBC, taxanes are a basis of systemic chemotherapy, exploiting the high mitotic index of these tumors to achieve tumor regression.[19] Despite their efficacy, both subtypes face the common challenge of resistance to taxanes-based regimens.[20] Mechanisms such as overexpression of drug efflux transporters, alterations in tubulin dynamics, activation of survival pathways like PI3K/Akt/mTOR and autophagy-mediated stress adaptation contribute to the limited effectiveness of taxanes over time.[21,22] These insights underscore the importance of taxanes in BC therapy while highlighting the need for continued innovation to overcome resistance and maximize therapeutic benefits for patients with these aggressive subtypes.[23] The determination of taxane resistance in BC has driven a wide range of research. Emerging approaches aim for formulation include the use of nanotechnology like (nanocarriers, nanoparticle) to enhance delivery of drug and stability, combination therapies and targeted therapy that act on multiple pathways and innovations in personalized medicine that tailor treatment to individual genetic profiles.[24,25] These advancements hold the potential to not only enhance the efficacy of taxane-based regimens but also improve overall outcomes for patients facing resistant forms of BC.[26]

The pharmacokinetics and pharmacodynamics associated with PTX and DTX, integral to BC treatment, reveal marked variability.[27,28] Their limited solubility necessitates the use of solvents such as polysorbate-80 (for DTX) and Cremophor EL (for PTX) which can cause hypersensitivity reactions that are typically mitigated through premedication protocols.[29,30] Both agents demonstrate dose-dependent pharmacokinetics, however PTX is characterized by non-linear kinetics attributed to saturable protein binding.[31,32] The metabolism of these compounds in the liver occurs via CYP2C8 (for PTX) and CYP3A4 (for DTX), necessitating the adjustment of dosages in patients with liver impairment to prevent potential toxicity.[33]

This review highlights the need for ongoing research into therapeutic innovations to address advancing BC complications particularly in TNBC and HER2 and overcome treatment resistance through optimization of taxanes-based therapeutic regimens by various methodologies enhancing therapeutic effectiveness while mitigating the adverse effects, subsequently improving clinical outcomes in patients.

## MECHANISMS OF ACTION OF TAXANES IN BREAST CANCER THERAPY

PTX and DTX are potent anticancer agents primarily used to treat breast, ovarian and other malignancies. They exert their therapeutic effects, as described in Figure 1 by disrupting microtubule dynamics, inducing apoptosis, by targeting cancer cells, influencing microenvironment of cell which is essential for cell division and various intracellular processes.[34]

### Microtubule Stabilization and Disruption of Dynamic Instability

The polymerization and stabilization are promoted by binding of PTX to microtubules, which results in a G2/M phase arrest of the cell cycle. It prevents the normal depolymerization of microtubules and disrupts the dynamic equilibrium required for accurate chromosome segregation during cell division.[27] DTX stabilizes microtubules which lead to the inhibition of the normal disassembly of mitotic spindle and lead to prolong mitotic arrest in cancer cell. The arrest prevents the completion of mitosis and causes cell death.[35]

### Induction of Apoptosis through Bcl-2 Phosphorylation

Apoptosis often governed by the B-cell Lymphoma-2(Bcl-2) protein family, which encompasses both pro-apoptotic and anti-apoptotic constituents.[36] PTX and DTX phosphorylates Bcl-2, this phosphorylation activates pro-apoptotic proteins such as Bax, which compromise the integrity of the mitochondrial membrane.[37,38] The resultant destabilization release cytochrome-c from the mitochondria into the cytosol, thereby facilitate disassembly of cellular constituents, ultimately resulting in apoptosis.[39] PTX overcome Bcl-2 mediated resistance to apoptosis also by Endoplasmic Reticulum (ER) calcium release.[40]

### Targeting Cancer Stem Cells (CSCs) and Influencing the Tumor Microenvironment

PTX inhibits pathways like SRC-Kinase signaling which is important for CSCs maintenance and Epithelial to Mesenchymal Transition (EMT) which lead to suppression in the proliferation and enhance chemotherapeutic activity.[41] PTX influences TME by inhibiting proliferation, stimulating immunological cell death, by activating natural killer cells and CD8+T lymphocytes.[42] DTX combination with Notch inhibitors i.e. γ-secretase inhibitors or Hedgehog inhibitors reduces CSCs population and overcome resistance in TNBC.[43]

