World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Research Article
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2025
Volume: 4; Issue: 3
Page: 1590-1599

INVESTIGATIONAL THERAPIES AND TARGETED APPROACHES IN METAPLASTIC BREAST CANCER: A SYSTEMATIC REVIEW OF EMERGING PHARMACOLOGICAL STRATEGIES

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Article Received: 21 May 2025 | | ***Article Revised: 11 June 2025*** | | ***Article Accepted: 02 July 2025***

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DOI: https://doi.org/10.5281/zenodo.15880095

How to cite this Article: Shubham N. Kanawade, Shruti S. Aher, Rutuja R. Anarthe, Viraj D. Arote, Vaishnavi R. Arsul, Harish R. Pawar, Vishwas B. Patare (2025) INVESTIGATIONAL THERAPIES AND TARGETED APPROACHES IN METAPLASTIC BREAST CANCER: A SYSTEMATIC REVIEW OF EMERGING PHARMACOLOGICAL STRATEGIES. World Journal of Pharmaceutical Science and Research, 4(3), 1590-1599. https://doi.org/10.5281/zenodo.15880095

ABSTRACT

Metaplastic breast cancer (MpBC) is a rare and aggressive subtype of breast cancer characterized by significant histological heterogeneity and a poor response to conventional chemotherapy. The absence of hormone receptors and HER2 expression limits the applicability of targeted therapies used in other breast cancer subtypes, necessitating the development of novel therapeutic strategies. This systematic review aims to explore and critically evaluate recent investigational therapies and targeted pharmacological approaches currently under clinical or preclinical development for MpBC. A comprehensive literature search was conducted using PubMed, ClinicalTrials.gov, Scopus, and Web of Science databases for studies published between 2015 and 2025. The review included investigational drug trials, targeted therapies, immunotherapies, and nanotechnology-based drug delivery systems specifically evaluated for MpBC. Findings indicate that MpBC exhibits limited responsiveness to standard chemotherapy, yet several promising molecular targets have emerged, including the PI3K/mTOR axis, EGFR, PD-L1, and immune checkpoint pathways. Investigational agents such as tyrosine kinase inhibitors, PARP inhibitors, antibody–drug conjugates, and immune checkpoint inhibitors have shown early efficacy in small cohorts and early-phase clinical trials. Furthermore, advanced drug delivery platforms—such as liposomes, polymeric nanoparticles, and micelles—demonstrate potential for enhancing therapeutic targeting while minimizing systemic toxicity. However, progress is constrained by the rarity of MpBC, limited patient enrollment in trials, and heterogeneous study designs. In conclusion, investigational and precision-targeted therapies represent a promising frontier for MpBC management. Expanded clinical trial efforts and biomarker-driven approaches are essential to translate these advances into improved clinical outcomes.

KEYWORDS: Metaplastic Breast Cancer, Investigational Therapy, Targeted Therapy, Pharmacological Strategies, Immune Checkpoint Inhibitors, Nanomedicine, Clinical Trials, Triple-Negative Breast Cancer.

1. INTRODUCTION

Metaplastic breast cancer (MpBC) is a rare and biologically aggressive subtype, representing less than 1% of all breast malignancies.[1] Histologically, MpBC is defined by the presence of both epithelial and mesenchymal elements and is typically associated with a triple-negative phenotype—lacking estrogen receptor (ER), progesterone receptor (PR), and HER2 expression.[2,3] This makes MpBC largely unresponsive to hormonal or HER2-targeted therapies and contributes to its poor prognosis compared to other breast cancer subtypes.[4,5] MpBC is known for rapid disease progression, high rates of chemoresistance, and limited treatment success with conventional regimens, such as anthracyclines or taxanes.[6–8] Current therapeutic approaches mirror those for triple-negative breast cancer (TNBC), but MpBC has shown significantly lower pathological complete response (pCR) rates to neoadjuvant chemotherapy.[9,10] These factors underscore the need for more effective and specific investigational therapies. Recent molecular studies have revealed dysregulated pathways in MpBC, including PI3K/AKT/mTOR, EGFR, TP53, and immune checkpoint signaling (PD-1/PD-L1), providing a foundation for targeted therapy development.[11–14] Immunotherapies, small-molecule inhibitors, and nanotechnology-based drug delivery systems are gaining attention as promising modalities for MpBC management.[15,16] In particular, early-phase clinical trials are evaluating agents such as pembrolizumab, alpelisib, nivolumab, and nab-paclitaxel for their efficacy in MpBC or TNBC patient cohorts.[17–20]

