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Triple-Negative Breast Cancer And Cancer Stem Cells: Reviewing Strategies To Reverse Chemoresistance

Danya Sri Anantha Prakash
Dr. Prahlad Parajuli
Wayne State University, Barbara Ann Karmanos Cancer Institute

Abstract:
Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer that is characterized by the absence of the estrogen receptor (ER), the progesterone receptor (PR), and human epidermal growth factor receptor (HER2). Therefore, it is recalcitrant to conventional targeted treatments. While the tumor is initially chemotherapy-sensitive, TNBC is also distinguished by an inappropriately high rate of failure, relapse, and metastasis. Numerous studies attribute such resistance to the presence of a small but highly influential population of tumor cells: the cancer stem cells (CSCs). The stem-like cell population is able to renew itself, be pluripotent, enter into dormancy, and is able to survive the standard therapies and lead to the tumor regrowing and progressing. The principal signaling pathways such as Notch, Wnt/β-catenin, and Hedgehog, epigenetic modulators, and tumor microenvironmental factors such as hypoxia are all implicated in CSC maintenance and survival. Other markers such as $CD44^{+}/CD24^{-}$ and ALDH are also of greatest importance in defining these cells and are targets for therapies. A thorough review of published articles and recent/ongoing clinical studies indicate that the targeting of CSC-related pathways or surface markers via immunotherapy or chemotherapy is promising in reversing treatment-resistance. This review provides evidence for increasing consensus that effective treatment of TNBC must extend beyond traditional chemotherapy and radiation therapy. By attacking CSC-selective targets and by addressing tumor cell heterogeneity, these new approaches are poised to reduce relapse rates significantly and to improve long-term survival in TNBC.

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I. Introduction

Breast cancer is the leading malignancy in women with over 2.3 million newly diagnosed cases annually, and nearly 685,000 deaths worldwide *(WHO, 2021)*. While treatment advancement has increased the chances of recovery, drug resistance is an insurmountable clinical challenge in aggressive subtypes like triple-negative breast cancer (TNBC). TNBC lacks the expression of the estrogen receptor (ER), the progesterone receptor (PR), and human epidermal growth factor receptor (HER2) which are the three prime targets of the available therapies *(Bianchini et al., 2016)*. Without these targets, TNBC is treated primarily with chemotherapy, yet this approach is often undermined by high resistance rates and early recurrence *(Lehmann et al., 2011; Dent et al., 2007)*. Interestingly, breast cancer is not a homogeneous entity but rather an accumulation of biologically heterogeneous subtypes, including hormone receptor-positive, HER2-positive, and triple-negative subtypes *(Carey et al., 2006)*. These subtypes of breast cancers have different prognoses, molecular characteristics, as well as sensitivity to treatment *(Perou et al., 2000)*. Importantly, breast cancer is not a single disease but a collection of biologically diverse subtypes, including hormone receptor-positive, HER2-positive, and triple-negative *(Sorlie et al., 2001)*.

TNBC, which makes up 10–20% of breast cancers, predominantly afflicts young as well as African or Hispanic women and is known for early metastasis and poor prognosis *(Anders et al., 2010; Carey et al., 2006)*. It is distinguished from other breast cancers by early metastatic dissemination as well as poor prognosis *(Dent et al., 2007)*. The absence of hormone as well as HER2 receptors precludes endocrine or HER2-directed therapy, so chemotherapy is the only available therapy, leaving patients with limited alternatives *(Bianchini et al., 2016)*. Regrettably, recurrence is not uncommon, in that 40% of patients may recur within five years *(Kassam et al., 2009)*. Cancer stem cells (CSCs) have recently emerged as major facilitators of chemoresistance in TNBC *(Liu et al., 2013)*.

In this review article, we explore the role of CSCs in TNBC chemoresistance, current therapeutic strategies targeting these cells, and emerging approaches, including epigenetic and immunotherapies, that hold promise for overcoming resistance and improving long-term outcomes.

II. Methodology:

This is a literature review of how cancer stem cells (CSCs) mediate chemoresistance in triple-negative breast cancer (TNBC) with the specific focus on translational science and clinical trials.
Data Sources and Search Strategy: Journal articles and clinical trials were sourced using PubMed, Google Scholar, and ClinicalTrials.gov. Keywords included "TNBC," "cancer stem cells," "Trop-2," "epigenetic therapy," and "immune checkpoint blockade." Specific trial numbers cited within the paper (e.g., NCT00048633, NCT02395627, NCT06274515) were also used to locate relevant studies on ClinicalTrials.gov.

Trial Inclusion Criteria: Trials specifically named in the literature article by name or by NCT number or directly related to the CSC-targeting therapies within the frame of TNBC (by trial title or mechanism) and ascertained on ClinicalTrials.gov to have precise endpoints and to be interventional were included.

Exclusion Criteria: Excluded were articles that were not peer-reviewed or were untested hypotheses without clinical or mechanism-based evidence, on subtypes of breast cancer that are not relevant to TNBC, on general reviews of chemotherapy not specifically on CSCs or the mechanism of resistance, or that did not employ systematic review protocol (e.g., PRISMA) because the review is targeted to high-impact, mechanism-relevant studies and not on an exhaustive survey of publications.

Overview of Breast Cancer

Breast cancer is an uncontrolled tumor or malignant growth within the breast tissue. It is one of the most common cancers found in women. It also occurs in men but less commonly. Breast cancer tends to originate in ducts that secrete the milk or the gland-like tissue known as the lobules although it also occurs in the breast's other cells, such as the epithelial cells (Society, American Cancer, 2020). Breast cancer accounted for more than 2.3 million new cases and almost 685,000 deaths in the global population in the year 2020 (Sung et al., 2021). The cause of breast cancer is multifactorial with interaction between the genes, environment, and the hormones. Inherited gene mutations within genes such as the BRCA1 and the gene BRCA2 significantly increase the risk for breast cancer occurrence but are to blame for only a small number of all breast cancers (Antoniou et al., 2003). Other risk factors, such as age, gender, family history, early menarche, late menopausal age, hormone replacement therapy, and lifestyle risk factors of alcohol use and physical inactivity, also add to an individual's risk (Collaborative Group on Hormonal Factors in Breast Cancer, 2012; Vainio & Bianchini, 2002). The management of breast cancer is primarily determined by the subtype, stage at diagnosis, and genetic make-up of the tumor.

Breast cancer can be classified into several molecular subtypes depending on the presence or absence of particular hormone receptors, including the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). The subtypes identified include hormone receptor-positive/HER2-negative, HER2-positive, triple-positive, and triple-negative breast cancer (TNBC), each with distinct prognostic factors and treatment responses. Hormone receptor-positive cancers, the most prevalent subtype, generally respond well to endocrine therapies targeting hormonal signaling pathways, including tamoxifen and aromatase inhibitors. While HER2-positive cancers have been considered more aggressive in the past, the development of HER2-targeted therapies, such as trastuzumab and pertuzumab, has resulted in better outcomes. Triple-positive breast cancers, which show expression of both the hormone receptors as well as HER2, are treated using a regimen combining endocrine therapy with HER2 inhibitors.