### Modulation of Signaling Pathways

PTX disrupts the PI3K/Akt/mTOR pathway by inhibiting Akt activation, reducing mTOR phosphorylation and slowing cancer cell proliferation while promoting apoptosis. It also activates the JNK pathway, enhancing apoptosis through pro-apoptotic gene expression and Bcl-2 inhibition.[44,45] PTX and DTX inhibits the Akt/mTOR pathway and suppress NF-κB signaling, weakening cancer cell survival mechanisms.[46-48] DTX modulates the TGF-β pathway, potentially limiting BC metastasis by reducing EMT. p53 also get activated (tumor suppressor) drives cell cycle arrest and apoptosis.[49,50] In HER2 and TNBC, where pathways like PI3K/Akt, NF-κB, and TGF-β are frequently dysregulated, taxane's ability to inhibit these survival and metastatic pathways is particularly effective. This dual action reduces tumor growth, enhances treatment responses, and lowers recurrence risk.[51-53]

**Table 1: Describes the molecular mechanisms of taxanes resistance in HER2 and TNBC.**

| Factor | Resistance | TNBC | HER-2 | Therapeutic Approaches | References |
|---|---|---|---|---|---|
| P-glycoprotein (Pgp) | Efflux drugs, ↓ intracellular drug. | ↓ drug bioavailability and efficacy. | ↓ drug bioavailability and efficacy. | Use inhibitors (verapamil), nanoparticle, combination therapies. | 61,95 |
| Tubulin | Structural protein targeted by microtubule inhibitors; ↓ drug binding. | Disrupted microtubule dynamics; + alter drug sensitivity. | Tubulin dynamics alteration ↓sensitivity. | Targeting specific tubulin dynamics or use non-tubulin dependent therapies. | 90,97 |
| β-Tubulin Isotypes | Biii-Tubulin are linked to drug resistance due to ↓ drug-tubulin interaction. | Overexpression of βiii-Tubulin leads to resistance. | Upregulation of βiii-Tubulin. | Tubulin-specific inhibitors or combination with non-taxane agents. | 90,99 |
| Mutation of β-Tubulin | Alter microtubule stability and drug binding, leading to ↓efficacy. | B-tubulin mutations are often observed in resistant TNBC tumors. | Resistance to HER-2 therapies indirectly by ↓interaction with taxanes. | Combination therapies targeting complementary pathways. | 100,101 |
| p53 tumor protein | ↓Effectiveness of drug and promote tumor growth. | Mutant p53 is a hallmark of TNBC, promoting resistance and tumor progression. | Disrupts apoptosis pathways, reducing sensitivity to HER-2 targeted therapies. | Reactivation of p53 via genes (proline rich membrane anchor 1) or alternative apoptosis-inducing strategies. | 102,103 |
| Apoptosis | Involve evasion of apoptosis. | Dysregulated apoptosis pathways are central to TNBC resistance and survival. | Overexpression of anti-apoptotic protein, impairs apoptosis. | Bcl-2 inhibitors, mitochondrial-targeted therapies. | 63,104 |
| Cell Cycle | Alterations allow cell division and ↓ drug efficacy. | Disruption of cell cycle checkpoints contributes to the treatment. | Overexpression of cyclin can impair cell cycle-dependent drug action. | Use cyclin dependent kinase inhibitors or targeting cell cycle regulation. | 66,105 |

### Induction of Autophagy

PTX induces autophagy by inhibiting the various signaling pathway, activating autophagy-related genes like beclin-1 and Atg5 and increasing Reactive Oxygen Species production. While moderate autophagy helps BC cells adapt, excessive autophagy induced by PTX leads to autophagic cell death, amplifying its anti-tumor effects.[54,55] DTX also induces autophagy through pathway inhibition and activation, microtubule stabilization and mitotic arrest. It also affects the p62/SQSTM1 pathway, promoting autophagosome accumulation and further cancer cell death.[56,57] Despite its cytotoxic effects, early autophagy may protect cancer cells, prompting the exploration of combination therapies using taxanes and autophagy inhibitors to improve BC treatment outcomes.[58,59]

