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Emerging Drug Targets and Novel Therapeutic Strategies in Triple-Negative Breast Cancer

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Abstract

Triple-negative breast cancer (TNBC) is approximately 10–20% of all breast-cancer diagnoses and is a clinically aggressive, biologically heterogeneous phenotype that results as concomitant deficiency of estrogen receptor, progesterone receptor, and HER2 expression. In its turn, this molecular signature limits the number of targeted therapies and is associated with a dreadful prognosis and a high recurrence rate compared to other subtypes of breast-cancer. Traditionally, the management was based on systemic cytotoxic chemotherapy; however, over the last ten years, there has been an impressive advancement that completely changed the treatment environment of TNBC. Antibody-drug conjugate (ADC) has become an essential therapeutic breakthrough, which enables the delivery of highly potent cytotoxic compounds to malignant cells in a targeted manner. Newer drugs like Sacituzumab govitecan and trastuzumab deruxtecan have produced significant effects on progression-free and overall survival particularly in HER2-low TNBC. There has also been an improvement in PD-L1 positive early-stage and metastatic TNBC with immune checkpoint inhibitors (ICIs), especially pembrolizumab, and synergy of chemo therapeutic agents.

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Additionally, poly(ADP-ribose) polymerase (PARP) inhibitors, among them olaparib and talazoparib have shown strong efficacy in the population with germline BRCA1/2 mutations through synthetic lethality. New treatment paradigms that query PI3K/AKT axis, androgen receptor signalling and DNA-damage-response (DDR) signatures are currently in strict development in biomarker-selected cohorts. Active clinical trials are testing the rational combination approaches that involve ADCs, ICIs, and PARP inhibitors among other targeted therapies which are expected to overcome the resistance to therapeutic effects and to prolong the duration of response.

Keywords: Triple-negative breast cancer; Antibody-drug conjugates; PARP inhibitors; Immune checkpoint inhibitors; PI3K/AKT pathway; Targeted therapy.

1. Introduction

Triple-negative breast cancer (TNBC) is a phenomenon of breast cancer that is not only clinically difficult but is also characterized by a deficiency of estrogen receptor (ER), progesterone receptor (PR), and the amplification of human epidermal growth factor receptor 2 (HER2). TNBC, which constitutes about 1020 per cent of all breast cancers, is unfairly linked with rapid disease progression, aggressive tumour biology, and a high tendency of early metastases to the visceral and central nervous systems [1]. Absence of these molecular targets eliminates the possibility of the typical receptor-directed therapy, including endocrine agents and HER2-targeted therapies, making cytotoxic chemotherapy the hitherto dominant mode of therapy. Though TNBC presents some form of chemosensitivity at the outset, a significant percentage of patients ultimately develop the relapse effect, hence the failure in long-term survival [2].

The understanding of the TNBC biology was significantly sharpened in the past decade with the recent development of genomic technologies, in-depth molecular profiling and translational research. Elaborate molecular characterisation has shown that TNBC is not a uniform single disease but rather a heterogeneous group of subtypes, each of which is characterised by specific signalling cascades, immune micro-environment and sensitivity to a particular therapy [3]. These findings have not only enabled the discovery of several druggable targets but also initiated the process of creating new therapeutic agents that are already undergoing the process of renewing the standard of care [4].

The poly (adenosine diphosphate -ribose) polymerase (PARP) inhibitors targeting synthetic lethality in BRCA -mutated TNBC; antibody -drug conjugates (ADC) exemplified by Sacituzumab, govitecan; and immune checkpoint inhibitors, which have

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also shown survival improvements, especially in PD -L1 -positive tumours, are among the most important therapeutic advances to date. Also, agents that specifically target the PI3K/AKT/mTOR axis, androgen receptor (AR)-signalling, as well as DNA damage response (DDR) are becoming promising in precision medicine in this disease scenario [5].