In contrast, triple-negative breast cancer lacks expression of ER, PR, and HER2, making it unresponsive to hormonal or HER2-directed treatments and considerably more difficult to manage. TNBC accounts for approximately 10–15% of all breast cancer cases and is more common in younger women, individuals of African or Hispanic descent, and those with BRCA1 mutations. It is characterized by high-grade, rapidly proliferating tumors with a greater tendency to metastasize to the brain, liver, and lungs. Because targeted therapies are ineffective in TNBC, chemotherapy remains the primary treatment, though recurrence and resistance are common.

Recent advances have led to the use of PARP inhibitors in BRCA-mutated TNBC and immune checkpoint inhibitors, such as pembrolizumab, for PD-L1–expressing tumors. Additionally, antibody-drug conjugates like sacituzumab govitecan offer new hope by delivering targeted cytotoxic agents to tumor cells. Despite these emerging therapies, TNBC continues to be associated with poorer outcomes, and ongoing research seeks to identify novel therapeutic targets to improve survival in this aggressive breast cancer subtype.
Prevention of breast cancer, as well as in high-risk populations, is an essential part of care.

Modifiable lifestyle exposures, including diet, regular exercise, and minimizing alcohol consumption, reduce the risk of breast cancer (Vainio & Bianchini, 2002). For women at high genetic risk, as in the case of mutations in the genes BRCA1 and 2, alternatives involving risk-reducing mastectomy or the use of chemopreventive drugs such as tamoxifen can drastically decrease the risk of cancer incidence (Rebbeck et al.,

2018). Detection at an early, treatable stage through mammography, gene screening, and breast self-exam is still one of the best ways to detect breast cancer. Continuing effort to develop screening techniques and mitigate access barriers is crucial to global early detection rates. Breast cancer treatment is very different across the globe.

Molecular Subtypes of Breast Cancer:

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Globally, breast cancer is the most commonly diagnosed cancer in women and it remains a leading cause of cancer-related mortality. In fact, breast cancer symptomatically constitutes 1 out of 3 new female cancers in the United States each year. The diagnostic process typically begins with imaging, either through mammography or ultrasound, and proceeds with biopsy and immunohistochemistry (IHC) to assess receptor status (ER, PR, HER2) and classification/treatment: Risk factors for breast cancer include mutations such as BRCA1 and BRCA2, family history, hormonal exposure, obesity, and advanced age. Breast cancers are further classified based on the presence or absence of ER, PR, and HER2 receptor expression.

For hormone receptor-positive (ER+ or PR+) and HER2-positive cancers, targeted therapies including tamoxifen, aromatase inhibitors, and trastuzumab (Herceptin) have been very successful in improving survival rates (Slamon et al., 2011). Surgical treatment in the form of mastectomy or lumpectomy is typically followed by radiation therapy to annihilate any cancer cells that might have remained after surgery. Chemotherapy is still a cornerstone therapy, especially in aggressive subtypes, but is usually followed by relevant side effects as well as the possibility of relapse, mainly in specific subtypes of breast cancer, such as TNBC (Fisher et al., 2004). Perhaps the most significant development in breast cancer has been the classification of tumors into subtypes according to molecular markers like hormone receptors and the HER2 protein. This has enhanced diagnosis, prognosis, and treatment decision-making significantly. The majority of breast cancers are hormone receptor-positive (HR+), i.e., they arise because of estrogen and/or progesterone stimulation and are generally treated with endocrine therapy.

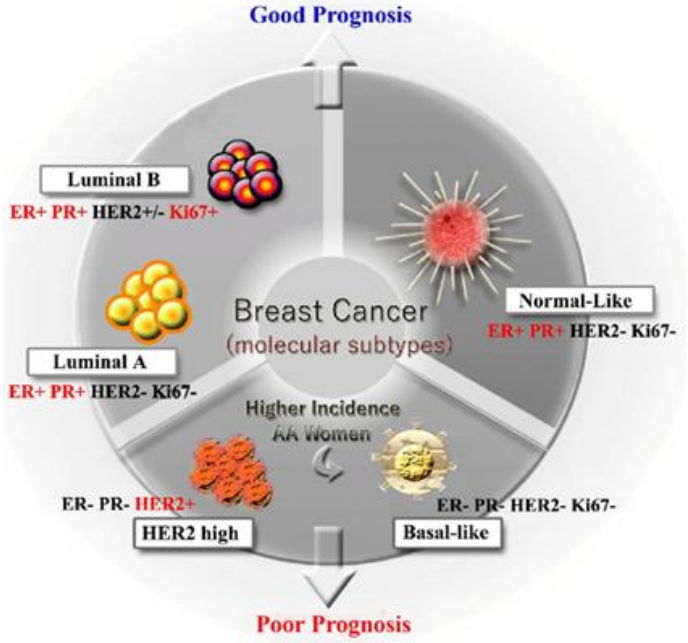

Figure 1: Different Molecular Subtypes of Breast Cancer. This figure illustrates the molecular subtypes of breast cancer, categorized by the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). The subtypes are arranged in a circular diagram, with Luminal A at the top, followed by Luminal B, HER2-enriched, and Triple-negative breast cancer (TNBC) at the bottom. Each subtype is associated with its respective prognosis, ranging from good to poor.
Source: Hussain, S., Charan, M., Verma, A. K., & Ganju, R. K. (2020). Molecular and Cellular Factors Associated with Racial Disparity in Breast Cancer. *Frontiers in Oncology*.

HER2-positive breast cancers express the human epidermal growth factor receptor 2, which accelerates the growth of the cells but which are also susceptible to HER2-directed drugs including trastuzumab. The four most significant breast cancer subtypes are HR+/HER2-, HR+/HER2+, HR-/HER2+, and triple-negative breast cancer (TNBC), which lacks all three markers. The subtypes vary in aggressiveness, treatment response, and prognosis. HR+/HER2- breast cancers are the most common and are best overall because they are most responsive to hormone therapy. HER2-positive subtypes develop and spread faster but can be very effectively managed using targeted therapies.TNBC is most aggressive and most difficult to treat as it lacks any known hormone or protein targets. These subtypes underscore the necessity of personalized medicine in breast cancer treatment since the molecular signature of a tumor immediately affects therapy.

Triple-Negative Breast Cancer (TNBC): Characteristics, Treatment Challenges, and Therapeutic Advances

Triple-Negative Breast Cancer (TNBC) is an aggressive and unique subtype of breast cancer that is characterized by the lack of three important receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This receptor negativity makes hormonal therapies (e.g., tamoxifen) and HER2-targeted agents (e.g., trastuzumab) ineffective and thus chemotherapy remains the cornerstone of treatment. TNBC represents about 10–20% of all breast cancers and is more commonly diagnosed in young women, African American women, and carriers of the BRCA1 mutation. Clinically, TNBC is marked by high histological grade, early relapse (most often in the first 3–5 years), and a greater tendency toward visceral metastasis, with predominance in the brain and lungs. Because of its heterogeneity and absence of targeted therapies, TNBC represents a huge clinical challenge with a worse prognosis for overall survival compared to other breast cancer subtypes. Current research is directed towards the assessment of new treatment strategies like immunotherapy, PARP inhibitors, and anticancer stem cell and epigenetic targeted therapy in an endeavor to enhance patient outcomes.

