J Nanostruct 15(2): 422-430, Spring 2025

RESEARCH PAPER

Olaparib-Loaded Iron Oxide Nanoparticles for the Transgenic Treatment of Triple-Negative Breast Cancer (TNBC): Integrating Targeted Therapy and MRI Imaging: A Review

Abitov Ilnur Ildusovich [1], Rustam Kushatov [2], Ixtibar Tuychiyeva [3], Shoira Urazmetova [4], Isaeva Nilufar [5], Alimova Iroda Anvarovna [6], Naimova Shokhida Anvarovna [7], Otabek Bobojonov [8], Gullola Umarova Abdurashid qizi [6], Rayimqulova Charos Axmatovna [9], Allayarov Muhammed-Yar Atamuratovich [10], Sarvar Temurovich Islomov [11], N. Esanmurodova [12, 13, 14]*

[1] *Department of Agronomy, Navoi State Mining and Technological University, Navoi, Uzbekistan*

[2] *Samarkand State University named after Sharof Rashidov, Uzbekistan*

[3] *Tashkent State Technical University after named Islam Karimov, Tashkent, Uzbekistan*

[4] *Urgench Branch of Tashkent University of Information Technologies named after Muhammad al-Khwarizmi, Urganch, Uzbekistan*

[5] *Alfraganus University, Tashkent, Uzbekistan*

[6] *Fergana Medical Institute of Public Health, Fergana, Uzbekistan.*

[7] *Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Uzbekistan*

[8] *Department of Fruits and Vegetables at the Urganch State University, Uzbekistan*

[9] *Samarkand State Medical University, Samarkand, Uzbekistan*

[10] *Karakalpak State University named after Berdakh, Nukus,Uzbekistan*

[11] *Department of Oncology and Hematology, National Children's Medical Center, Tashkent, Uzbekistan*

[12] *Tashkent Institute of Irrigation and Agricultural Mechanization Engineers, National Research University, Tashkent, Uzbekistan*

[13] *Kimyo International University in Tashkent, Uzbekistan*

[14] *Baku Eurasian University, Baku, AZ 1073, Azerbaijan*

ARTICLE INFO

Article History:
Received 14 January 2025
Accepted 25 March 2025
Published 01 April 2025

Keywords:
Breast Cancer
Iron Oxide
Nanoparticles
Triple-Negative

ABSTRACT

Triple-negative breast cancer (TNBC) remains one of the most aggressive and treatment-resistant subtypes of breast cancer, characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). The lack of targeted therapies and high rates of relapse underscore the urgent need for innovative treatment strategies. Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, has shown promise in BRCA-mutated and homologous recombination-deficient (HRD) TNBC, but its clinical utility is limited by poor bioavailability, systemic toxicity, and intrinsic resistance. Iron oxide nanoparticles (IONPs) offer a transformative platform to address these challenges by enabling tumor-targeted drug delivery and non-invasive magnetic resonance imaging (MRI). This review explores the design, development, and theranostic potential of Olaparib-loaded IONPs, emphasizing their dual functionality as therapeutic carriers and imaging contrast agents. Preclinical advancements, clinical translation challenges, and future directions are critically analyzed to provide a comprehensive perspective on bridging nanomedicine with precision oncology in TNBC.

How to cite this article
Ildusovich A., Kushatov R., Tuychiyeva I., Urazmetova S. et al. Olaparib-Loaded Iron Oxide Nanoparticles for the Transgenic Treatment of Triple-Negative Breast Cancer (TNBC): Integrating Targeted Therapy and MRI Imaging: A Review J Nanostruct, 2025; 15(2):422-430. DOI: 10.22052/JNS.2025.02.004

* *Corresponding Author Email: abitov_ilnur@mail.ru*

This work is licensed under the Creative Commons Attribution 4.0 International License.
To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

INTRODUCTION

Triple-negative breast cancer (TNBC) accounts for 10–15% of all breast cancers and is associated with poor prognosis due to its aggressive biology, metastatic potential, and limited treatment options. Unlike hormone receptor-positive or HER2-positive subtypes, TNBC lacks actionable molecular targets, leaving chemotherapy as the mainstay of treatment [1]. However, chemotherapy often fails to eradicate residual disease, leading to relapse of patients within five years. The discovery of synthetic lethality between PARP inhibitors and BRCA mutations has revolutionized the management of BRCA1/2-mutated TNBC, but only 10–20% of TNBC cases harbor these mutations [2]. Furthermore, PARP inhibitors like Olaparib exhibit suboptimal pharmacokinetics, including rapid clearance and dose-limiting hematologic toxicity [3]. Nanoparticle-based drug delivery systems, particularly iron oxide nanoparticles (IONPs), have emerged as a promising solution to enhance drug bioavailability, reduce off-target effects, and integrate diagnostic imaging [4].

This article evaluates the convergence of Olaparib and IONP technology, focusing on their synergistic potential to overcome TNBC's therapeutic and diagnostic challenges.

To address these challenges, this review highlights the innovative integration of Olaparib with iron oxide nanoparticles (IONPs) as a multifunctional theranostic platform. Unlike conventional delivery systems, Olaparib-loaded IONPs uniquely combine pH-responsive drug release, active tumor targeting (e.g., via folate or EGFR ligands), and MRI-guided monitoring into a single nanoscale construct. This approach not only enhances intratumoral drug accumulation but also enables real-time visualization of drug delivery and therapeutic response—a feature absents in existing PARP inhibitor regimens. Furthermore, the magnetic properties of IONPs allow external field-guided targeting, bypassing stromal barriers and improving penetration into hypoxic tumor cores. By co-encapsulating Olaparib with siRNA or immune modulators, this platform extends therapeutic utility beyond BRCA-mutated TNBC, offering a synergistic strategy to sensitize homologous recombination-proficient tumors.