2. Molecularly Defined Vulnerabilities in TNBC

2.1 TROP-2 and Antibody–Drug Conjugates (ADCs)

Trophoblast cell -surface antigen -2 (TROP -2) has become a critical molecular target in triple-negative breast cancer (TNBC). TROP -2 being a transmembrane glycoprotein, is involved in cellular proliferation, invasion and epithelial -mesenchymal transition and numerous genomic and proteomic studies have reported the elevation of TROP -2 in most TNBC tumours compared to other breast cancer types. This biased and enhanced expression on tumour cells that is combined with its limited expression in normal tissues forms the basis of the targeted therapies created e.g. antibody-drug conjugates (ADCs) The most advanced TROP 2 directed ADC is sacituzumab govitecan (SG), which has completely revolutionized the treatment of metastatic TNBC [6]. SG is a humanized anti-TROP -2 monoclonal antibody conjugated to the active metabolite SN -38 of irinotecan through a moderately stable, hydrolyzable linker, thus enabling efficient delivery of the cytotoxic payload to TROP -2 expressing tumour cells but reducing systemic toxicity. The ASCENT trial, the first trial of its kind, showed that SG provides a significant progression-free survival (PFS) and overall survival (OS) advantage to patients with heavily pretreated metastatic TNBC over standard chemotherapy, making SG a treatment of choice after two or more alternative treatments have failed [7].

Outside SG, there is a fast-growing development of the field with the introduction of next-generation TROP-2 ADCs. To improve potency, stability and tumour selectivity, these next-generation agents combine the linker-payload designs, such as DNA-damaging agents, topoisomerase I inhibitors and microtubule-disrupting agents. Other ADCs may take advantage of the so-called bystander effects, allowing cytotoxic payload to enter into the cells adjacent to the tumour, thus enhancing their efficacy in heterogeneous tumours [8]. Also, new technologies of site-specific conjugation and improved antibody engineering approaches are being evaluated to reduce off-target toxicity and evade resistance. All in all, TNOP 2 directed ADCs constitute a significant clinical innovation in TNBC, which provides a targeted and clinically significant form of treatment to a cancer type that once was challenging to treat [9].

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2.2 DNA Damage Response (DDR) and PARP Inhibitors

Triple-negative breast cancer (TNBC) displays a strong connection with the malfunction of the DNA damage response (DDR) network, which is, in large part, due to higher occurrence of germline mutations in BRCA1 and BRCA2 and general homologous recombination deficiency (HRD). These mutations disrupt the ability of the tumour to repair the DNA damage of double-strand DNA with high fidelity, thus creating a treatment vulnerability that can be exploited by poly (ADP -ribose) polymerase (PARP) inhibitors [10]. The PARP enzymes are critical towards repair of a single strand DNA break; their inhibition leads to the accumulation of genomic lesions and cell death especially in tumours already lacking homologous recombination repair. The two most heavily clinically validated PARP inhibitors are olaparib and talazoparib, and both have demonstrated statistically significant progression-free survival benefits in patients with germline BRCA1/ 2 -mutated TNBC [11]. As this is accompanied by a largely attractive tolerability profile, in addition to the uniquely target-specific mechanism of action, this places them as either essential component of precision-medicine regimens in early-stage and metastatic disease settings. However, the clinical utility of PARP-inhibition is limited to a group of patients, and resistance, both intrinsic and acquired, is still an enormous challenge [12].

In order to expand the range of therapeutic applications of PARP inhibition, a continuum of combinatorial strategies is undergoing testing. ATR, CHK1, or WEE1 inhibitors used together with PARP inhibitors are aimed to increase the damage to DNA and overcome the developed resistance mechanisms [13]. Moreover, combination of PARP inhibitors and immunodulators is also pursued, and it assumes that immune responsiveness of tumours exposed to DNA-damage-induced immunogenic cues can be boosted. These rational combination mechanisms are potentially beneficial in attenuating the advantages of PARP blockade not only to the BRCAMutated malignancies but also in enhancing long-term clinical outcome in TNBC [14].

2.3 Immune Checkpoint Blockade

ICIs have become a key adjunct agent in the treatment arsenal of triple-negative breast cancer (TNBC), which is an immunogenic subtype. Interestingly, PD-1/PD-L1 guided agents, such as pembrolizumab and atezolizumab, have shown significant survival benefits when given alongside cytotoxic chemotherapy in patients with a positive tumor (PD-L1) with metastatic TNBC. Within the context of the neoadjuvant therapy of early-stage disease, pembrolizumab has demonstrated a significant enhancement of the rates of pathological complete response in high-risk groups, thus re-defining the standard of care [15]. However, the prognostic value of the modern biomarkers, including the PD-L1

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levels expression, the tumor-infiltrating lymphocytes level, and tumor mutations level are not optimal. Existing phase III clinical trials are comprehensively testing combinatoric regimens that combine ICIs with antibody-drug conjugates, poly (ADP-ribose) polymerase inhibitors, and precision-targeted therapeutic modalities in a bid to increase both the level and scope of antitumor reaction [16].