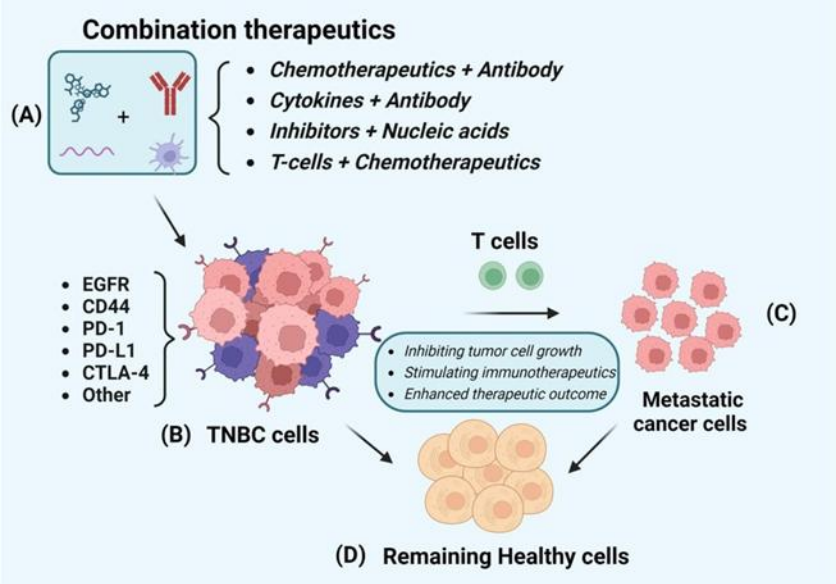

Figure 2. Schematic Representation of Combination Therapy for Triple-Negative Breast Cancer (TNBC).

This figure illustrates a combination therapy strategy for treating TNBC. Panel (A) depicts the various therapeutic agents used in the combination treatment. Panel (B) shows TNBC cells expressing multiple ligands, which are crucial for the interaction with the therapeutics. Panel (C) highlights the metastatic cancer cells that have spread from the primary tumor site to other regions of the body. Finally, panel (D) demonstrates the remaining healthy tissue after the combination treatment, showing the potential for targeted therapy with minimal damage to normal cells. (Created by DSAP using Biorender). Since ER, PR, and HER2 receptors are lacking in Triple-Negative Breast Cancer (TNBC), conventional hormonal and HER2-directed therapies are ineffective, and chemotherapy forms the cornerstone of treatment.

Neoadjuvant and adjuvant chemotherapy regimens often include anthracyclines (e.g., doxorubicin), taxanes (e.g., paclitaxel), and platinum agents (e.g., cisplatin or carboplatin) that have shown some benefit in improving pathologic complete response rates. In spite of this,

TNBC has a propensity to relapse early and chemoresist. To avoid these limitations, newer treatments are being studied. PARP inhibitors olaparib and talazoparib have demonstrated potential in patients carrying BRCA1/2 mutations by exploiting the cancer cell's impaired DNA repair mechanism. Immune checkpoint inhibitors in the form of anti-PD-L1 medications atezolizumab and pembrolizumab have also been beneficial when used in combination with chemotherapy, with the most success seen in PD-L1–positive tumors. Targeted therapies against androgen receptors, antibody-drug conjugates (e.g., sacituzumab govitecan), and kinase inhibitors are also under investigation.

Targeting CSCs with histone deacetylase inhibitors, bromodomain inhibitors, and with such agents as CFI-402411 and entinostat is being explored for their potential in sensitizing CSCs for chemotherapy or their depletion *(Dawson et al., 2011; Yardley et al., 2013)*. Immunotherapy targeting and depletion of CSC-like phenotypes are also in the spotlight *(Ginestier et al., 2007)*. While these are exciting results, much of what is being done is in its infancy, and an integrated knowledge of CSC-mediated resistance in TNBC remains lacking *(Takebe et al., 2015)*. Bridging that knowledge gap could lead the way for longer-lasting, target-based, even curative therapies for one of the toughest types of breast cancer. Despite their central role, CSCs remain inadequately addressed in current treatment protocols *(Liu et al., 2013)*.

While these therapies demonstrate promising results, especially in metastatic TNBC, their effectiveness often hinges on tumor genetics and immune microenvironment, indicating the need for increasingly personalized approaches to treatment.

Concept of CSC and its role in BC drug resistance and recurrence

CSCs comprise an infrequent but potent subpopulation of tumor cells with self-renewal capability, multilineage differentiation, and tumor regenerating ability *(Al-Hajj et al., 2003)*. With their dormant nature, ability to overcome apoptosis, and presence in niched tumor locales, the CSCs can avoid cytotoxic therapy *(Dean et al., 2005)*. Epigenetic mechanisms such as DNA methylation, histone modification, and chromatin remodeling further contribute to their insusceptibility, with CSCs thus being an otherwise under-addressed target for current therapies *(Baylin & Jones, 2011)*. Consequently, ongoing clinical trials are examining novel methods of targeting CSCs directly, with particular focus on epigenetic and immunotherapy modalities *(Sharma*

et al., 2010).

CSCs in breast cancer are typically recognized by surface markers such as $CD44^{+}/CD24^{-}$, ALDH1, and EpCAM that differentiate them from non-tumorigenic cancer-marked cells (Al-Hajj et al., 2003; Ginestier et al., 2007; Munro et al., 2011). These surface markers not only serve as identifiers of CSCs, but also have functional roles in enhancing the invasive and metastatic abilities of the tumor (Mani et al., 2008). CSCs and their ability to initiate new tumor growth through self-renewal and differentiation contribute to tumor progression by maintaining intra-tumoral heterogeneity (Peitzsch et al., 2017). The Wnt/β-catenin, Notch, and Hedgehog pathways are common mechanisms employed to ensure CSCs maintain self-renewal, proliferate, and acquire pro-survival advantages (Takebe et al., 2015). The resistance observed in cancer stem cells (CSCs) stems from a variety of features: dormancy that eludes cycle-dependent chemotherapies, overexpression of ATP-binding cassette (ABC) efflux pumps to extrude cytotoxic agents, and an enhanced capacity for DNA repair (Dean et al., 2005; Diehn et al., 2009). Moreover, all of these features also mediate the persistence of CSCs post-treatment and may contribute to tumor recurrence, ultimately resulting in a more aggressive, therapy-resistant disease (Batlle & Clevers, 2017). A distinct understanding of the molecular and functional aspects of CSCs is necessary in order to construct interventions capable of eradicating CSCs and ultimately preventing long-term relapse.