## TAXANE RESISTANCE IN BREAST CANCER

The management of BC often faces significant challenges due to a variety of resistance mechanisms as shown in Figure 2, particularly concerning taxanes, which are critical chemotherapeutic agents. Even though several molecular mechanisms of drug resistance have been reported as mentioned in Table 1, we only have focused on taxanes resistance that occurs in BC.[60]

### Efflux Transporters

Resistance cause by Efflux Transporters causes expel of chemotherapeutic agents from cancer cells, thereby decreasing therapeutic efficacy and intracellular concentrations.[61] Activation of HER2 can modulate transporters. The downstream signaling pathways, Hypoxia and TME can upregulate the efflux transporters.[62] PTX and DTX are influenced by efflux transporters particularly ATP-Binding Cassette (ABC) family such as P-glycoprotein (P-gp) i.e. ABCB1(MDR1) and ABCC3(MRP3).[63] P-gp eliminates PTX by systemic circulation as it restricts oral uptake.[64,65]

### Altered Microtubule Dynamics

Increased level of specific β-tubulin (isotypes), mainly class III, associated with reduced (PTX and DTX) drug binding and altered microtubule stability.[66] Alteration hampers the ability of PTX to effectively stabilize microtubules, leading to diminished therapeutic efficacy of the drugs.[67] Mutations in β-tubulin isotypes, such as β1-tubulin, have been found in cancer cells that are resistant to taxanes. For example, ovarian cancer cells with mutations A364T and F270V and prostate cancer cells with mutation F270L that are resistant to DTX.[68,69] But as such there are less evidence to confirm mutation of β1-tubulin has effect on PTX resistance in BC. Amelia *et al.* reported that these structural variations are expected to exert an influence on clinical outcomes in a manner analogous to that of modified tubulin expression.[70] Tua is potential biomarker of taxanes which bind and stabilizes microtubules in BC.[61] High tua shows poor PTX response in HER-2.[71]

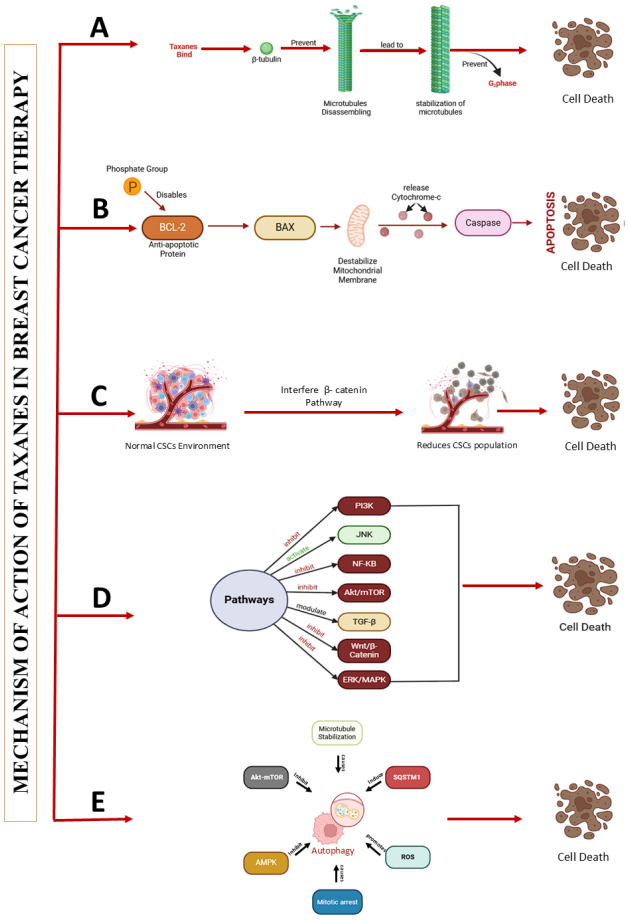


**Figure 1:** Represent the different mechanism of action of taxanes in BC therapy. Where A - Microtubule Stabilization and Disruption of Dynamic Instability, B - Induction of Apoptosis through Bcl-2 Phosphorylation, C - Targeting Cancer Stem Cells (CSCs) and Influencing the Tumor Microenvironment (TME), D - Modulation of Signaling Pathways, E - Induction of Autophagy.