2.4 PI3K/AKT/mTOR Pathway

The phosphoinositide 3 -kinase (PI3K)/mammalian target of rapamycin (mTOR) cascade is a central signal transduction pathway controlling cellular growth, survival and metabolic stability; its dysregulation is a common occurrence in triple negative breast carcinoma (TNBC) [17]. Hyperactivation of the PI3K/AKT/mTOR signaling pathway is associated with somatic alterations, such as the activation of PIK3CA through activating mutagenesis, AKT phosphorylation-dependent activation, and loss-of-function mutation of the tumor suppressor phosphatase and tensin homolog (PTEN). These molecular pathology anomalies hold clinical significance to targeting PI3K/AKT/mTOR axis as part of a precision -medicine system. [18].

The AKT suppressors, especially capivasertib and ipatasertib, have had a promising effect, especially in biomarker-enriched groups with the presence of PIK3CA, AKT1, or PTEN mutations. The evidence available on early-stage and randomised clinical trials on these agents shows that there is a measurable enhancement in the progression-free survival when such agents are used together with the traditional cytotoxic chemotherapy [19].

Due to the high heterogeneity of TNBC, there is an ongoing effort to enhance clinical benefit through the use of combinatorial approaches in its treatment. On-going research is considering the combination of AKT inhibition with conventional chemotherapy, androgen receptor-based approaches, and immune checkpoint inhibition, and hopes to overcome compensatory signalling pathways and avoid resistance mechanisms. Such research methods promise to narrow the specific treatment paradigms of specific TNBC subgroups [20].

2.5 Androgen Receptor (AR) in LAR Subtype

Triple negative breast cancer (TNBC) is characterized by intense androgen receptor (AR) expression and a hormone-regulated transcriptional pattern, thus the luminal androgen receptor (LAR) subtype and stands out among other TNBC subtypes.

This biologically different subgroup is relatively insensible to standard chemotherapy, but resistant to

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endocrine manipulation [21]. Antiandrogen based on enzalutamide and bicalutamide have elicited a small but clinically significant and sustainable response in AR-positive TNBC, especially in patients with high levels of AR expression. The joint use of AR inhibitors and PI3K/AKT pathway antagonists and immunotherapeutic modalities is the subject of current clinical trials to add therapeutic effect to this specific cohort [22].

2.6 DDR Kinases: ATR, CHK1/2, WEE1

The DDR kinases such as ATR, CHK1/2, and WEE1 are important towards maintaining genomic stability and inhibits all of them through pharmacotherapy is a potential approach to treating triple-negative breast cancer (TNBC). These kinases play a crucial role in the process of dealing with replication stress- a hallmark of TNBC due to uncontrolled cell growth as well as broken DNA damage repair systems [23]. ATR, CHK1/2 or WEE1 modulation interferes with cell-cycle checkpoints, which leads to the accumulation of DNA damage and selective activation of tumor cells death. The interphase clinical experiments have shown that the simultaneous interaction of the DDR kinase inhibitor with either PARP inhibitor or traditional chemotherapy entails the enhancement of antitumor activity via the synthetic lethality mechanism. Therefore, this approach is quickly becoming the powerful tool to overcome the therapeutic resistance and to improve the clinical outcomes of patients with TNBC [24].