Role of Cancer Stem Cells and Key Markers in Triple-Negative Breast Cancer

The cancer stem cells (CSCs) are involved in the initiation, growth, and chemoresistance of many cancers, including the triple-negative breast cancer (TNBC), which is an aggressive breast cancer with no targeted therapies. The CSCs are the minority population of the tumor cells that can self-renew, can give rise to many different cell types, and are able to generate tumors and metastasis. The detection and characterization of CSCs in TNBC also largely depend on the detection of cell surface markers specific to CSCs that can distinguish them from the bulk tumor population. The most extensively studied breast cancer as well as TNBC marker is the combination of markers CD44+ and CD24- (Al-Hajj et al., 2003; O'Brien et al., 2007). While the cell surface glycoprotein CD44 participates in cell cell interaction, cell migration, and cell adhesion, the differentiation marker is the one identified as CD24. While in the case of CSCs, the level of expression of CD44 is high and that of CD24 is low or null, it is of very crucial role for the isolation of stem cells of TNBC (Su et al., 2018; Sahoo et al., 2018). The other very important CSC marker is Aldehyde Dehydrogenase (ALDH), which has also been implicated in stem cell characteristics and chemoresistance. High level of ALDH has been found to be associated with CSC characteristics and resistance to chemotherapy and is another very important marker in the isolation of stem cells of TNBC (Ginestier et al., 2007; Zhang et al., 2018).

CSCs are involved in the resistance to the standard therapies, including the chemotherapy, which is targeted to the proliferating tumor cells but has no influence on the less proliferative CSCs (Baumann et al., 2008; Reya et al., 2001). For the TNBC, the CSCs are involved in the resistance to the treatment and the relapse, which are primary hindrances to the management of the breast cancer subtype. The rate of relapse is very high for the TNBC after chemotherapy, and the inability of the CSCs to be destroyed by the treatment has been found to be one of the primary causes of the relapse (Sharma et al., 2019). The TNBC CSCs are endowed with the potential to survive by the inherent resistance to the cytotoxic therapies, including the rapidly dividing tumor cell-targeted therapies (Liu et al., 2015; Visvader, 2011). The chemoresistance can be ascribed primarily to the ability of the CSCs to enter the dormancy, thereby withstanding the effects of the chemotherapy, which is targeted to proliferating cells, and leading to the survival of the tumor in the long-term (Hernandez et al., 2017).

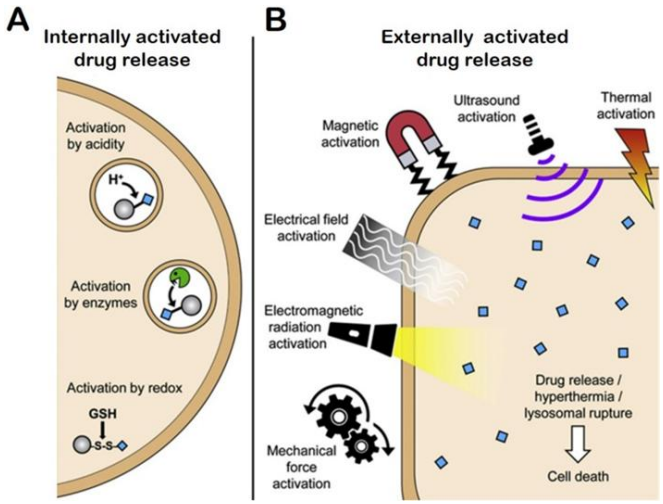

Figure 4. Schematic representation of breast cancer stem cell (CSC) functions and characteristics. CSCs possess

the ability to self-renew, differentiate into various tumor cell types, and resist standard chemotherapies, contributing to tumor initiation, metastasis, and relapse. The figure highlights critical CSC features including dormancy, immune evasion, and their interaction with the tumor microenvironment, factors that are particularly relevant in triple-negative breast cancer (TNBC), where CSC-driven chemoresistance leads to high relapse rates and poor outcomes.

Recent/Ongoing Clinical Studies on evaluating and targeting Cancer Stem Cells in TNBC

Triple-negative breast cancer (TNBC) is perhaps the most malignant subtype of breast cancer, and this is due in part to the fact that it does not express hormone receptors and HER2, which makes it resistant to targeted hormonal or HER2-directed therapies. Standard chemotherapy remains the treatment of choice, but it is often marred by high rates of recurrence and rapid acquisition of drug resistance, motivated to a great extent by tumor heterogeneity and the presence of CSCs. In trial NCT00048633, bevacizumab as an add-on to chemotherapies such as docetaxel and gemcitabine showed modest long-term benefit, pointing to the failure of cytotoxic drugs by themselves to eradicate aggressive tumor populations. This served as the rationale for trials that sought mechanisms of treatment escape, particularly those associated with CSCs. In order to overcome this resistance, the NCT02395627 study investigated the combination of Entinostat, a histone deacetylase inhibitor, with nivolumab. This trial aimed to epigenetically reprogram highly plastic cancer cells to become more immunogenic and checkpoint blockade sensitive. To support this approach, Manavalan et al. (2024) found that TNBC cells utilize histone modifications and non-coding RNAs to maintain stemness and evade treatment, showing the promise of epigenetic therapies in disrupting CSC-mediated resistance. Similarly, Liu et al. (2016) depicted CSCs possessing high drug efflux, enhanced DNA repair, and dormancy capacity, characteristics that enable them to circumvent traditional therapies and cause recurrence. The NCT06274515 trial took this strategy a step further by pairing Sacituzumab Govitecan, an antibody-drug conjugate that targets Trop-2, with Pembrolizumab, an immune checkpoint inhibitor. Trop-2 has also been implicated in CSC-like characteristics and EMT and thus is an attractive target for the eradication of refractory TNBC populations. This dual-pronged strategy attacks both proliferating tumor cells and the tumor microenvironment containing CSCs. Earlier research by Roche (WO44977) and the ASCENT trial demonstrated Sacituzumab Govitecan with significantly improved survival compared to chemotherapy alone in highly pre-treated TNBC patients, demonstrating its clinical efficacy. Together, these trials demonstrate a paradigm shift in the treatment of TNBC. While previous trials like NCT00048633 and its sequential counterparts (e.g., docetaxel followed by doxorubicin and cyclophosphamide) demonstrated that even chemotherapy multi-agent regimens could not overcome resistance, subsequent trials aim to change cell states or target subpopulations that cause therapeutic failure.

By targeting the mechanisms of resistance, i.e., CSC plasticity, epigenetic adaptation, and immune evasion, the trials propose a more targeted and potentially sustainable therapeutic approach. Mechanistic studies also confirm that CSCs are at the center of failure of conventional treatment. They interact dynamically with the tumor microenvironment, contribute to immune suppression, and often remain in a dormant phenotype that renders them invisible to drugs targeting proliferating cells. A paper by Lee et al. (2023) pointed out that the disruption of epigenetic maintenance of stemness would cause CSCs to differentiate, reducing their ability to regenerate tumors. This research platform educates current clinical attempts to pair immune

therapies with targeted agents with an eye toward deep, durable responses instead of fleeting tumor regression. Taken together, these studies and trials point to a changing clinical approach to TNBC: one that goes beyond merely killing cancer cells to eliminating or reprogramming the most treatment-resistant cell subpopulations. The future of TNBC therapy probably involves the combination of epigenetic modulation, immune checkpoint inhibitors, and precision targeting of the tumor microenvironment, thereby creating a multi-faceted treatment strategy that overcomes current therapeutic limitations and offers hope for long-term survival.