## Enhanced DNA Damage Repair

Enhanced mechanisms of DNA damage repair can be observed in the resistance to chemotherapeutic drugs like PTX and DTX, as they enable cancer cells to withstand and proliferate despite the genotoxic effect of chemotherapy.[72] Taxanes induce DNA damage through microtubule stabilization, various DNA repair pathways get activated, including Non-Homologous End Joining (NHEJ) and Homologous Recombination (HR).[73]

## Cell Cycle Modulation

PTX and DTX disrupts microtubule dynamics lead to cell cycle arrest; prolonged arrest may lead to polyploidy which lead to resistance and can give rise to aggressive cancer phenotypes.[35,74] In Zhang, Zhe *et al.* study, Gene Set Enrichment Analysis (GSEA) showed significant association between G Protein Signaling Modulator 2 (GPSM2) and cell cycle related gene sets. GPSM2's role in PTX-induced G2 phase arrest in BC cells was examined, revealing that knockdown of GPSM2 markedly diminished this arrest.[75]

## Apoptosis Inhibition

Changes in the intrinsic pathway of apoptosis constituted an essential component in the development of resistance to PTX, which was acquired by either a decrease in proapoptotic Bcl-2 proteins or an increase in antiapoptotic Bcl-2 proteins.[76] Bcl-2 proteins, Inhibitors of Apoptosis (IAPs) such as X-linked inhibitor of apoptosis protein can also block the activation of caspases, further lead to resistance against taxane-induced apoptosis.[77] MiR-129-3p microRNA overexpression in DTX-resistant cells decreases apoptosis by targeting centriolar coiled coil protein i.e. CP110, thus reduces cell cycle arrest. CP110 downregulation inhibits apoptosis and lead to resistance.[78]

## Stem Cell-like Properties

BC steam cells such as CD44, CD24 play a crucial role in TNBC.[79] PTX resistance increases stem cells CD44, CD24.[80] TME amplify stem cell-like features by providing supportive signals that protect these cells from the cytotoxic effects of PTX and DTX.[81] Aldehyde dehydrogenase-1 increases in neoadjuvant chemotherapy. Epigenetic modifications not only acquire stem cell-like properties but also in altering gene expression profiles that promote survival and therapeutic resistance.[82] Dysregulation of checkpoint proteins involve either overexpression or functional alterations that permit cancer cells to continue advancing through the mitotic phase, despite the presence of errors that prompt cell cycle arrest.[83]

## Enhanced Survival Signaling

PTX and DTX resistant cells lead to the activation of signaling pathways (NF-κB, PTEN/PI3K/AKT/mTOR, JAK/STAT) facilitate the removal of the cytotoxic effects.[84] TNFR2 signaling and Tumor Necrosis Factor alpha (TNF-α) increases NF-κB activation which lead to cell survival even in drug exposure.[85] Resistance to PTX activate HER2/β-catenin which enhance survival of cancer cells.[86] MiR-145 level reduces DTX resistance of BC cells, target AKT3 directly and inhibit pathway(PI3K/AKT).[87] PTX and DTX resistance can occur due to TNF toxicity pathway.[87] mTOR signaling is associated with the resistance to HER-2 BC its activation can lead to PI3K pathway mutation.[88,89] JAK2/STAT3 signaling cascade mediates the resistance, partially through the mechanisms of cAMP/PKA signaling and a transition in cellular states, which can be effectively mitigated by the application of PTX in conjunction with JAK2 inhibitors.[90]

## Drug Metabolism

Alterations in drug metabolism, particularly through enzymes belonging to the Cytochrome P450 (CYP) family, have emerged as critical factors contributing to PTX and DTX resistance in BC.[91] CYP3A4 has been reported as the main enzyme responsible for the metabolism of PTX and DTX.[92] High expression levels of CYP3A4 in cancer cells can cause increase in the metabolism of these drugs, thereby reducing their effectiveness and contributing to therapeutic resistance.[93,94]

# STRATEGIES TO OVERCOME TAXANES RESISTANCE

Although therapeutic management of BC employing Taxanes has faced various huddles however, a range of innovative strategies are developing to mitigate this concern as shown in Table 2. Strategies involve novel pharmaceutical interventions, combinational treatment

protocols and targeted molecular approaches which ultimately aim to increase the therapeutic efficacy of taxanes, including PTX and DTX in BC.