This article aims to critically evaluate the design, efficacy, and clinical potential of Olaparib-loaded IONPs as a transformative solution for TNBC. Specifically, it explores (1) the mechanistic basis for combining PARP inhibition with nanomedicine, (2) advances in IONP engineering to optimize drug loading, tumor targeting, and MRI contrast, and (3) preclinical and clinical evidence supporting their theranostic utility. Additionally, it discusses unresolved challenges, including long-term biocompatibility, scalability, and biomarker-driven patient stratification. By synthesizing interdisciplinary insights from oncology, nanotechnology, and imaging sciences, this review underscores the potential of Olaparib-IONP hybrids to redefine precision therapy in TNBC, bridging the gap between targeted treatment and non-invasive diagnostics in one of oncology's most formidable malignancies.

BIOLOGY OF TRIPLE-NEGATIVE BREAST CANCER

Triple-negative breast cancer (TNBC) is a highly heterogeneous malignancy characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression [5]. Molecular subtyping, based on gene expression profiling, identifies six distinct subtypes under the Lehmann classification: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) [6]. BL1, representing approximately 35% of TNBCs, is driven by proliferative signatures linked to cell cycle genes, such as CCNE1 and CDK6, as well as DNA damage response pathways involving ATR and CHEK1 [7]. BL2 tumors exhibit metabolic addiction, characterized by overexpression of growth factor receptors like EGFR and FGFR1 and enzymes critical to glycolysis, including HK2 and LDHA [8]. The IM subtype is marked by elevated levels of CXCL9 and CXCL10 chemokines and enhanced antigen presentation via HLA-DR and CD80 [9]; however, immune evasion is facilitated by activation of the PD-L1/PD-1 axis and infiltration of regulatory T cells and exhausted CD8+ T cells expressing FOXP3 and LAG-3. Mesenchymal and MSL subtypes are associated with epithelial-mesenchymal transition (EMT), featuring the loss of E-cadherin, gain of N-cadherin, and the activity of transcription factors like SNAI1 and TWIST1 [10]. These subtypes promote metastasis and resistance to anthracyclines through matrix remodeling mediated by enzymes such as MMP2 and LOXL2 [11]. LAR tumors are distinct in their reliance on androgen receptor (AR) signaling and frequent PIK3CA mutations, making them sensitive

CC BY

to AR antagonists such as enzalutamide, while exhibiting resistance to standard chemotherapy [12]. At the genomic level, TNBC frequently harbors TP53 mutations, found in approximately 80% of cases. These mutations, often truncating variants like R175H and R248Q, result in loss of p53's apoptotic function [13]. Alterations in BRCA1 and BRCA2 genes occur in 15–20% of TNBC cases, with germline mutations accounting for 70% and somatic mutations for 30% of these alterations [14]. Additional homologous recombination deficiencies are driven by mutations in PALB2, RAD51C, and ATM, which contribute to genomic instability [15]. Oncogenic alterations include MYC amplifications observed in 30% of cases, associated with chemoresistance, and PTEN deletions seen in 15%, which activate the PI3K/AKT/mTOR pathway [16]. The tumor microenvironment (TME) plays a significant role in TNBC progression and therapeutic resistance. Hypoxia, mediated by HIF-1α, drives the expression of genes such as CAIX and GLUT1 [17]. Cancer-associated fibroblasts (CAFs) enhance interstitial fluid pressure through the deposition of collagen and fibronectin. CAF-derived exosomes transfer microRNAs like miR-21 and miR-155 to tumor cells, silencing tumor suppressors such as PTEN and BRCA1 [18]. Metabolic interactions between tumor cells and CAFs include lactate transfer via MCT4 and MCT1, fueling oxidative phosphorylation, and the production of glutamine to support nucleotide synthesis [19]. Immune suppression is driven by IDO1+ dendritic cells, which catabolize tryptophan into kynurenine, suppressing T cell function [20]. Pembrolizumab shows limited efficacy in PD-L1-positive TNBC due to low tumor mutational burden and TGF-β-mediated exclusion of cytotoxic T cells [21]. Emerging strategies, including inhibitors targeting EMT transcription factors, collagen crosslinking, and metabolic symbiosis, aim to overcome these resistance mechanisms and improve treatment outcomes [22].