2.7 Tumor Microenvironment (TME)

There is a strong deterministic impact of the tumor microenvironment (TME) on therapeutic outcomes in triple-negative breast cancer (TNBC), and in specificity to the efficacy of immune checkpoint inhibitors (ICIs). The TNBC often has an immunosuppressive TME, which is defined by a dense population of tumor-associated macrophages (TAMs), dysfunctional T-cells populations, and stromal remodelling. The combination of these factors interferes with the successful antitumor immunity [25]. Transforming growth factor -2 (TGF -2) signalling, as a central signalling pathway, helps to promote immune exclusion via fibrosis and inhibition of penetration of cytotoxic T cells into the tumor core. Likewise, colony-stimulating factor- 1 receptor (CSF1R) regulates the process of the recruitment and polarization of immunosuppressive macrophages, which promotes the growth of tumors, angiogenesis, and metastasis. Angiogenesis through Vascular endothelial growth factor (VEGF) also impairs immune cell trafficking as well as establishing a hypoxic, tolerogenic niche [26].

The approach to attack these TME constituents has become an interesting idea to enhance the activity of ICIs in TNBC. TGF -B inhibitors are meant to reverse immune exclusion, CSF1R inhibitors are meant to deplete or reprogram TAMs to a pro-inflammatory

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phenotype, and anti-VEGF therapies are meant to normalise tumor vasculature, thereby increasing immune infiltration. Combination regimens of these agents with ICIs are in clinical trials and with a promising future. These strategies will reestablish effective immune surveillance and significantly improve patient responses to the use of checkpoint blockade by modulating the suppressive TME and increasing immune accessibility [27].

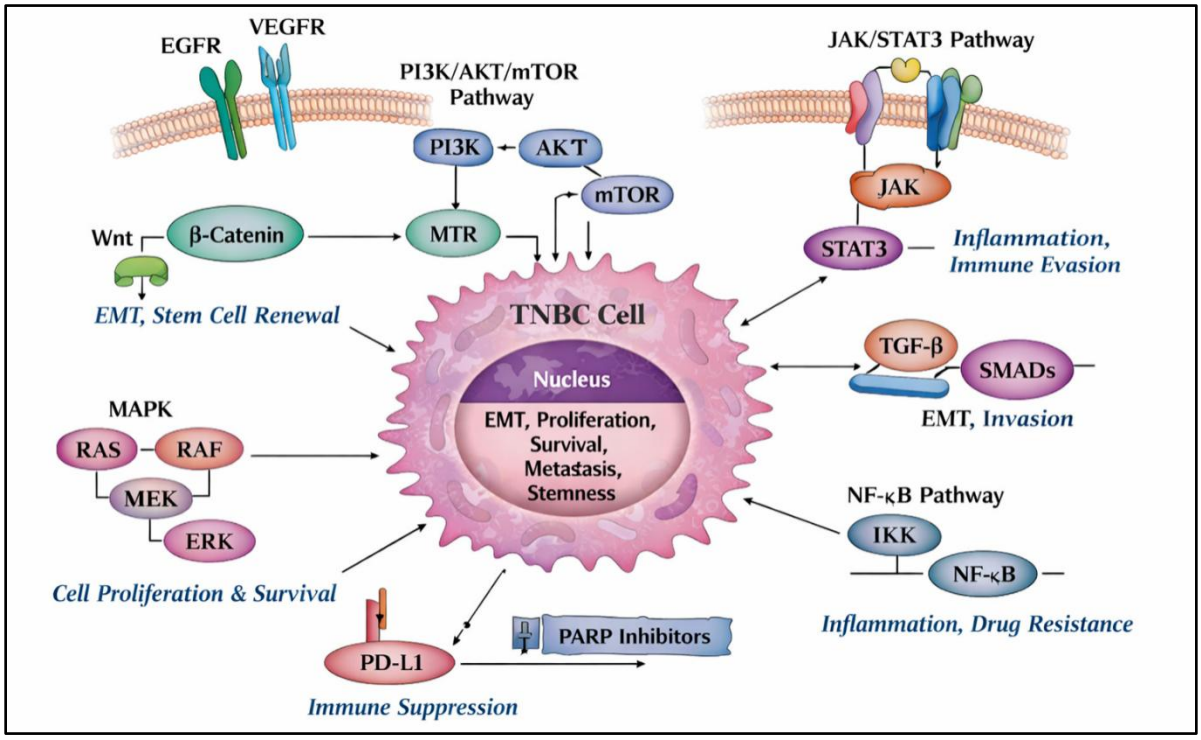

Figure 1. Major signalling pathways and therapeutic targets in triple-negative breast cancer (TNBC).