Clinical trials:

NCT00048633 – *Bevacizumab and Chemotherapy in Advanced Breast Cancer*

This trial provides context on chemotherapy regimens for treating advanced breast cancer and the limitations of these therapies, which is background to the rationale behind your question in the first place. Although not on triple-negative breast cancer or cancer stem cells, it is relevant because it highlights the persistent issue of chemoresistance despite combination regimens. An understanding of how metastatic tumors develop resistance to or grow out of existing therapies such as docetaxel and gemcitabine brings into perspective the need for new therapies, especially in aggressive cancers such as the TNBC where there are no targeted therapies. The trial is an acceptance of the reality that chemotherapy is not enough because of tumor heterogeneity, clonal evolution, and resistance, all of which are enhanced in the case of the TNBC. This trial is the antithesis of the literature review, illustrating why there is a trend towards the use of molecularly informed techniques such as targeting cancer stem cells.

NCT02395627 – *Study of Chemotherapy Resistance in Triple-Negative Breast Cancer*

This trial is highly relevant to your work because it is investigating the use of epigenetic modifiers, in this instance the histone deacetylase inhibitor Entinostat, to modulate immune response and treat resistance to treatment in HER2-negative breast cancer, including triple-negative breast cancer (TNBC). Epigenetic dysregulation is one of the new biologic mechanisms that confer stem-like properties and resistance phenotypes on cancer cells and is within the area of your subject matter of how the molecular heterogeneity of cancer and non-genetic plasticity, in particular, may be targeted to treat chemoresistance. This trial is where the areas of cancer biology, resistance to treatment, and therapeutic innovation meet and highlights the requirement to target the tumor microenvironment and cancer stem cell–like characteristics of TNBC. The employment of an HDAC inhibitor is also relevant to recent literature that has shown epigenetic modification is able to suppress CSC self-renewal and sensitize resistant tumors to standard treatment regimens.

NCT06274515 – *Targeting Cancer Stem Cells in Triple-Negative Breast Cancer*

This trial is extremely relevant to this researchas it evaluates the efficacy of the antibody-drug conjugate, Sacituzumab Govitecan, targeted to the highly expressed tumor antigen on triple-negative breast cancer and cancer stem-like characteristics, Trop-2. This trial also evaluates Pembrolizumab, an immune check-point inhibitor, exhibiting an additive strategy to the maximization of tumor effect. The target, Trop-2, has been shown to be involved in the biologic activities of the self-renewal, epithelial-mesenchymal transition (EMT), and resistance to therapy—biologic activities intimately tied to cancer stem cells. The rationale behind the combination therapies is in the necessity to target the bulk of the tumor but the treatment-refractory, subpopulace of CSCs most often implicated in relapse and metastasis in TNBC. This trial provides an extremely translational strategy to your manuscript in that it demonstrates how targeted therapies are being engineered to target the biologic heterogeneity and resistance profiles that standard chemotherapy is unable to overcome. Its existence is directly in service to your thesis that the targeting of cancer stem cells has the power to revolutionize the treatment of TNBC.

Global Advances, Future Directions, and Innovative Therapeutic Approaches

Recent studies on breast cancer established the function of other biomarkers beyond the frontline estrogen receptor (ER), progesterone receptor (PR), and HER2. One of them is mutations within the gene PIK3CA, which occur in the bulk of hormone receptor-positive (HR+) breast cancers and are able to predict therapy resistance (Mayer et al., 2017). Furthermore, blood-based testing of tumor DNA using liquid biopsy has gained popularity for the detection of early cancer, monitoring drug response, and relapse detection, particularly metastatic breast cancer (Zhao et al., 2019). Side effects of the breast cancer treatment decrease the quality of life. General side effects of chemotherapy and radiation are fatigue, nausea, hair loss, and neuropsychiatric impairment, which take long-term effects on physical and mental status (Kaiser et al., 2020).

Accordingly, appreciation has increased for the contribution of palliative care, the function of the supportive therapies and mental health services to prevent these side effects and in helping the patients to maintain well-being during and after treatment. Survivor care packages address these areas and provide long-term care, including counseling and rehabilitation services, to improve well-being and the quality of life of the patient. Immunotherapy has revolutionized the treatment of various cancers, including breast cancer. For the example of the case of TNBC, which is not expressing the characteristic hormone receptors and HER2, immune check inhibitors pembrolizumab and atezolizumab are promising when given in combination with chemotherapy, particularly in the case of PD-L1 tumors (Gatti-Mays et al., 2021). Current investigation is looking into the potential use of CAR-T cell therapy and cancer vaccines, which are designed to initiate the immune system to specifically target and kill cancer cells. The changing role of tumor-infiltrating lymphocytes (TILs) and how it correlates with response to immunotherapy is one that is increasingly being researched. Although chemotherapy is the mainstay treatment for TNBC, new therapies are imminent. Epigenetic therapies targeting histone modification or non-coding RNAs are an interesting potential new direction in the treatment of TNBC, with preliminary trials indicating inhibiting maintenance by cancer stem cells improves response to treatment and lessens relapse (Manavalan et al., 2024). Gene editing tools, such as CRISPR-Cas9, are promising to edit cancer-related mutations directly, and provide a new avenue to precision medicine for the treatment of breast cancer (Knott & Doudna, 2018). New drug delivery, including the delivery using nanoparticle-based delivery vehicles, is being engineered to target hard-to-reach areas, including the blood-brain barrier, the greatest challenge to treating metastatic TNBC.

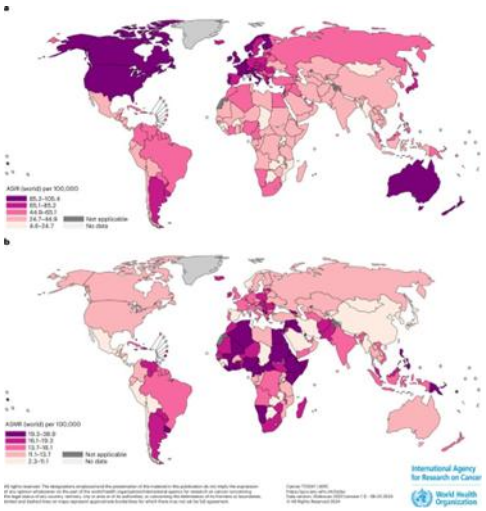

Figure 3. Global female breast cancer burden patterns in 2022, estimated incidence (a) and death (b) rates per 100,000 women in 185 countries. The map shows regional incidence and death differences, demarcating areas of higher and lower rates. Reproduced data from International Agency for Research on Cancer (IARC) and World Health Organization (WHO) (2025), reproduced in relation. Copyright 2025 IARC/WHO.(Torre et al., 2015).