OLAPARIB: MECHANISM OF ACTION AND CLINICAL LIMITATIONS

Olaparib, a potent inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes (PARP1/2), exerts its therapeutic effect by disrupting the base excision repair (BER) pathway, a critical mechanism for repairing single-strand DNA breaks (SSBs) [23]. PARP enzymes detect SSBs, recruit repair proteins, and synthesize poly(ADP-ribose) (PAR) chains to signal downstream repair. By binding to PARP's catalytic domain, Olaparib prevents PAR synthesis and traps PARP-DNA complexes, converting transient SSBs into persistent double-strand breaks (DSBs) [24]. In tumors with BRCA1/2 mutations or homologous recombination deficiency (HRD), the loss of homologous recombination repair (HRR) renders cells unable to resolve these DSBs, leading to synthetic lethality—a collapse of genomic integrity and apoptotic cell death [25]. Beyond BRCA mutations, HRD can arise from epigenetic silencing (e.g., BRCA1 promoter methylation) or defects in HRR-associated genes (e.g., PALB2, RAD51) [26]. Olaparib has improved progression-free survival in BRCA-mutated TNBC, with landmark trials (e.g., OlympiAD) showing a median PFS of 7.0 months vs. 4.2 months for chemotherapy [27]. However, its efficacy is undermined by pharmacokinetic limitations: oral bioavailability ranges from 10% (fasted state) to 60% (with high-fat meals), and rapid hepatic metabolism by cytochrome P450 enzymes (CYP3A4) necessitates frequent dosing. Systemic exposure correlates with dose-dependent hematologic toxicity, including grade 3/4 anemia (40%) and thrombocytopenia (30%), often requiring dose interruptions [28]. Furthermore, acquired resistance emerges via PARP1 overexpression (amplifying DNA repair capacity), upregulation of drug efflux pumps (ABCB1, ABCC1) [29], or restoration of HRR through secondary BRCA1/2 mutations ("reversion mutations") or stabilization of replication forks via loss of PTIP or PARI [30]. Tumor-targeted delivery systems, such as nanoparticle encapsulation, are critical to circumvent these limitations by enhancing intratumoral drug accumulation, reducing systemic exposure, and overcoming efflux-mediated resistance [31].

IRON OXIDE NANOPARTICLES (IONPS) IN CANCER THERANOSTICS

Iron oxide nanoparticles (IONPs) are magnetically responsive materials, typically composed of magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3), with sizes ranging from 10–100 nm to optimize magnetic properties and biodistribution [32]. Their synthesis varies based on precision requirements. Co-precipitation involves alkaline precipitation of Fe^{2+}/Fe^{3+} salts, producing hydrophilic IONPs, while thermal decomposition of organometallic precursors like iron oleate in high-boiling solvents creates monodisperse,

CC BY

hydrophobic IONPs that require further ligand exchange for biocompatibility [33]. Microemulsion methods allow controlled size synthesis in confined nanoreactors, but scalability remains limited [34].

Post-synthesis, functionalization enhances stability and targeting. Polyethylene glycol (PEG) coatings reduce immune clearance and extend circulation times, while targeting ligands like folate or trastuzumab enable receptor-mediated uptake in tumors overexpressing folate receptors or HER2 [35]. Stimuli-responsive polymers, such as poly(N-isopropylacrylamide), provide temperature- or pH-triggered drug release, improving therapeutic precision [36]. The superparamagnetic core of IONPs provides strong T2/T2 MRI contrast, aiding in high-resolution imaging of tumor margins, angiogenesis, and metastases [37]. As drug delivery agents, IONPs exploit the enhanced permeability and retention (EPR) effect for passive tumor accumulation, while external magnetic fields (0.5–1 T) can improve localization [38]. Their theranostic capabilities integrate diagnostic imaging and targeted therapy; MRI monitors real-time nanoparticle biodistribution, while loaded drugs like doxorubicin or paclitaxel are released at tumor sites, reducing systemic side effects [39].

Recent advancements highlight multifunctional IONPs co-loaded with siRNA for gene silencing and conjugated with fluorophores for combined MRI and near-infrared fluorescence imaging [40]. These developments expand their utility for multimodal imaging and therapy. However, challenges persist, particularly regarding long-term iron metabolism and renal clearance, which require further study to ensure safety in clinical applications [41]. IONPs represent a versatile platform for cancer diagnosis and therapy, combining magnetic responsiveness with targeted delivery. Their dual functionality and potential for multimodal applications position them as critical tools in advancing personalized medicine [42].

DESIGN AND DEVELOPMENT OF OLAPARIB-LOADED IONPS

Olaparib incorporation into iron oxide nanoparticles (IONPs) requires precise engineering to achieve optimal drug loading, stability, and controlled release. Various strategies have been employed to address these challenges [43, 44]. Encapsulation of Olaparib within biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA) or chitosan is commonly achieved using techniques like solvent evaporation or nanoprecipitation [45]. These methods yield drug loading efficiencies (DLE), providing a balance between loading capacity and sustained release. Another approach involves electrostatic adsorption of protonated Olaparib onto negatively charged IONP surfaces, such as those coated with citrate [46]. Covalent conjugation offers a more stable alternative, employing pH-sensitive linkers such as hydrazone or cis-aconityl bonds [47]. These linkers hydrolyze selectively in the acidic tumor microenvironment (pH 6.5–6.8), allowing targeted drug release. For example, carboxylated IONPs can be modified with hydrazide groups that form hydrazone bonds with Olaparib's ketone groups. This strategy achieves payload retention in neutral pH conditions, drug release in acidic environments, demonstrating effective tumor-specific delivery [48].

Targeting ligands further enhance the specificity of Olaparib-loaded IONPs. Functionalizing the nanoparticle surface with ligands like anti-EGFR antibodies, such as cetuximab, facilitates receptor-mediated uptake in TNBC cells, which commonly overexpress EGFR [49]. This modification increases cellular uptake by threefold compared to non-targeted formulations, improving therapeutic efficacy. Stimuli-responsive systems, such as magnetic hyperthermia-triggered release, provide additional control [50]. In these systems, alternating magnetic fields (AMF) in the range of 100–500 kHz generate localized heat (42–45°C), destabilizing the lipid bilayer or polymer matrix encapsulating Olaparib. This technique synergizes with hyperthermia-induced apoptosis and inhibition of heat shock protein 90 (HSP90), sensitizing tumors to PARP inhibition [51]. In MDA-MB-231 xenografts, these hybrid nanoparticles achieved 60% tumor regression compared to 35% with free Olaparib [52]. However, several challenges remain, including optimizing AMF parameters to prevent damage to healthy tissues and ensuring nanoparticle stability under magnetic or thermal stress [53].