## Nano-Medicine Based Approaches

Drug therapies based on nanomedicine, such as Abraxane®, liposomes, and nanoparticles, offer a promising way to treat BC patients that have become resistant to taxanes.[106,107] This strategy reduces adverse effects and addresses MDR mechanisms by improving the effectiveness of chemotherapeutic drugs like PTX through the use of nanoparticle-based drug delivery systems.[108] Drug solubility and stability can be enhanced via nanoparticles, which can target tumor regions passively or actively, enhance bio-availability, decreases toxicity and can overcome drug resistance mechanism.[109] Nab-PTX is an approved nanoparticle albumin bound PTX.[110] Utilizing nanoparticles to deliver PTX alongside other agents like doxorubicin or nano-quercetin has shown the potential to enhance therapeutic outcomes and reduce recurrence.[111] Verapamil and PTX co-encapsulation in solid lipid nanoparticles shown potential for BC as a controlled-release formulation.[112] While nano-medicine offers significant advancements in overcoming taxane resistance, challenges such as cost-effectiveness and the need for extensive clinical validation remain critical considerations in its broader application in BC therapy.[113]

## Targeted Therapies

Targeted therapy using taxanes, particularly PTX, has shown promise in overcoming resistance in BC treatment.[114] Targeted therapies, including trastuzumab (Herceptin) and pertuzumab (Perjeta), interact with HER2, inhibiting signaling pathways and resulting in diminished tumor proliferation and enhanced patient prognoses.[115] Empirical studies have substantiated that these therapeutic agents, particularly when administered in conjunction, substantially reduce recurrence rates and improve overall survival among patients diagnosed with HER2-positive BC.[116] PTX and gemcitabine co-delivery via a self-assembling nanoparticle targeted treatment showed promising result.[117] Innovative therapeutic approaches are also being investigated for TNBC, a variant that currently lacks targeted therapeutic modalities. Recent advancements encompass the application of immune checkpoint inhibitors and Polyadenosine diphosphate Ribose Polymerase (PARP) inhibitors are effective in causing cell death in BC mutant cells, which have exhibited potential in clinical environments.[118]

## Combination Therapies

Combination therapy for BC, particularly involving taxanes, has gained importance due to its ability to enhance therapeutic efficacy and mitigate MDR.[119] This approach integrates various agents to target multiple pathways, thereby improving patient outcomes. Chemotherapeutic drugs like atezolizumab, bevacizumab given in combination therapy with taxanes have shown effective therapeutics outcome in TNBC.[120] Nab-PTX combination with carboplatin and gemcitabine has also shown clinical benefit.[121] Hendler *et al.* reported that taxanes with vinorelbine in conjunction with trastuzumab and pertuzumab for HER-2 showed progression-free survival and overall survival.[122] Everolimus and PTX combination also found to be effect for the treatment.[123] Menghuan Li *et al.* reported PTX and apigenin (flavonoid) co-administration overcomes the resistance.[124] Combination therapies often demonstrate lower toxicity compared to monotherapies, enhancing patient tolerance. Despite the promising effect of combination therapies, challenges such as identifying synergistic drug pairs and managing some side effects remain an important challenge to overcome.[125] Although it shows enhancing treatment efficacy but it is necessary to determine the patient-specific responses and complexities of drug interactions to optimize therapeutic strategies.[126]