Figure 1. Key signalling pathways driving triple-negative breast cancer (TNBC) progression, including PI3K/AKT/mTOR, MAPK, JAK/STAT3, Wnt/β-catenin, TGF-β/SMAD, and NF-κB, regulating EMT, proliferation, survival, immune evasion, metastasis, and therapeutic resistance

3. Novel Therapeutic Strategies

3.1 Antibody–Drug Conjugates (ADCs)

Antibody-drug conjugates (ADCs) have become one of the most exciting therapeutic strategies to be used in the treatment of triple-negative breast cancer (TNBC), especially in the situation of relapses or metastases. The bispecific ADC Sacituzumab govitecan (SG), which targets Trop-2 antigen and is conjugated with topoisomerase-I inhibitor

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SN38, has been proven to have a beneficial impact on overall survival and has successfully redefined the standard of care in pre-treated TNBC [28]. The success of SG highlights the ability of ADCs to target tumour cells with potent cytotoxic agents that have a significantly lower rate of systemic toxicity, and has inspired the design of the next generation of ADCs, with new antigen targets and novel payload chemistries, which are in clinical development [29].

One of the topics of increasing interest is the combination of ADCs and immune checkpoint inhibitors (ICIs). ADCs have the potential to induce tumour cell death which can result in the release of neoantigens, dendritic cell activation and T- cell priming hence amplifying antitumour immune responses. Clinical trials, which combine ADCs with ICIs early, are underway to utilize this immunogenic synergy, with the aim to not only more effectively transform the response rate, overcome therapeutic resistance, and provide patients with TNBC with more long-term disease control [30].

3.2 Immune Checkpoint Inhibitors (ICIs)

The use of immune checkpoint inhibitors (ICIs) has revolutionized the therapeutic approach of a subdivision of triple-negative breast cancer (TNBC), especially when the tumor is PD-L1-positive. ICIs, including pembrolizumab, have shown significant progression-free and overall survival advantages when used together with chemotherapy through the activation of antitumor immune. Nevertheless, the answer to this question is still inconsistent, which underlines the necessity of more specific patient-selection plans. The current literature is interested in finding improved biomarkers - in place of PD-L1 - including tumor-infiltrating lymphocytes (TILs), genomic signatures and immune-related pathways to better predict response [31].

ICI in neoadjuvant combination has also been promising with improvement of pathological complete response rates and potential longevity. Also, new combination design methods are under consideration, such as the association of ICIs with antibody-

drug conjugates (ADCs) or PARP inhibitors (PARPi). The objectives of the combinations are to improve immunogenic cell death, increase immune infiltration, and resistance circumvention. All these strategies aim to increase the immunotherapy benefits to more TNBC patients [32].

3.3 Beyond PARP Inhibitors

Although the PARP inhibitors (PARPi) have shown great success in the treatment of homologous recombination-deficient tumors, therapeutic resistance is also a limiting

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factor. Resistance is usually mediated by restoration of homologous recombination (HR) repair mechanisms, secondary mutations that revert BRCA loss, enhancement of drug efflux through ABC transporters or stabilization of replication forks [33]. In order to overcome such mechanisms, new approaches are aimed at rational combination therapies. PARPi in combination with ATR inhibitors may take advantage of replication stress and inhibit HR repair, increasing synthetic lethality. Equally, the use of PARPi with anti-angiogenic substances may lead to hypoxia in tumors, which may also worsen the process of repairing DNA. These new generation strategies are to enhance durability and extend patient benefit [34].

Table 1: Mechanisms of PARP Inhibitor Resistance and Strategies to Overcome Them

Category	Description	References
Resistance to PARP Inhibitors Mechanisms.	Resurrection of homologous recombination (HR) repair. Hybrid alleles, BRCA1/2 reversion mutations reconstituting protein function. ABC transporter-mediated increased efflux of drugs. Replication fork stabilization inhibiting cytotoxic DNA defects.	[35]
New Measures to break the resistance.	PARP inhibitors + ATR inhibitors to take advantage of stress in replication and inhibit HR repair. PARP inhibitors + anti-angiogenic agents in order to cause tumor hypoxia and to inhibit DNA repair.	[36]
Therapeutic Rationale	Enhance the response durability, bypass response resistance pathways, and benefit more patients.	[37]