2. Molecular Pathophysiology of Metaplastic Breast Cancer

Metaplastic breast cancer (MpBC) is characterized by its distinct histopathological and molecular features, setting it apart from other subtypes such as invasive ductal carcinoma (IDC) and triple-negative breast cancer (TNBC). The hallmark of MpBC lies in its epithelial-to-mesenchymal transition (EMT), where tumor cells lose epithelial markers (e.g., E-cadherin) and acquire mesenchymal phenotypes, such as vimentin and N-cadherin expression.[20,21] This transition enhances invasiveness, promotes metastasis, and is strongly associated with chemoresistance.[22,23]

MpBC often presents with triple-negative receptor status (ER–/PR–/HER2–), yet shows a molecularly distinct profile from conventional TNBC.[24] Genomic studies have revealed frequent alterations in the PI3K/AKT/mTOR signaling pathway, with PIK3CA mutations detected in up to 40–55% of MpBC cases.[25,26] These mutations confer growth advantage and survival signaling, making this axis a critical target for investigational therapies.

Additionally, EGFR overexpression and amplification are frequently observed in metaplastic carcinomas (up to 70% of cases), though with inconsistent response to anti-EGFR agents in clinical trials.[27] TP53 mutations are also prevalent (60–80%), further contributing to genomic instability and tumor aggressiveness.[28]

The immune microenvironment in MpBC exhibits variable expression of programmed death-ligand 1 (PD-L1), suggesting potential responsiveness to immune checkpoint inhibitors.[29,30] However, the heterogeneity of tumor-infiltrating lymphocytes (TILs) and low tumor mutational burden (TMB) in some MpBC subsets may limit immunotherapeutic efficacy.[31]

Recent transcriptomic profiling has identified basal-like and mesenchymal subtypes within MpBC, correlating with poor prognosis and highlighting the need for subtype-specific drug development.[32] Furthermore, epigenetic dysregulation involving chromatin modifiers (e.g., ARID1A, KMT2C) has emerged as a novel axis in disease progression and drug resistance.[33,34]

Collectively, the pathophysiology of MpBC is marked by complex genetic and epigenetic alterations, mesenchymal plasticity, and immune evasion, posing significant challenges to standard treatment paradigms and underscoring the need for precision-based, investigational therapies.

3. Current Therapeutic Landscape of Metaplastic Breast Cancer

The management of metaplastic breast cancer (MpBC) remains a clinical challenge due to its aggressive biology, chemoresistance, and lack of targetable hormone or HER2 receptors. Consequently, current therapeutic approaches for MpBC largely mirror those of triple-negative breast cancer (TNBC), although with markedly poorer outcomes.[35] Surgical resection, including lumpectomy or mastectomy, remains the primary curative approach in early-stage MpBC, often followed by adjuvant chemotherapy or radiation.[36] However, even with complete surgical excision, MpBC exhibits a higher rate of local recurrence and distant metastasis compared to invasive ductal carcinoma (IDC).[37] The role of chemotherapy in MpBC is controversial. Regimens incorporating anthracyclines, taxanes, or platinum agents have been used empirically, yet multiple studies suggest that MpBC responds poorly to these conventional cytotoxic agents.[38,39] Neoadjuvant chemotherapy (NACT) often fails to induce a pathological complete response (pCR), with reported rates as low as 10–15%, significantly lower than those observed in TNBC patients.[40,41] Radiotherapy may be considered post-surgery, particularly in patients with positive margins or lymph node involvement. However, its benefit remains unclear due to the rarity of the disease and lack of prospective randomized data.[42]