Strategic Approaches to Combat Resistance via Stem Cell Targeting

Cancer stem cells (CSCs) are one of the main barriers to the successful treatment of triple-negative breast cancer (TNBC) due to the inherent resistance of CSCs to chemotherapy and because the CSC is implicated in cancer relapse. Multiple strategies are being explored and trialled specifically to target the CSCs to counteract chemoresistance and enhance patient prognosis. One of these is through the inhibition of the key pathways involved in CSC maintenance and survival. Pathways such as the Notch, Wnt/β-catenin, and Hedgehog are all implicated directly in the maintenance and survival potential of CSCs in TNBC (Takebe et al., 2011; Im et al., 2018). Inhibitors of the Notch pathway such as the gamma-secretase inhibitors (GSIs) are promising in preclinical models to suppress the CSCs' capacity at self-renewal and sensitization to chemotherapy (McAuliffe et al., 2012; Meurette & Mehlen, 2018). Wnt pathway inhibitors such as LGK974 and PRI-724 are also shown to destabilize the CSC niche and suppress chemoresistance (Kahn, 2014; Krishnamurthy et al., 2015). Hedgehog pathway inhibitors such as Vismodegib are also promising to reduce the number of CSCs when given adjuvantly to the standard treatment (Sims-Mourtada et al., 2015). Another strategy is targeting CSC-specific markers. Monoclonal anti-CD44, anti-ALDH, and anti-EpCAM antibodies and small molecules have been produced to target the CSCs selectively with the hope of inhibiting tumor growth and metastasis. Anti-CD44 antibodies, for instance, are found to inhibit the growth of tumors and metastasis in the models of TNBC (Zhou et al., 2010), whereas ALDH inhibitors such as disulfiram are explored for the potential to disrupt the CSC function and to sensitize the cell to chemotherapy (Yip et al., 2011; Liu et al., 2020). Another major strategy is to target the tumor microenvironment, in the form of hypoxic niches and the stromal networks to which the

CSCs are held. Hypoxia-activated prodrugs and hypoxia-inducible factor (HIF) inhibitors are explored to destabilize the stem cell-protective microenvironment and enhance the response to the treatment (Heddleston et al., 2009; Semenza, 2012). In addition, the modulation of interaction with the immune system by immunotherapy is an exciting direction. The CSCs are able to evade immune detection by the expression of PD-L1 and other modulators, and the immune checkpoint inhibitors are able to restore immune perception and CSC elimination (Schatton & Frank, 2009; Dong et al., 2017). Immune checkpoint blockade is explored with CSC-targeting treatment in preclinical models to produce synergism in the context of TNBC (Gupta et al., 2016). Nanotechnology-based delivery systems are also being engineered to enhance targeting and delivery of anti-CSC therapy. Nanocarriers are engineered to target CSCs specifically using surface markers or environmental signals to enhance the specificity of drugs and reduce off-target effects (Wang et al., 2020). Some of these include nanoparticles conjugated with anti-CD44 or ALDH ligands to deliver chemotherapeutic drugs into the CSC niche. Lastly, epigenetic modulators such as histone deacetylase (HDAC) inhibitors and inhibitors of DNA methyltransferase were also shown to suppress CSC characteristics and reduce chemoresistance as combination therapies (Lu et al., 2015; Easwaran et al., 2014). Through modification of the epigenetic profile of CSCs, these drugs are able to reduce the stem-like characteristics of these populations and cause these populations to undergo differentiation, which makes them susceptible to standard therapies. Together, these sophisticated techniques demonstrate the potential of targeting CSCs as the key to overcoming chemoresistance in TNBC.

Additional work is needed to further perfect these techniques and transition them into viable therapies for the clinic.

CSC Signaling Pathways and Therapeutic Targets

Furthermore, stem cell characteristics-controlling signaling pathways have played a role in the course of TNBC. The Notch, Wnt/β-catenin, and Hedgehog pathways have all found to play important functions in regulating the maintenance of CSC characteristics in TNBC (Briest et al., 2010; Im et al., 2018). For instance, the Notch pathway regulates the self-renewal and differentiation of CSC and is characteristically associated with high metastasis and poor prognosis in the case of TNBC (Garnier et al., 2015; Kar et al., 2019). Similarly, Wnt/β-catenin pathway is essential to the maintenance of CSC and has further been associated with chemoresistance in the case of TNBC. The pathway enhances the proliferative capacity and the self-renewal capability of the CSC, which is one of the reasons why it is one of the primary targets of new therapies which are being developed to overcome chemoresistance (Brabletz et al., 2011; Santos et al., 2016). Aside from these markers and signaling pathways, epigenetic modifications and the tumor microenvironment are also involved in CSC chemoresistance and behavior in TNBC. The tumor hypoxic environment, as found in TNBC, has already shown to contribute to CSC maintenance through the stabilization of the hypoxia-inducible factors (HIFs), which trigger survival signaling leading to chemoresistance (Sharma et al., 2019; Li et al., 2017). CSC interaction with stromal, endothelial, and immune cells within the tumor microenvironment is noted to trigger CSC survival and metastasis in TNBC (Liu et al., 2017; Hossain et al., 2018).

Druggable targets to target and eradicate CSCs in TNBC are needed to counteract chemoresistance and to provide improved treatment outcomes. Various strategies are being examined, including the creation of small molecules and monoclonal antibodies to target the CSC-enriched markers CD44, ALDH, and EpCAM (Li et al., 2020; Donnenberg et al., 2019). Blockade of critical molecules in the key signaling pathways such as the Notch and Wnt/β-catenin is also being examined as an approach to disrupt CSC self-renewal and survival, and the potential to increase sensitivity to chemotherapy and reduce relapse rates (Vassilev et al., 2018; Tannock et al., 2006). Immune therapies are also being investigated as one of the ways to target CSCs in TNBC. Immune checkpoint therapies are promising in other cancers, and there is increasing interest in how these therapies are to be formulated to target the immunonevasion capabilities of CSCs in TNBC (Dong et al., 2017; McGranahan et al., 2016). Understanding the molecular and cell determinants regulating CSC function in TNBC are critical to the creation of novel therapeutic regimens to overcome chemoresistance and to generate improved patient outcomes.

Table #1: Clinical Trials Evaluating Therapeutic Strategies in Triple-Negative Breast Cancer (TNBC)

Trial ID/Name	Phase & Design	Patient Population	Interventions
NCT00048633	Phase III, Randomized	Women with metastatic breast cancer	Sequential chemotherapy: Docetaxel followed by Doxorubicin + Cyclophosphamide
NCT02395627	Phase I/II, Open-label	Patients with hormone receptor-negative breast cancer, including TNBC	Combination of Entinostat (HDAC inhibitor) and Nivolumab (PD-1 inhibitor)
NCT06274515	Phase I, Dose-escalation	Patients with advanced or metastatic TNBC	Sacituzumab Govitecan (Trop-2-directed ADC) + Pembrolizumab (PD-1 inhibitor)
ASCENT Trial (NCT02574455)	Phase III, Randomized	Patients with relapsed or refractory metastatic TNBC	Sacituzumab Govitecan monotherapy
NCT03179943	Phase I, Dose-escalation	Patients with advanced solid tumors, including TNBC	CFI-402411 (BET inhibitor)
WO44977 (Roche Patent)	Preclinical Development	Not applicable	Development of Trop-2-targeted ADCs