3.4 PI3K/AKT/mTOR Inhibitors

Inhibition of PI3K/AKT/mTOR-pathway is an encouraging treatment option in selected cases of triple-negative breast cancer (TNBC), specifically PI3K-pathway-altered tumors. The clinical value of these agents is also, however, usually limited by dose limiting toxicity, adverse metabolic effects and single agent efficacy that is small [38]. The existing studies are aimed at maximising the combination approaches to improve the overall therapeutic outcomes, with the least amount of toxicity. The combination of PI3K/AKT/mTOR

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inhibitors with established chemotherapy and the addition of PI3K/AKT/mTOR inhibitors to androgen receptor (AR) inhibitors have synergised with potential efficacy in AR-positive TNBC. Also, it is being investigated to work with immunotherapy to enhance immune responsiveness and overcome resistance mechanisms [39].

3.5 Emerging Therapies

New treatments to the routine of triple-negative breast cancer (TNBC) have recently become larger beyond the mainstream target therapies with bispecific antibodies, cellular immunotherapies, and re-purposed drug mechanisms revealing potential effectiveness. Bispecific antibodies can bind tumor-associated antigens and immune effector cells simultaneously with greater tumor specific cytotoxicity [40]. Although CAR-T cell therapy is still in its infancy in solid tumors, it is being developed to gain entry to the immunosuppressive microenvironment and enhance tumor penetration. Also, the possible anticancer effect of repurposed drugs such as beta-blockers has been proven by balancing stress-response pathways and lowering metastatic development. Together, these new directions provide new opportunities to change the outcomes of therapy in TNBC [41].

4. Clinical Trial Evidence

The biology and heterogeneity of triple-negative breast cancer (TNBC) are currently being met with a wide range of emerging therapeutic targets and modalities that can improve treatment. TROP-2-targeted therapy, specifically the antibody-drug conjugate Sacituzumab govitecan, has shown great clinical efficacy in selective delivery of SN-38 cytotoxic payload to tumor cells and is approved to use in metastatic TNBC previously treated [42]. Correspondingly, the homologous recombination repair (HRR) faults have also been targeted with significant progress being made by inhibitors of the polyadenosine polyphosphate enzyme PARP, which benefit from synthetic lethality in BRCA-mutated or HR-deficient tumors and are now approved in this context [43].

Immunotherapy remains one of the rapidly growing areas of treatment, with PD-1/PD-L1 inhibitors, including pembrolizumab and atezolizumab, increasing the effect in biomarker-selected TNBCs, mostly those with PD-L1-positive tumors [44].

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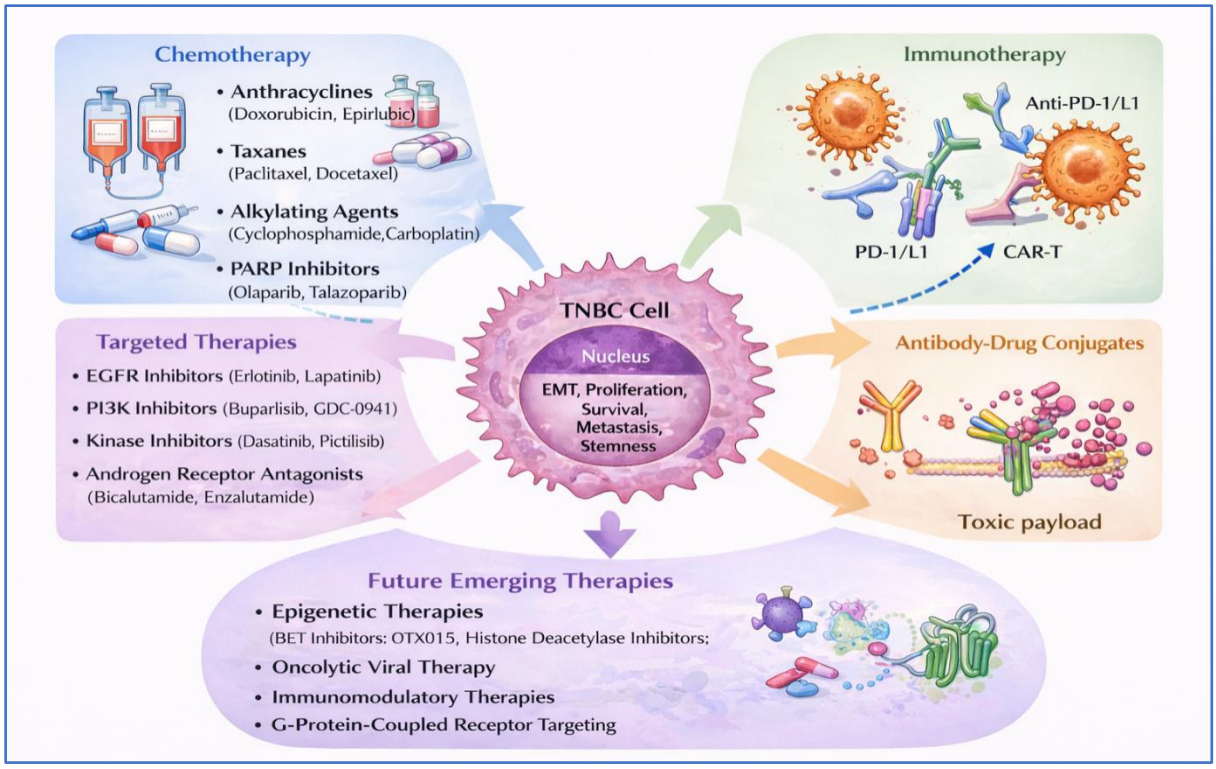