TRANSGENIC TREATMENT APPROACHES IN TNBC

The integration of PARP inhibition with nanoparticle-enabled gene editing and immune modulation signifies a transformative approach to triple-negative breast cancer (TNBC) therapy [54]. This strategy addresses both the genetic vulnerabilities and the immunosuppressive tumor

CC BY

microenvironment (TME), paving the way for more effective treatment paradigms [55]. A key application involves the co-delivery of Olaparib, a PARP inhibitor, with small interfering RNA (siRNA) targeting DNA repair genes such as BRCA2, RAD51, and FANCD2 [56]. These combinations enhance synthetic lethality in homologous recombination-deficient (HRD) tumors. Lipid-coated iron oxide nanoparticles (IONPs) co-loaded with Olaparib and BRCA2-targeting siRNA have shown remarkable synergy, inducing the accumulation of double-strand breaks (DSBs) and reducing IC50 values in BRCA1-wildtype TNBC cell lines like MDA-MB-231. This dual-targeted approach maximizes DNA damage while exploiting existing HRD pathways in cancer cells [57].

Beyond genetic editing, IONPs also address the immunosuppressive TME of TNBC. Silencing of cancer-associated fibroblast (CAF)-derived transforming growth factor-beta (TGF-β) through siRNA-loaded IONPs has shown significant therapeutic benefit. TGF-β blockade reduces collagen I deposition by 70%, alleviating the dense stroma that hinders drug penetration [58]. This stromal modulation enhances Olaparib delivery to tumor cores, improving treatment outcomes. Concurrently, IONPs loaded with agents promoting M2-to-M1 macrophage polarization, such as interleukin-12 (IL-12) mRNA or STAT3 inhibitors, further reprogram the TME. This reprogramming increases CD8+ T-cell infiltration by threefold, creating a more immunogenic microenvironment that enhances the efficacy of immune checkpoint inhibitors like PD-1 antibodies [59]. Immunomodulatory strategies extend to the activation of dendritic cells for improved antigen presentation. IONPs co-loaded with Olaparib and toll-like receptor (TLR) agonists, such as resiquimod (TLR7/8 agonist), have been shown to trigger dendritic cell maturation, boosting T-cell priming and expanding tumor-specific immune responses [60].

Challenges remain, particularly in ensuring the intracellular delivery of nucleic acids and avoiding off-target effects with gene-editing tools like CRISPR-Cas9 [61]. Strategies such as proton-sponge polymers (e.g., polyethyleneimine, PEI) or fusogenic peptides are being employed to enhance endosomal escape, while optimized single-guide RNA (sgRNA) designs aim to improve editing specificity [62]. Bioresponsive IONPs represent another promising development, incorporating HIF-1α-responsive promoters to restrict Cas9 expression to hypoxic TMEs, minimizing off-target activity in normal tissues [63]. Integrating PARP inhibitors with advanced nanoparticle delivery systems enables a multipronged attack on TNBC by targeting its genetic vulnerabilities, reversing chemoresistance, and reshaping the TME. This comprehensive approach has the potential to redefine treatment outcomes for this aggressive cancer type, creating a pathway toward more durable and effective therapies [64].

INTEGRATION OF TARGETED THERAPY AND MRI IMAGING

The theranostic potential of Olaparib-loaded iron oxide nanoparticles (IONPs) lies in their capacity to combine precision therapy with advanced diagnostic imaging, enabling simultaneous treatment and real-time monitoring [65]. This dual functionality addresses critical challenges in oncology, providing targeted drug delivery while employing high-resolution magnetic resonance imaging (MRI) to assess therapeutic responses and adjust strategies dynamically [66].

The superparamagnetic properties of the iron oxide core allow for significant T2/T2 relaxation effects, producing negative contrast (signal voids) on MRI scans [67]. These signal changes directly correlate with nanoparticle accumulation within the tumor, offering precise insights into their biodistribution. Quantitative T2 mapping, which measures local magnetic field variations, can detect intratumoral IONP concentrations with sensitivity as low as 0.1 mM Fe [68]. This allows for verification of nanoparticle targeting efficiency, enabling clinicians to refine external magnetic field parameters (typically 0.5–1 T) to enhance retention and distribution within tumors [69]. Dynamic contrast-enhanced (DCE) MRI, which can utilize either gadolinium-based contrast agents or the intrinsic contrast provided by IONPs, adds another layer of information. DCE-MRI evaluates pharmacokinetic parameters such as Ktrans (the volume transfer constant) and ve (extravascular extracellular space volume fraction), which are critical indicators of Olaparib penetration into the tumor and its effect on the stromal microenvironment [70]. Preclinical studies using orthotopic TNBC models have demonstrated Ktrans after IONP-based therapy correlates intratumoral Olaparib levels and a twofold induction of apoptosis, highlighting the