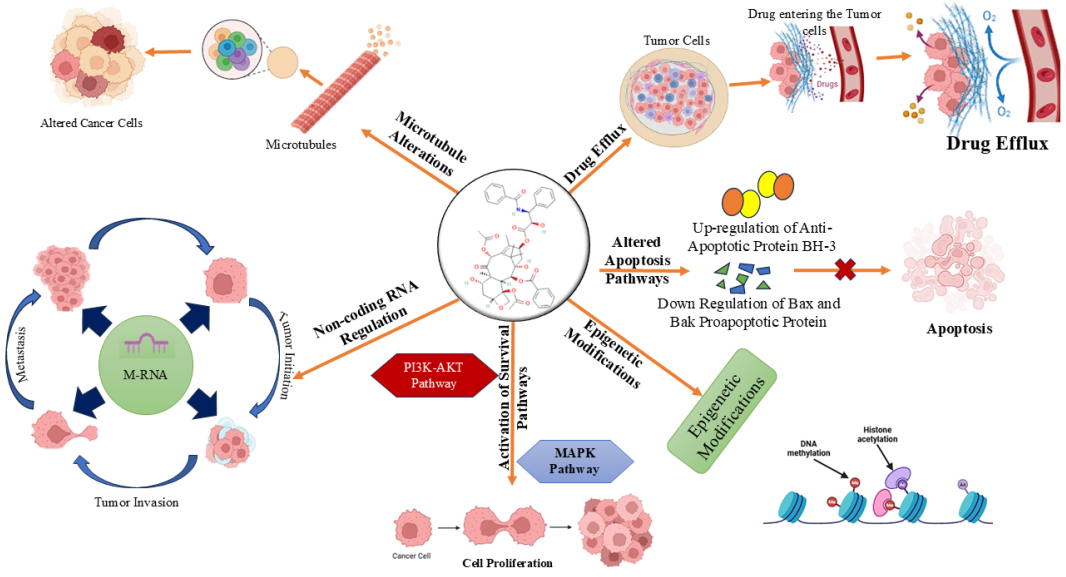


**Figure 2:** Illustrates the mechanisms of taxanes resistance, including microtubule alterations, drug efflux, altered apoptosis pathways, epigenetic modifications, activation of survival pathways, and regulation by non-coding RNAs.

**Table 2:** Represents brief information regarding strategies to overcome taxanes resistance in the breast cancer.

| HER2- | Therapy | Description | Therapeutic agents | Mechanism | Impact | References |
|---|---|---|---|---|---|---|
| Positive BC | Targeted Therapy | Monoclonal antibodies target HER2, block receptor signaling and deliver cytotoxic drugs. | Trastuzumab, T-DM1. | Signaling and induces microtubule- disrupting drugs. | Progression-free survival. | 137,138 |
| | HER2 Inhibitors + Taxanes | Combining HER2 inhibitors with taxanes (PTX) ↓ proliferation | Trastuzumab + PTX | Blocks signaling, taxanes stabilize microtubules. | Combination therapy ↓response rates. | 139,140 |
| | PI3K Inhibition | Targets PI3K signaling pathway often upregulated in HER2-positive cancers. | Alpelisib | Inhibits PI3K signaling, ↓cell proliferation and sensitivity. | Improves progression-free survival in PI3K-mutated BC. | 141,142 |
| TNBC | Immune Checkpoint Inhibitors with Taxanes | Combining immune checkpoint inhibitors (e.g., PD-1/PD-L1 inhibitors). | Atezolizumab + PTX | PD-L1 inhibitors restore T-cell activity; taxanes induce immunogenic cell death. | Boosts progression-free survival in TNBC with PD-L1 expression. | 143,144 |
| | Targeting DNA Repair Pathways | PARP inhibitors used with taxanes to exploit DNA repair defects | Olaparib + PTX | Inhibits PARP, leading to DNA impairment in cancer cells; inhibit cell division | Efficacy in patients with BRCA mutations. | 145,146 |
| | Modulation of Glucocorticoid Receptor (GR). | Targeting-GR linked to tumor growth and poor prognosis. | Dexamethasone + PTX | GR modulation alters transcriptional regulation. | Improved response rates in GR-modulated. | 147,148 |
| | Nanomedicine to Overcome Resistance. | Nanocarriers deliver taxanes directly to tumor cells, ↓ efflux pump-mediated resistance. | Nanoparticle- based PTX | Encapsulation in nanocarriers bypasses drug efflux pumps and improves drug bioavailability. | Nanoparticle albumin-bound (nab) PTX enhances delivery and efficacy. | 149,150 |
| | Targeting TME | Targeting stromal cells, extracellular matrix, or hypoxia. | Anti-vascular endothelial growth factor + Taxanes | ↓tumor angiogenesis, ↓penetration. | Bevacizumab + PTX combination in metastatic BC. | 151,152 |
| | P-glycoprotein | Combining P-gp inhibitors + taxanes ↓drug efflux. | Tariquidar + DTX | P-gp inhibitors block efflux transporters. | Clinical trials demonstrate intracellular drug levels. | 153,154 |