Figure 2. Current and Emerging Therapeutic Landscape in Triple-Negative Breast Cancer.

Figure 2. Overview of current and emerging therapeutic strategies for triple-negative breast cancer (TNBC), including conventional chemotherapy, targeted therapies, immunotherapy, antibody–drug conjugates, and future treatment approaches aimed at inhibiting tumor growth, metastasis, and therapeutic resistance.

In addition to the strategies that are already in place, there are a number of avenues that are being explored. The AKT inhibitors are the result of dysregulation of the PI3K/AKT/mTOR signalling axis that is often involved in the proliferation and survival of TNBC, and which is currently being investigated in the clinical trials. The androgen receptor (AR) is also a logical target in luminal androgen receptor (LAR) subtype of TNBC and agents like enzalutamide have been shown to be active in Phase II [45]. DNA damage response (DDR) checkpoints inhibition, especially of ATR, CHK1, and WEE1, is another potentially useful approach to the elimination of replication stress and genomic instability, and clinical trials in the early phase have shown promising antitumor activity [46].

Lastly, therapeutic reprogramming of the tumor microenvironment (TME) is being

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considered; it involves the assessment of TGF-b and CSF1R blockers, which are expected to diminish immunosuppression and promote antitumor immunity; these agents are under trial at an early stage of development. Altogether, these new approaches promise to be an evolving TNBC treatment environment with numerous options to individualized and biomarker-guided treatment development [47].

Table 2. Emerging Drug Targets and Therapeutic Modalities in TNBC

Target	Agent/Approach	Mechanism	Status	References
TROP 2	Sacituzumab govitecan (antibody-drug conjugate).	Transfers the SN 38 to tumor cells.	Approved	[48]
BRCA/HRD	Olaparib and talazoparib	Synthetic lethality is promoted by inhibition of PARP.	Approved	[49]
PD -1/PD -L1	Pembrolizumab and atezolizumab.	Checkpoint blockade of the immune system is used.	Approved in selected pts	[50]
PI3K/AKT/mTOR	AKT inhibitors	The proliferative signaling is repressed.	Trials ongoing	[51]
AR (LAR subtype)	Enzalutamide	Anti-androgen treatment is done.	Phase II studies	[52]
ATR/CHK/WEE1	ATR/CHK inhibitors	Checkpoint inhibition of DNA damage repair is effected.	Early-phase trials	[53]
TME	TGF -b inhibitors and CSF1R inhibitors	The immigration of the immune microenvironment is sought.	Early-phase trials	[54]

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5. Resistance Mechanisms

Although the use of new therapeutic agents in triple-negative breast cancer (TNBC) has a promising efficacy, resistance development is a significant clinical challenge.