CC BY

effectiveness of combining imaging metrics with therapeutic interventions [71]. For metastatic TNBC, IONPs co-loaded with Olaparib and gadolinium-DOTA chelates offer dual MRI contrast modalities, enhancing the detection of metastatic lesions. These nanoparticles provide T1 (positive) contrast from gadolinium alongside T2 (negative) contrast from the iron oxide core. This dual-modality imaging significantly improves the detection of small metastases, particularly sub-5 mm lesions in the lungs and liver, which are challenging to identify with conventional imaging techniques [72]. Another innovative advancement includes hypoxia-sensitive IONPs coated with nitroimidazole derivatives [73]. These nanoparticles generate measurable T2 signal changes in response to tumor oxygenation levels, enabling targeted activation of alternating magnetic fields (AMFs) in hypoxic regions [74]. This approach has been shown to improve the precision of Olaparib delivery while reducing off-target exposure [75]. MRI-guided therapy using this approach reduces systemic Olaparib concentrations in critical organs, such as bone marrow and intestinal crypts, mitigating associated hematologic and gastrointestinal toxicity [76]. Diffusion-weighted imaging (DWI) further complements the theranostic capabilities of Olaparib-IONPs. By measuring changes in the apparent diffusion coefficient (ADC), DWI can detect early tumor responses to treatment [77]. Preclinical studies in patient-derived xenograft (PDX) models indicate that a 20% increase in ADC within 48 hours of treatment predicts an 80% reduction in tumor volume [78]. Despite these promising applications, clinical translation faces several hurdles. MRI protocols, including variations in magnetic field strength (1.5T vs. 3T) and pulse sequences (spin-echo vs. gradient-echo), can affect contrast quantification and require standardization [79].

PRECLINICAL AND CLINICAL ADVANCEMENTS

Francesco Schettini et al [80], investigated the effects of a 3-week olaparib (PARP inhibitor) treatment prior to standard neoadjuvant chemotherapy in 35 patients with early-stage breast cancer, including 27 with germline BRCA wild-type (gBRCA-wt) triple-negative breast cancer (TNBC) and 8 with gBRCA-mutated (gBRCA-mut) breast cancer (6 TNBC, 2 HR+/HER2-negative). Assessments included clinical, radiometabolic (via PET/CT), immune, and molecular analyses. Key findings showed partial clinical and radiometabolic responses in 40.7% and 50% of gBRCA-wt patients, respectively, indicating olaparib's potential benefit beyond BRCA-mutated cases. gBRCA-mut tumors exhibited higher tumor-infiltrating lymphocytes (TILs) and PD-L1 positivity. Clinical responders demonstrated immune shifts: reduced T-regs/T-eff ratio, B cells, and NK cells, alongside increased T-helper cells and CD4/CD8 ratio. Ki67 and TILs remained stable, while PD-L1 positivity non-significantly increased post-olaparib. The study concludes that olaparib may benefit early-stage TNBC regardless of BRCA status and suggests integrating TILs, PD-L1, and BRCA status in future trials to optimize treatment strategies involving PARP inhibitors.

CONCLUSION AND FUTURE PERSPECTIVES

Despite their promise, Olaparib-loaded IONPs face translational hurdles. Long-term IONP biocompatibility remains uncertain, with concerns about iron accumulation in the liver and spleen. Scalability of Good Manufacturing Practice (GMP)-compliant synthesis and regulatory approval for multifunctional nanoparticles are additional barriers. TNBC heterogeneity necessitates biomarker-driven patient stratification, such as BRCA status or HYAL1 expression, to identify likely responders. Future innovations may include dual-drug-loaded IONPs (e.g., Olaparib + paclitaxel) or immune-modulatory designs incorporating anti-PD-L1 antibodies. Artificial intelligence (AI)-driven MRI analysis could personalize dosing schedules based on real-time tumor response. In conclusion, Olaparib-loaded IONPs represent a paradigm shift in TNBC theranostics, merging precision therapy with advanced imaging to address unmet clinical needs. Collaborative efforts among researchers, clinicians, and regulators are essential to translate this technology from bench to bedside, offering hope for one of oncology's most formidable challenges.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES

1. Kumar P, Aggarwal R. An overview of triple-negative breast

(cc) BY

cancer. Arch Gynecol Obstet. 2015;293(2):247-269.
2. Dilmac S, Ozpolat B. Mechanisms of PARP-Inhibitor-Resistance in BRCA-Mutated Breast Cancer and New Therapeutic Approaches. Cancers (Basel). 2023;15(14):3642.
3. Bruin MAC, Sonke GS, Beijnen JH, Huitema ADR. Pharmacokinetics and Pharmacodynamics of PARP Inhibitors in Oncology. Clin Pharmacokinet. 2022;61(12):1649-1675.
4. Al-Thani AN, Jan AG, Abbas M, Geetha M, Sadasivuni KK. Nanoparticles in cancer theragnostic and drug delivery: A comprehensive review. Life Sci. 2024;352:122899.
5. Derakhshan F, Reis-Filho JS. Pathogenesis of Triple-Negative Breast Cancer. Annu Rev Pathol. 2022;17:181-204.
6. Lee Y-M, Oh MH, Go J-H, Han K, Choi S-Y. Molecular subtypes of triple-negative breast cancer: understanding of subtype categories and clinical implication. Genes and Genomics. 2020;42(12):1381-1387.
7. Esquea EM, Reginato M. Targeting Metabolic Vulnerabilities in Breast Cancer Brain Metastasis: Drexel University Libraries.
8. Tsui J, Qi S, Perrino S, Leibovitch M, Brodt P. Identification of a Resistance Mechanism to IGF-IR Targeting in Human Triple Negative MDA-MB-231 Breast Cancer Cells. Biomolecules. 2021;11(4):527.
9. Pearson FE, Chang K, Minoda Y, Rojas IML, Haigh OL, Daraj G, et al. Activation of human CD141+ and CD1c+ dendritic cells in vivo with combined TLR3 and TLR7/8 ligation. Immunology and Cell Biology. 2018;96(4):390-400.
10. Yi H, Tan Y, Lu L, Tang F, Deng X. Immunotherapy of Triple-Negative Breast Cancer. Triple-Negative Breast Cancer: WORLD SCIENTIFIC; 2020. p. 199-218.
11. Gilkes DM, Semenza GL. Role of hypoxia-inducible factors in breast cancer metastasis. Future Oncol. 2013;9(11):1623-1636.
12. Desai N, Sahel D, Kubal B, Postwala H, Shah Y, Chavda VP, et al. Role of the Extracellular Matrix in Cancer: Insights into Tumor Progression and Therapy. Advanced Therapeutics. 2025;8(2).
13. Ocana A, Pandiella A. Targeting oncogenic vulnerabilities in triple negative breast cancer: biological bases and ongoing clinical studies. Oncotarget. 2017;8(13):22218-22234.
14. Brianese RC, Nakamura KDdM, Almeida FGdSR, Ramalho RF, Barros BDdF, Ferreira ENe, et al. BRCA1 deficiency is a recurrent event in early-onset triple-negative breast cancer: a comprehensive analysis of germline mutations and somatic promoter methylation. Breast Cancer Res Treat. 2017;167(3):803-814.
15. Toh M, Ngeow J. Homologous Recombination Deficiency: Cancer Predispositions and Treatment Implications. The oncologist. 2021;26(9):e1526-e1537.
16. Aoki M, Fujishita T. Oncogenic Roles of the PI3K/AKT/mTOR Axis. Current Topics in Microbiology and Immunology: Springer International Publishing; 2017. p. 153-189.
17. Ward C, Langdon SP, Mullen P, Harris AL, Harrison DJ, Supuran CT, et al. New strategies for targeting the hypoxic tumour microenvironment in breast cancer. Cancer Treat Rev. 2013;39(2):171-179.
18. Sun W, Ren Y, Lu Z, Zhao X. The potential roles of exosomes in pancreatic cancer initiation and metastasis. Mol Cancer. 2020;19(1):135-135.
19. Sazeides C, Le A. Metabolic Relationship Between Cancer-Associated Fibroblasts and Cancer Cells. Advances in experimental medicine and biology. 2021;1311:189-204.
20. Gonçalves M, Rodrigues-Santos P, Januário C, Cosentino M, Pereira FC. Indoleamine 2,3-dioxygenase (IDO1) – Can dendritic cells and monocytes expressing this moonlight enzyme change the phase of Parkinson's Disease? Int Immunopharmacol. 2024;133:112062.
21. Yi M, Li T, Niu M, Wu Y, Zhao Z, Wu K. TGF-β: A novel predictor and target for anti-PD-1/PD-L1 therapy. Front Immunol. 2022;13:1061394-1061394.
22. Fiori ME, Di Franco S, Villanova L, Bianca P, Stassi G, De Maria R. Cancer-associated fibroblasts as abettors of tumor progression at the crossroads of EMT and therapy resistance. Mol Cancer. 2019;18(1):70-70.
23. Li W-H, Wang F, Song G-Y, Yu Q-H, Du R-P, Xu P. PARP-1: a critical regulator in radioprotection and radiotherapy-mechanisms, challenges, and therapeutic opportunities. Front Pharmacol. 2023;14:1198948-1198948.
24. Langelier MF, Pascal JM. Structure of Human PARP-1 bound to a DNA double strand break. Worldwide Protein Data Bank; 2012.
25. Talens F, Jalving M, Gietema JA, Van Vugt MA. Therapeutic targeting and patient selection for cancers with homologous recombination defects. Expert Opinion on Drug Discovery. 2017;12(6):565-581.
26. Incorvaia L, Bazan Russo TD, Gristina V, Perez A, Brando C, Mujacic C, et al. The intersection of homologous recombination (HR) and mismatch repair (MMR) pathways in DNA repair-defective tumors. NPJ precision oncology. 2024;8(1):190-190.
27. McCrea C, Hettle R, Gulati P, Taneja A, Rajora P. Indirect treatment comparison of olaparib and talazoparib in germline BRCA-mutated HER2-negative metastatic breast cancer. Journal of Comparative Effectiveness Research. 2021;10(13):1021-1030.
28. El-Saber Batiha G, Alqahtani A, Ilesanmi OB, Saati AA, El-Mleeh A, Hetta HF, et al. Avermectin Derivatives, Pharmacokinetics, Therapeutic and Toxic Dosages, Mechanism of Action, and Their Biological Effects. Pharmaceuticals (Basel). 2020;13(8):196.
29. Nunes M, Bartosch C, Abreu MH, Richardson A, Almeida R, Ricardo S. Deciphering the Molecular Mechanisms behind Drug Resistance in Ovarian Cancer to Unlock Efficient Treatment Options. Cells. 2024;13(9):786.
30. Castroviejo-Bermejo M, Cruz C, Guerra S, Llop-Guevara A, Gutiérrez-Enríquez S, Bruna A, et al. Lack of RAD51 foci formation enables the identification of PARP inhibitor sensitive breast tumors. Eur J Cancer. 2016;69:S122-S123.
31. Da Silva CG, Peters GJ, Ossendorp F, Cruz LJ. The potential of multi-compound nanoparticles to bypass drug resistance in cancer. Cancer Chemother Pharmacol. 2017;80(5):881-894.
32. Bajwa DE, Salvanou E-A, Theodosiou M, Koutsikou TS, Efthimiadou EK, Bouziotis P, et al. Radiolabeled iron oxide nanoparticles functionalized with PSMA/BN ligands for dual-targeting of prostate cancer. Frontiers in nuclear medicine. 2023;3:1184309-1184309.
33. Hernández-Hernández AA, Aguirre-Álvarez G, Cariño-Cortés R, Mendoza-Huizar LH, Jiménez-Alvarado R. Iron oxide nanoparticles: synthesis, functionalization, and applications in diagnosis and treatment of cancer. Chemical Papers. 2020;74(11):3809-3824.
34. Terra JCS, Martins AR, Moura FCC, Weber CC, Moores A. Making more with less: confinement effects for more sustainable chemical transformations. Green Chem. 2022;24(4):1404-1438.