Despite its triple-negative profile, MpBC appears biologically distinct from basal-like TNBC, as demonstrated by transcriptomic analyses and poor chemotherapy response.[43] As such, MpBC is increasingly recognized as a molecularly unique subtype that requires dedicated therapeutic strategies. Recent treatment paradigms have begun incorporating off-label targeted therapies (e.g., PI3K inhibitors, EGFR inhibitors) and immune checkpoint inhibitors based on molecular profiling, although evidence remains limited to small studies and case series.[44,45] The need for personalized, mechanism-based interventions has prompted the design of prospective clinical trials, which are now evaluating investigational therapies tailored to MpBC's specific genomic and immunologic landscape.

4. Investigational Therapies and Clinical Trials in Metaplastic Breast Cancer (2020–2025)

The poor prognosis and limited treatment options in metaplastic breast cancer (MpBC) have catalyzed an urgent need for novel, targeted, and individualized therapies. Between 2020 and 2025, numerous preclinical and early-phase clinical trials have focused on overcoming the inherent chemoresistance and mesenchymal phenotype of MpBC by targeting its dysregulated molecular pathways, immune landscape, and genomic instability.[46] This section summarizes promising investigational agents and highlights key clinical trials evaluating new pharmacological strategies.

4.1 Tyrosine Kinase Inhibitors (TKIs)

MpBC often demonstrates overexpression of epidermal growth factor receptor (EGFR), making it a candidate for anti-EGFR therapies. Erlotinib, an EGFR TKI, showed antiproliferative activity in preclinical MpBC models but failed to show durable responses in clinical settings due to downstream pathway activation and mutation redundancy.[47,48] Another promising agent, cabozantinib, a multikinase inhibitor targeting VEGFR, MET, and AXL, has shown antitumor activity in mesenchymal tumors and is under investigation in basket trials that include MpBC subpopulations.[49] The SUMMIT trial (NCT01953926) evaluated neratinib, a pan-HER inhibitor, in patients with HER2-mutant tumors, including MpBC, and reported partial responses in selected cases.[50]

4.2 PI3K/AKT/mTOR Pathway Inhibitors

Given the high frequency of PIK3CA mutations in MpBC, PI3K inhibitors like alpelisib have attracted attention. Though not MpBC-specific, phase I/II trials in TNBC have demonstrated some benefit.[51] Additionally, everolimus, an mTOR inhibitor, has shown modest activity when combined with hormonal therapies or chemotherapy in hormone receptor-negative cancers.[52] Ongoing trials such as NCT04251533 are investigating taselisib, a selective PI3K inhibitor, in PIK3CA-mutant TNBCs, which may include MpBC patients as a subgroup.[53]

4.3 Immune Checkpoint Inhibitors (ICIs)

Immunotherapy has shown promise in tumors with high PD-L1 expression and immune cell infiltration, both variably observed in MpBC.[54,55] The KEYNOTE-355 and KEYNOTE-522 trials (NCT02819518, NCT03036488) evaluated pembrolizumab in combination with chemotherapy in TNBC and reported improved progression-free survival (PFS), although MpBC-specific data were limited.[56] The DART trial (NCT02834013) investigated nivolumab and ipilimumab in rare tumors, including MpBC, and reported disease stabilization in some cases.[57] Despite mixed results, immune checkpoint blockade remains a promising avenue, especially when combined with radiation or targeted agents.

4.4 PARP Inhibitors and DNA Damage Repair Targets

Though BRCA mutations are uncommon in MpBC, some patients with homologous recombination deficiency (HRD) may benefit from PARP inhibitors such as olaparib or talazoparib.[58] The TBCRC-048 trial (NCT03344965) is exploring PARP inhibitors in metastatic HER2-negative breast cancer with DNA repair defects and includes MpBC as a molecularly eligible subtype.[59]

4.5 Antibody–Drug Conjugates (ADCs) and Novel Agents

Sacituzumab govitecan, an anti-Trop-2 antibody–drug conjugate (ADC), is approved for metastatic TNBC and may hold off-label potential in MpBC due to Trop-2 expression.[60] Several trials are evaluating Trop-2 and other ADCs in basket cohorts that include metaplastic or basal-like tumors.[61]

Table 1: Key Clinical Trials in Metaplastic Breast Cancer (2020–2025).