5.1. PARP inhibitors (PARPi): PARP inhibitors have been shown to be resistant to by repairing homologous recombination (HR) through reversion mutations at BRCA1/2. Also, the augmented drug efflux through association with ATP-binding cassette (ABC) transporters leads to diminished intracellular concentration of drugs and therapeutic failure [55].

5.2. Immune checkpoint inhibitors (ICIs): Tumor resistance to ICIs may be caused by immune evasion e.g., loss of antigen presentation machinery, interferon signalling pathway mutations, or by an immunosuppressive tumor microenvironment. Antigenicity of tumors is also low and this decreases immunotherapy responsiveness [56].

5.3. Antibody-drug conjugates (ADCs): There are three methods of resistance to ADCs: antigen downregulation, nonhomogeneous target expression, and drug payload sensitivity. Therapeutic efficacy is also limited by efflux of the cytotoxic payload by the drug transporters [57].

5.4. Tumor heterogeneity: Inter and intra-tumor heterogeneity both make it difficult to treat. The active development of resistant clones requires real-time observation with the help of high-tech biomarkers, including circulating tumor DNA (ctDNA) and liquid biopsy methods [58].

6. Safety and Tolerability

Although the treatment of triple-negative breast cancer (TNBC) has seen impressive advancement of treatment, safety and tolerability are crucial factors in clinical decision-making. The antibody-drug conjugates (ADCs) are linked with haematological adverse effects like neutropenia, gastrointestinal adverse effects, especially diarrhoea [59]. Poly (ADP-ribose) polymerase (PARPi) often lead to anemia and exceptionally, some have the potential to increase the risk of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Unless otherwise stated, immune checkpoint inhibitors (ICIs) are well-tolerated but can cause immune-related adverse events, such as thyroid dysfunction, colitis, and pneumonitis, which must be closely monitored and treated in time [60].

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The mechanism of PI3K/AKT blockers is promising; nevertheless, they frequently exhibit side effects that are challenging to manage, like hyperglycemia and skin reactions, e.g., rash. Thus, patient selection, overseeing, and dose adjustments should be cautious to achieve efficacy and safety in various modalities of treatment of TNBC [61].

7. Future Directions

TNBC therapeutic area is changing at a fast pace, and various good prospects are being actively explored. The predictive biomarkers (programmed death-ligand 1 (PD-L1), homologous recombination deficiency (HRD), and tumor-infiltrating lymphocytes (TILs)) should be standardized so that they are able to maximize patient stratification and guarantee the reproducibility between clinical trials. The rational way of increasing the durability of response is to use adaptive combination strategies, including ADCs with either ICIs or PARPi with ataxia telangiectasia and Rad3-related (ATR) inhibitors to counteract resistance mechanisms. In addition to this, emerging tumor microenvironment (TME)-controlling drugs have a potential to redefine immune suppression and enhance treatment results. The novel modalities with a potential to be translated to TNBC include cellular therapies such as chimeric antigen receptor (CAR) T-cells and bispecific antibodies. The use of drug repurposing can also offer both cost-efficient and globally available solutions to the inequities in care. Lastly, patient-use de-escalation strategies in patients with low-risk TNBC are under consideration to reduce long-term toxicities as well as overtreatment to improve precision oncology in such a difficult-to-treat breast cancer subtype.

8. Conclusion

There is a rapid evolution of the therapeutic paradigm of triple-negative breast cancer (TNBC), shifting much more than in the past when chemotherapy was the sole treatment method to far more specific and biomarker-directed treatment approaches. Antibody-drug conjugates (ADCs), PARP inhibition, and immune checkpoint inhibitor (ICI) have significantly improved specific groups of patients, thus becoming a new standard of care. At the same time, new specific agents, such as PI3K/AKT signalling pathway inhibitors, luminal androgen receptor (LAR) subtype specific androgen receptor-directed therapy, and DNA damage response (DDR) kinase inhibitors ATR, CHK1 and WEE1 are in the pipeline of clinical trials. Besides this, cellular immunotherapies and innovative biologics are also increasing the therapeutic horizon. The following stage of development will depend on the discovery of potent predictive biomarkers, the development of rational drug regimens, which will break resistance, and the enhancement of access to novel treatment all over the world. To make these scientific advances meaningful clinical

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benefits to all TNBC patients, it will be necessary to make them affordable and equitably distributed.

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