## Immunotherapy

Recombinant antibody-based passive immunotherapy has shown promise as a treatment for HER-2-positive BC.[127] Immunotherapy shows effective result with checkpoint inhibitors, however modest response rate, immune evasion and resistance mechanisms remain significant challenges.[128] Jose *et al.* conducted clinical trials of the anti-programmed cell death Protein-1(PD-L1) antibody atezolizumab in combination with doxorubicin, PTX, and cyclophosphamide to treat patients with TNBC.[129,130] The nab-PTX with atezolizumab was the initial Immunotherapy reported.[131] In TNBC, PD-1 inhibitors have shown favorable results in combination therapy and neoadjuvant treatment.[132] High levels of tumor-infiltrating lymphocytes correlate with better outcomes, indicating their role as a biomarker for immunotherapy response.[133] Combination chemotherapy with the anti-PD-L1 monoclonal antibody atezolizumab has been approved.[134] Further research can focus on approaches to block immune checkpoints, developing monoclonal antibodies, cytokines therapy and use of genetically engineered cells to fully determine potential.[135,136]

## CONCLUSION

This review addresses the important advancements and difficulties in the treatment of BC, with a special emphasis on the therapeutic potential of taxane-based treatments. The taxanes encounter significant limitations, particularly in aggressive subtypes such as HER2-positive and TNBC, where the phenomenon of drug resistance substantially obstructs favorable treatment outcomes. Studies regarding taxanes resistance have uncovered complex mechanisms that encompass microtubule dynamics, drug efflux mechanisms, and survival signaling. The exploration of innovative strategies presents promising opportunities to enhance the efficacy of taxanes and mitigate resistance. Moreover, strategies such as Nano-medicine-based therapy, Immunotherapy, Targeted therapy and incorporation of combination therapies enhances treatment efficacy but it is necessary to determine the patient-specific responses and complexities of drug interactions to optimize therapeutic strategies. Future studies should prioritize approaches that integrate these advancements into clinical practice, enabling effective management of HER2-positive and TNBC cases.

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## ABBREVIATIONS

**BC:** Breast cancer; **HER-2:** Human epidermal growth factor receptor-2; **TNBC:** Triple-negative breast cancer; **MDR:** Multidrug resistance; **PR:** Progesterone receptor; **ER:** Estrogen receptor; **PTX:** Paclitaxel; **DTX:** Docetaxel; **TME:** Tumor microenvironment; **EMT:** Epithelial to mesenchymal transition; **ABC:** ATP-binding cassette; **P-gp:** P-glycoprotein; **BCL-2:** B-cell Lymphoma-2; **IAPs:** Inhibitors of apoptosis; **GPSM2:** G-protein signaling modulator-2; **CSCs:** Cancer steam cells; **PD-L1:** Programmed cell death protein-1; **PARP:** Polyadenosine diphosphate ribose polymerase; **TNF:** Tumor necrosis factor; **NAB-PTX** - Nanoparticle albumin-bound paclitaxel; **GR:** Glucocorticoid receptor.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## SUMMARY

The manuscript titled "Advancing Strategies to Overcome Taxane Resistance in HER2-Positive and Triple-Negative Breast Cancer" highlights the challenges posed by taxane resistance in aggressive breast cancer subtypes, particularly HER2-positive and Triple-Negative Breast Cancer (TNBC). Taxanes, such as paclitaxel and docetaxel, are pivotal in disrupting cancer cell division, but resistance mechanisms—including drug efflux, microtubule alterations, and survival pathway activation—limit their long-term efficacy. The manuscript explores advanced therapeutic strategies to combat this resistance, including nanoparticle-based drug delivery, targeted therapies, combination approaches, and immunotherapy. These innovations aim to enhance drug delivery, improve therapeutic outcomes, and overcome resistance mechanisms. Future research should focus on integrating personalized medicine and innovative strategies to address patient-specific responses, advancing clinical outcomes for these high-risk breast cancer subtypes.

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