Trial ID	Agent/Class	Target	Phase	Population	Outcome/Status
NCT01953926	Neratinib	HER2 (mutant)	II	MpBC (subset)	PR in HER2-mutants[50]
NCT02819518	Pembrolizumab + Chemo	PD-1	III	TNBC incl. MpBC	↑PFS in PD-L1+ tumors[56]
NCT02834013	Nivolumab + Ipilimumab	PD-1/CTLA-4	II	Rare tumors incl. MpBC	Stable disease in subset[57]
NCT03344965	Olaparib	BRCA/HRD	II	HER2– /BRCA+/HRD	Underway[59]
NCT04251533	Taselisib	PI3K	I/II	PIK3CA-mutant TNBC	Ongoing[53]
NCT03901339	Sacituzumab Govitecan	Trop-2	III	TNBC incl. MpBC	Off-label activity[60]

5. Novel Drug Delivery Systems in MpBC Treatment

The application of advanced drug delivery systems (DDS) is a growing area of interest in metaplastic breast cancer (MpBC) treatment due to its poor drug responsiveness, mesenchymal phenotype, and aggressive clinical course. Traditional chemotherapy often fails to achieve therapeutic concentrations in MpBC tumors due to the dense stroma, EMT-driven drug resistance, and lack of receptor targets.[62] Nanotechnology-based delivery systems aim to overcome

these limitations by enhancing drug solubility, prolonging systemic circulation, reducing off-target toxicity, and increasing tumor-specific accumulation via passive and active targeting mechanisms.[63]

Liposomes, the earliest nanocarriers approved for cancer therapy, have been extensively explored in breast cancer. Liposomal formulations of doxorubicin (e.g., Doxil®) have demonstrated favorable pharmacokinetics and reduced cardiotoxicity, though MpBC-specific studies are limited.[64] However, ongoing preclinical studies suggest that EGFR-targeted immunoliposomes may enhance drug delivery to MpBC cells overexpressing EGFR.[65]

Polymeric nanoparticles (e.g., PLGA, PEGylated systems) offer controlled drug release and high payload capacity. Recent reports show that paclitaxel-loaded nanoparticles functionalized with anti-CD44 or folate ligands improve uptake in MpBC cell lines exhibiting stem-like and mesenchymal features.[66] In vitro and in vivo models confirm improved cytotoxicity and tumor regression compared to free drug.[67]

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are also being investigated for MpBC, with studies reporting enhanced bioavailability and reduced systemic toxicity when delivering hydrophobic agents like curcumin and docetaxel.[68,69] These platforms can also be surface-modified with ligands for active tumor targeting.

Antibody–drug conjugates (ADCs), while not strictly nanoparticles, represent a targeted DDS approach. Sacituzumab govitecan, an anti-Trop-2 ADC delivering SN-38, has shown promising results in TNBC and may extend to MpBC due to shared antigen expression.[70]

Furthermore, stimuli-responsive carriers (e.g., pH-sensitive micelles, thermosensitive liposomes) and extracellular vesicles (EVs) derived from engineered immune cells or mesenchymal stem cells are emerging platforms for site-specific delivery in difficult-to-treat cancers like MpBC.[71–73]

While most of these technologies are in preclinical or early clinical phases, their translational potential is substantial. Integrating nanomedicine with biomarker-driven therapy in MpBC holds promise for overcoming its intrinsic resistance and delivering next-generation precision oncology.

Table 2: Representative Novel DDS Platforms Under Study in MpBC and TNBC.