Table #2: Endpoints of Clinical Trials in TNBC

Trial ID/Name	Phase & Design	Primary and Secondary Endpoints
NCT00048633	Phase III, Randomized	Primary: Overall survival Secondary: Progression-free survival, response rate, toxicity
NCT02395627	Phase I/II, Open-label	Primary: Safety and tolerability Secondary: Objective response rate, progression-free survival
NCT06274515	Phase I, Dose-escalation	Primary: Safety, tolerability, recommended phase II dose Secondary: Preliminary efficacy measures
ASCENT Trial (NCT02574455)	Phase III, Randomized	Primary: Progression-free survival Secondary: Overall survival, objective response rate, safety
NCT03179943	Phase I, Dose-escalation	Primary: Safety, tolerability, pharmacokinetics Secondary: Preliminary antitumor activity
WO44977 (Roche Patent)	Preclinical Development	Not applicable

Table #3: Key Findings and Implications for CSC-targeted Therapy in TNBC

Trial ID/Name	Phase & Design	Key Findings	Implications for CSC-targeted therapy
NCT00048633	Phase III, Randomized	Limited improvement in overall survival; need for more effective treatments	Highlights the need for therapies targeting resistant cell populations (CSCs) that may contribute to relapse and metastasis.
NCT02395627	Phase I/II, Open-label	Well-tolerated; some patients had partial responses; Entinostat enhanced Nivolumab efficacy	HDAC inhibition may sensitize CSCs to immune checkpoint blockade, offering a way to overcome immune evasion in TNBC.
NCT06274515	Phase I, Dose-escalation	Manageable safety profile; signs of antitumor activity; potential synergy between ADC and checkpoint inhibition	Targeting Trop-2 (CSC marker) and PD-1 may eliminate both bulk tumor cells and CSCs, addressing chemoresistance and recurrence.
ASCENT Trial (NCT02574455)	Phase III, Randomized	Significantly improved survival compared to standard chemotherapy; new standard of care	Supports role of CSC-associated antigens in TNBC progression; shows ADCs' potential in targeting resistant cells.
NCT03179943	Phase I,	Well-tolerated; evidence	BET inhibition may disrupt transcriptional
	Dose-escalation	of disease stabilization; more research needed	programs key to CSC maintenance; novel approach to target resistant TNBC cells.
WO44977 (Roche Patent)	Preclinical Development	Patent outlines Trop-2 ADC design and rationale	Trop-2 targeting strategies aim to eliminate CSCs and overcome chemoresistance in TNBC.

Current Clinical Studies in Triple-Negative Breast Cancer and Emerging Therapeutic Strategies:

Recent trials of triple-negative breast cancer (TNBC) have initiated a shift in the therapeutic strategy with investigation of the underlying mechanisms of drug resistance, stemness, and immune evasion. The ASCENT trial (NCT02574455) was a landmark Phase III trial of sacituzumab govitecan, an anti-Trop-2 antibody-drug conjugate, in heavily pre-treated metastatic TNBC. Trial outcomes demonstrated an impressive improvement in both progression-free survival (PFS) (5.6 vs. 1.7 months) and overall survival (OS) (12.1 vs. 6.7 months) over standard chemotherapy, with the drug approved in 2021. Importantly, expression of Trop-2 is found in both bulk tumor and cancer stem-like cells, positioning sacituzumab govitecan in the therapeutic window for targeting CSCs in TNBC. Building on this foundation, the NCT06274515 study is underway to study the combination of sacituzumab govitecan with pembrolizumab, a PD-1 check-point inhibitor, for the purpose of targeting both immune-suppressive microenvironments and stem-like populations. Within the epigenetic therapeutic space, NCT02395627 investigated the combination of entinostat, a histone deacetylase inhibitor, with nivolumab in metastatic TNBC. Preliminary data indicate that epigenetic reprogramming with entinostat may re-sensitize previously drug-resistant tumors to immune-checkpoint blockade, with a demonstration of the role of chromatin remodeling in dampening CSC-promoted immunoevasion. Consistent with this, the NCT03167619 study explores the combination of olaparib, a PARP inhibitor, with durvalumab, with promising toxicity profiles and preliminary evidence of synergy in

BRCA-mutant TNBC through simultaneous targeting of dysfunctional DNA repair mechanisms and stimulation of anti-tumor immunity. The TONIC trial (NCT02499367) also investigated short-course induction with low-dose chemotherapy or radiation to promote immunogenicity of the tumor prior to administration of nivolumab, with the discovery that inducing DNA damage before introduction of immunotherapy may "prime" the immune system, specifically in stem-like tumor cells. Trials such as NCT04877816, evaluating a Wnt/β-catenin inhibitor, are directly targeting stemness-associated pathways in advanced TNBC, based on evidence that Wnt signaling sustains CSC populations and contributes to treatment failure. Additionally, NCT04468061, which explores a TGF-β inhibitor in combination with checkpoint inhibitors reflects a growing recognition of the role of stromal-CSC interactions in therapeutic resistance.

These findings collectively underscore a paradigm shift in TNBC therapy, away from non-specific cytotoxic regimens and toward mechanism-driven combination therapies that aim to eliminate CSCs, reverse immune resistance, and exploit tumor-specific vulnerabilities. While many trials remain in early-phase development, they have already demonstrated that addressing epigenetic plasticity, CSC survival, and immune escape mechanisms can yield durable responses, particularly in patient subgroups stratified by molecular biomarkers such as BRCA mutation status, PD-L1 expression, or Trop-2 positivity.

The promising results of recent clinical trials signal a dramatic shift in the future lines of treatment for triple-negative breast cancer (TNBC). Contrary to the sole reliance upon traditional cytotoxic chemotherapy, future therapeutic strategies are envisioned to center on targeted molecular therapies, the reactivation of immune responses, and the clearance of cancer stem cell (CSC) reservoirs. The success of drugs like sacituzumab govitecan is a testament to the promise of antibody-drug conjugates to preferentially attack the bulk tumor cells as well as the stem-like subpopulations, while combination studies with checkpoint inhibitors

suggest that two-hit treatment strategies may effectively impair immune escape and therapeutic resistance. Epigenetic therapies involving the inhibition of histone acetylation or BET proteins have been shown to have the potential to re-program resistant CSCs towards more immunogenic and responsive phenotypes, best exploited in the presence of immunotherapies or DNA-damaging drugs.

Stratification of the patient population based on biomarkers like BRCA status, PD-L1 expression, Trop-2 positivity, and CSC-associated signatures is likely to increasingly dictate treatment choices going ahead, making adaptive therapies the norm instead of the exception.

Further, the imminent convergence of liquid biopsies, multi-omics analysis, and AI-guided predictive models offers the possibility of simultaneous real-time tracking of tumor progression and resistance mechanisms, enabling earlier therapeutic intervention and minimizing the risk of relapse. As the coming clinical trials continue to enlighten the mechanistic basis of TNBC, including the role of the tumor microenvironment and epigenetic plasticity, the future of TNBC treatment is increasingly imagined to be based not upon the inhibition of a single pathway but upon patient-specific, customized regimens aimed at clearing the most treatment-refractory compartments of the tumor. Such breakthroughs are a renewed promise towards sustained remission and enhanced survival rates for a subtype of breast cancer that has struggled to establish consistent therapies.