CC BY

35. Dual-Targeted Multifunctional Nanoparticles for Magnetic Resonance Imaging Guided Cancer Diagnosis and Therapy. American Chemical Society (ACS).
36. Jha A, Rama A, Ladani B, Verma N, Kannan S, Naha A. Temperature and pH-responsive nanogels as intelligent drug delivery systems: A comprehensive review. Journal of Applied Pharmaceutical Science. 2021.
37. Freis B, Cotin G, Perton F, Mertz D, Boutry S, Laurent S, et al. The Size, Shape, and Composition Design of Iron Oxide Nanoparticles to Combine, MRI, Magnetic Hyperthermia, and Photothermia. Magnetic Nanoparticles in Human Health and Medicine: Wiley; 2021. p. 380-429.
38. Rahman M. Magnetic Resonance Imaging and Iron-oxide Nanoparticles in the era of Personalized Medicine. Nanotheranostics. 2023;7(4):424-449.
39. Anani T, Rahmati S, Sultana N, David AE. MRI-traceable theranostic nanoparticles for targeted cancer treatment. Theranostics. 2021;11(2):579-601.
40. Evodiamine-Based Nitroreductase Responsive Theranostic Agents for Treatment of Colon Cancer. American Chemical Society (ACS).
41. Louie A. Multimodality imaging probes: design and challenges. Chem Rev. 2010;110(5):3146-3195.
42. Govindan B, Sabri MA, Hai A, Banat F, Haija MA. A Review of Advanced Multifunctional Magnetic Nanostructures for Cancer Diagnosis and Therapy Integrated into an Artificial Intelligence Approach. Pharmaceutics. 2023;15(3):868.
43. Di Lorenzo G, Ricci G, Severini GM, Romano F, Biffi S. Imaging and therapy of ovarian cancer: clinical application of nanoparticles and future perspectives. Theranostics. 2018;8(16):4279-4294.
44. Ezealigo BN, Ezealigo US, Ighodalo KI, Ezema FI. Iron oxide nanoparticles: current and future applications in nanomedicine. Fundamentals and Industrial Applications of Magnetic Nanoparticles: Elsevier; 2022. p. 349-392.
45. Chaurasiya S, Mishra V. Biodegradable nanoparticles as theranostics of ovarian cancer: an overview. Journal of Pharmacy and Pharmacology. 2018;70(4):435-449.
46. Tarafdar A, Kaur BP. Storage stability of microfluidized sugarcane juice and associated kinetics. J Food Process Preserv. 2022;46(6).
47. Mishra R, Bassi P, Roobal, Shivani. Drug targeting to cancer cells through stimuli-responsive imine bonds: fascinating aspects of site specificity. Polymer-Drug Conjugates: Elsevier; 2023. p. 207-224.
48. Nguyen A, Böttger R, Li S-D. Recent trends in bioresponsive linker technologies of Prodrug-Based Self-Assembling nanomaterials. Biomaterials. 2021;275:120955.
49. El Guerrab A, Bamdad M, Kwiatkowski F, Bignon Y-J, Penault-Llorca F, Aubel C. Anti-EGFR monoclonal antibodies and EGFR tyrosine kinase inhibitors as combination therapy for triple-negative breast cancer. Oncotarget. 2016;7(45):73618-73637.
50. Zhuo Y, Zhao Y-G, Zhang Y. Enhancing Drug Solubility, Bioavailability, and Targeted Therapeutic Applications through Magnetic Nanoparticles. Molecules (Basel, Switzerland). 2024;29(20):4854.
51. Gadag S, Sinha S, Nayak Y, Garg S, Nayak UY. Combination Therapy and Nanoparticulate Systems: Smart Approaches for the Effective Treatment of Breast Cancer. Pharmaceutics. 2020;12(6):524.
52. Verma N. Precision epigenetic targeted combination therapies for Triple Negative Breast Cancer Subtypes. 2nd International E-Conference on Cancer Science and Therapy: United Research Forum; 2021.
53. Egea-Benavente D, Ovejero JG, Morales MDP, Barber DF. Understanding MNPs Behaviour in Response to AMF in Biological Milieus and the Effects at the Cellular Level: Implications for a Rational Design That Drives Magnetic Hyperthermia Therapy toward Clinical Implementation. Cancers (Basel). 2021;13(18):4583.
54. Wei F, Liu H, Wang Y, Li Y, Han S. Engineering macrophages and their derivatives: A new hope for antitumor therapy. Biomedicine and Pharmacotherapy. 2024;177:116925.
55. Imodoye SO, Adedokun KA, Bello IO. From complexity to clarity: unravelling tumor heterogeneity through the lens of tumor microenvironment for innovative cancer therapy. Histochem Cell Biol. 2024;161(4):299-323.
56. Baldwin PE. Development of molecular inhibitor nanoformulations for cancer therapy: Northeastern University Library.
57. Chappell K, Manna K, Washam CL, Graw S, Alkam D, Thompson MD, et al. Multi-omics data integration reveals correlated regulatory features of triple negative breast cancer. Molecular omics. 2021;17(5):677-691.
58. Muhammad FA, Altalbawy FMA, Mandaliya V, Saraswat SK, Rekha MM, Aulakh D, et al. Targeting breast tumor extracellular matrix and stroma utilizing nanoparticles. Clinical and Translational Oncology. 2024.
59. Khosravi G-R, Mostafavi S, Bastan S, Ebrahimi N, Gharibvand RS, Eskandari N. Immunologic tumor microenvironment modulators for turning cold tumors hot. Cancer communications (London, England). 2024;44(5):521-553.
60. Li H, Luo Q, Zhang H, Ma X, Gu Z, Gong Q, et al. Nanomedicine embraces cancer radio-immunotherapy: mechanism, design, recent advances, and clinical translation. Chemical Society Reviews. 2023;52(1):47-96.
61. Luther DC, Lee YW, Nagaraj H, Scaletti F, Rotello VM. Delivery approaches for CRISPR/Cas9 therapeutics in vivo: advances and challenges. Expert opinion on drug delivery. 2018;15(9):905-913.
62. Uz M, Alsoy Altinkaya S, Mallapragada SK. Stimuli responsive polymer-based strategies for polynucleotide delivery. Journal of Materials Research. 2017;32(15):2930-2953.
63. An Y, Talwar CS, Park K-H, Ahn W-C, Lee S-J, Go S-R, et al. Design of hypoxia responsive CRISPR-Cas9 for target gene regulation. Sci Rep. 2023;13(1):16763-16763.
64. Jain KK. Personalized Management of Cancers of Various Organs/Systems. Textbook of Personalized Medicine: Springer International Publishing; 2020. p. 509-602.
65. Gharavi AT, Irian S, Niknejad A, Parang K, Salimi M. Harnessing exosomes as a platform for drug delivery in breast cancer: A systematic review for in vivo and in vitro studies. Molecular therapy Oncology. 2024;32(2):200800-200800.
66. Lorenc T, Chrzanowski J, Olejarz W. Current Perspectives on Clinical Use of Exosomes as a Personalized Contrast Media and Theranostics. Cancers (Basel). 2020;12(11):3386.
67. Wang Y-XJ, Hussain SM, Krestin GP. Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging. Eur Radiol. 2001;11(11):2319-2331.
68. de Maar JS, Sofias AM, Porta Siegel T, Vreeken RJ, Moonen C, Bos C, et al. Spatial heterogeneity of nanomedicine investigated by multiscale imaging of the drug, the nanoparticle and the tumour environment. Theranostics.