III. Discussion:

Triple-negative breast cancer causes a formidable challenge to the science of oncology, due mainly to their inherent molecular characteristics, high rates of metastatic potential, and the common occurrence of therapeutic resistance (Bianchini et al., 2016). Whereas chemotherapy has long been considered the mainstay treatment for TNBC, the effectiveness of this treatment is greatly marred by the survival of a special subpopulation of cancer cells that are capable of resisting cytotoxic therapies, undergoing the process of dormant existence, and later triggering recurrence in the tumor (Creighton et al., 2009). The literature reviewed here elucidates very convincingly how the persisting ineffectiveness of the standard therapies for TNBC is mainly due to the resistance and plasticity of these cancer stem cells (CSCs), along with their ability to interact with and remodel the tumor microenvironment perpetually (Liu et al., 2014).

The trials discussed in this review reveal a positive trend in therapeutic strategies, with a transition from standard treatment regimens to combination regimens targeting both the bulk tumor mass and the CSC niche. For example, the ASCENT study and follow-up research demonstrate that antibody-drug conjugates such as sacituzumab govitecan can efficiently deliver cytotoxic agents to Trop-2–expressing cells, which also harbor characteristics of CSCs (Bardia et al., 2021). When combined with immune checkpoint inhibitors like pembrolizumab, these multimodal regimens have the potential to overcome both tumor-induced and immune-related resistance mechanisms (Adams et al., 2019). Clinical studies add to the emerging consensus that epigenetic therapy, using agents like entinostat and olaparib, can resensitize CSCs to immune-mediated killing and DNA-damaging therapy by reversing chromatin states dictating stemness (Sharma et al., 2010; Lord & Ashworth, 2017). It is interesting to note that the efficacy of these regimens is substantially influenced by the genomic and immunological milieu of the tumor, including factors such as BRCA mutation status, PD-L1 positivity, and Trop-2 positivity, thus highlighting the importance of biomarker-driven precision medicine (Schmid et al., 2018).

Additionally, research on cancer stem cell-specific signaling pathways, for example, the Wnt/β-catenin pathway and TGF-β pathway (e.g., NCT04877816, NCT04468061), suggests that inhibiting pathways that are linked to stemness may destabilize the processes through which cancer stem cells (CSCs) maintain quiescence, evade immune detection, and drive recurrence (Takebe et al., 2015). These discoveries support a more nuanced therapeutic strategy: instead of viewing triple-negative breast cancer (TNBC) as a homogenous, rapidly dividing cancer, it should instead be considered a hierarchical, heterogeneous disease where targeting drug-resistant subpopulations, like CSCs, is critical to achieving true remission.

In parallel, the development of liquid biopsy techniques, multi-omic approaches, and AI-enabled predictive tools is expected to be key to the detection of minimal residual disease, the tracking of real-time response to therapies, and the anticipatory detection of resistance before the emergence of clinical progression (Siravegna et al., 2017; Duffy et al., 2019). This implies that future management of TNBC might require adaptive therapy platforms, in which treatment is continually modified based on dynamic biomarker information rather than adhering to static treatment algorithms.

Despite encouraging progress, challenges remain. Many of the ongoing clinical trials are still in early-phase development, and long-term data on durability of response, toxicity, and resistance evolution are still lacking (Dean et al., 2005). Moreover, while many agents demonstrate preclinical or early-phase activity against CSCs, there is a need for clinically validated CSC-specific biomarkers, as well as standardization in CSC detection and quantification (Phi et al., 2018). There is also concern that targeting CSCs alone may be insufficient without simultaneously modulating the tumor microenvironment, including hypoxia, stromal

signaling, and immune cell exclusion, all of which contribute to stem cell survival (Junttila & de Sauvage, 2013). In summary, the evidence supports a growing shift in TNBC therapy toward combination strategies that aim to dismantle the CSC hierarchy, reverse immune resistance, and leverage epigenetic reprogramming to improve patient outcomes. While there is no single "silver bullet" for TNBC, the convergence of targeted therapy, immunotherapy, and CSC-directed interventions suggests a future in which long-term control, and perhaps even cure, of this aggressive disease becomes increasingly possible.

Health system strengthening and global awareness campaigns, and access to essential therapies and screening, are key to reduce these disparities. For instance, global action has targeted the enhancement of access to chemotherapy, and the use of cost-saving diagnostic technologies, to deliver more equitable breast cancer care to the global population (Ginsburg et al., 2020). In the future, AI and ML research has the potential to revolutionize breast cancer treatment. These technologies can scrutinize extensive patient data files to predict treatment response and guide target therapy using genetic profiles, imaging, and disease outcomes (Esteva et al., 2019). Use of AI to assist in early detection, treatment planning, and monitoring growth of the tumor has the potential to revolutionize patient outcomes. Moreover, novel target drugs, including the DNA repair pathway proteins, and enhanced understanding of the tumor microenvironment are leading areas for targeted and effective therapies against the HR+ and the TNBC breast cancers (Lord & Ashworth, 2016). In low- and middle-income countries, access barriers including the unavailability of diagnostic equipment, the absence of proper treatment centers, and delayed diagnosis are the reasons for poorer survival rates (Torre et al., 2015). Awareness campaigns and worldwide action to build the capacity of the health system, the provision of essential therapies, and the provision of screening are critical to mitigate these disparities. For instance, worldwide action has focused on improved access to chemotherapy and the innovation of cost-saving diagnostic tools to provide fairer care to breast cancer patients worldwide. In the future, the potential of artificial intelligence (AI) and machine learning (ML) is very promising to treat breast cancer. These technologies are capable of handling large data sets of patient information, including genetic, images, and outcomes, to inform the prediction of the response to therapy and drive personalized therapy (Esteva et al., 2019). The potential of AI to assist in early diagnosis, cancer treatment planning, and monitoring disease growth may be an unmitigated effect on patient outcomes. Moreover, new targets including the DNA repair proteins and the enhanced tumor microenvironment are promising ways to design and build more targeted and efficient therapies for HR+ and TNBC breast cancers.

IV. Conclusion:

This review highlights that the cause of chemoresistance, relapse, and failure of treatment in TNBC lies with the CSCs. Through various investigations and trials that included the introduction of the drugs Sacituzumab Govitecan, Entinostat, and CFI-402411, the information all points towards the understanding that traditional chemotherapy is suboptimal since it kills proliferating tumor cell populations but does not target the non-proliferating, stem-like populations. By connecting the dots on epigenetic reprogramming, immunotherapy with immune-checkpoint inhibitors, and Trop-2-targeted antibody-drug conjugates, the landscape appears to be one where therapeutic progress must include multi-modal modes of attack against the special survival features of the CSCs. These are the epigenetic reprogramming of the CSC epigenome, immunosensitization, and targeting the surface markers such as CD44, ALDH, and Trop-2 without the intervening steps. The takeaway is that therapies targeted at the CSCs are no longer optional, but mandatory as the next step in treating TNBC. As these concepts are continually validated in vivo by further trials, the landscape is at the stage where the therapies are no longer just longer lasting, but targeted therapies. CSC targeting is no longer just the prevention of relapse, hence, it is about transforming the management of the TNBC from one clinically unmanageable disease to one that is managed, personalized, and perhaps cured. Our challenge in the future is to take the knowledge to the bedside to reduce mortality, extend long-term survival, and instill hope in the patients with one of the deadliest breast cancers.

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