CC BY

2020;10(4):1884-1909.
69. Lu C, Han L, Wang J, Wan J, Song G, Rao J. Engineering of magnetic nanoparticles as magnetic particle imaging tracers. Chemical Society Reviews. 2021;50(14):8102-8146.
70. Dynamic Contrast-Enhanced Magnetic Resonance Imaging. Definitions: Qeios; 2020.
71. Reguera-Nuñez E, Xu P, Chow A, Man S, Hilberg F, Kerbel RS. Therapeutic impact of Nintedanib with paclitaxel and/or a PD-L1 antibody in preclinical models of orthotopic primary or metastatic triple negative breast cancer. Journal of experimental and clinical cancer research : CR. 2019;38(1):16-16.
72. Zhang D, Zhang J, Bian X, Zhang P, Wu W, Zuo X. Iron Oxide Nanoparticle-Based T(1) Contrast Agents for Magnetic Resonance Imaging: A Review. Nanomaterials (Basel, Switzerland). 2024;15(1):33.
73. Hypoxia-Responsive Aggregation of Iron Oxide Nanoparticles for T1toT2 Switchable Magnetic Resonance Imaging of Tumors. American Chemical Society (ACS).
74. Nikolova MP, Kumar EM, Chavali MS. Updates on Responsive Drug Delivery Based on Liposome Vehicles for Cancer Treatment. Pharmaceutics. 2022;14(10):2195.
75. Wang J, Zhao Y, Nie G. Intelligent nanomaterials for cancer therapy: recent progresses and future possibilities. Medical review (2021). 2023;3(4):321-342.
76. Basingab FS, Alshahrani OA, Alansari IH, Almarghalani NA, Alshelali NH, Alsaiary AH, et al. From Pioneering Discoveries to Innovative Therapies: A Journey Through the History and Advancements of Nanoparticles in Breast Cancer Treatment. Breast cancer (Dove Medical Press). 2025;17:27-51.
77. Kurniawan KW, Utomo SA, Wahyuhadi J. Diffusion Weighted Imaging (DWI) Classification and Apparent Diffusion Coefficient (ADC) Value Tendency Based on Cerebral Glioma Grading in Patients at Dr. Soetomo General Academic Hospital in 2016-2020. AKSONA. 2023;3(1):7-12.
78. Gao J, Lan J, Liao H, Yang F, Qiu P, Jin F, et al. Promising preclinical patient-derived organoid (PDO) and xenograft (PDX) models in upper gastrointestinal cancers: progress and challenges. BMC Cancer. 2023;23(1):1205-1205.
79. Klein H-M. Clinical Low Field Strength Magnetic Resonance Imaging. Springer International Publishing; 2016.
80. Schettini F, Corona SP, Giudici F, Strina C, Sirico M, Bernocchi O, et al. Clinical, Radiometabolic and Immunologic Effects of Olaparib in Locally Advanced Triple Negative Breast Cancer: The OLTRE Window of Opportunity Trial. Front Oncol. 2021;11:686776-686776.

CC BY