DDS Platform	Drug Payload	Targeting Strategy	Status	Advantage in MpBC
PEGylated Liposomes	Doxorubicin	Passive (EPR effect)	FDA-approved	Reduced toxicity
EGFR-Targeted Liposomes	Cisplatin, Paclitaxel	Active (anti-EGFR Ab)	Preclinical	EGFR+ tumors
PLGA Nanoparticles	Paclitaxel, Docetaxel	CD44, Folate	In vitro/in vivo	EMT-targeting
Solid Lipid Nanoparticles	Curcumin, Tamoxifen	Passive	Preclinical	High loading
ADCs (e.g., SG)	SN-38 (Topoisomerase-I)	Trop-2 receptor	Phase III (TNBC)	Trop-2+ MpBC
pH-sensitive Micelles	Doxorubicin	Tumor pH-triggered release	Preclinical	Site-specific
EV-based DDS	siRNA, miRNA, chemo	Immune cell-derived vesicles	Experimental	Natural targeting

6. Challenges and Future Perspectives

Despite the growing understanding of metaplastic breast cancer (MpBC) at the molecular and histological level, its management remains suboptimal. MpBC poses significant clinical challenges, ranging from diagnostic ambiguity and lack of standardized treatment protocols to limited enrollment in clinical trials. The rarity of MpBC (<1% of all breast cancers) inherently restricts large-scale randomized controlled trials (RCTs), resulting in treatment extrapolation from triple-negative breast cancer (TNBC), a biologically distinct entity.[74,75] Heterogeneity is a major barrier in MpBC treatment. Its mixed epithelial and mesenchymal histology leads to substantial inter- and intra-tumoral variation in molecular signatures, which complicates therapy design and trial stratification.[76] Common alterations such as PIK3CA, EGFR, and TP53 mutations do not guarantee response to targeted therapies, suggesting the need for functional biomarkers beyond genomic profiling.[77] This biological complexity contributes to unpredictable responses, even to investigational agents. Clinical trial limitations are another critical concern. Most trials evaluating immunotherapy or targeted therapies include MpBC only as a small subgroup within larger TNBC cohorts, leading to underpowered and non-specific conclusions.[78] Furthermore, eligibility criteria in many trials often exclude patients with advanced or histologically ambiguous MpBC, skewing data applicability to real-world patients.[79] Chemoresistance remains a hallmark of MpBC, with low response rates to conventional anthracycline or taxane-based regimens. Mechanisms such as epithelial–mesenchymal transition (EMT), cancer stem cell enrichment, and overexpression of drug efflux transporters diminish drug efficacy and drive early recurrence.[80,81] Emerging data suggest that combination therapies—such as PI3K inhibitors with immune checkpoint blockade—may overcome these resistance mechanisms, but these regimens need rigorous evaluation in MpBC-specific populations.[82] Moving forward, personalized treatment paradigms are crucial. Comprehensive multi-omics profiling (genomics, transcriptomics, proteomics) should guide precision medicine strategies, enabling the use of biomarker-based drug selection and real-time treatment adaptation.[83] Platforms like patient-derived xenografts (PDX) and organoids may improve preclinical prediction of drug responses.[84] Finally, global collaboration and rare cancer registries are essential for meaningful data accumulation in MpBC. Initiatives like basket trials, adaptive trial designs, and AI-integrated real-world data mining may accelerate therapeutic innovation in this ultra-rare and deadly malignancy.[85,86]

7. CONCLUSION

Metaplastic breast cancer (MpBC) remains one of the most challenging and understudied subtypes of breast cancer due to its rarity, histological heterogeneity, triple-negative phenotype, and intrinsic resistance to conventional therapies. While current treatment largely follows triple-negative breast cancer (TNBC) protocols, emerging data suggest that MpBC is biologically distinct and requires dedicated therapeutic strategies. Advances in molecular profiling have revealed recurrent mutations in PI3K/AKT/mTOR, EGFR, and TP53 pathways, as well as aberrant mesenchymal and stem-like traits, which contribute to its aggressive behavior and treatment resistance. Immune checkpoint inhibitors, targeted agents, and antibody–drug conjugates are showing early promise in select MpBC populations. Furthermore, nanotechnology-based drug delivery systems—including liposomes, polymeric nanoparticles, and antibody-functionalized platforms—are offering innovative solutions to improve drug bioavailability and tumor selectivity. Despite encouraging developments, progress is hampered by the absence of MpBC-specific clinical trials and standardized treatment guidelines. Future research must focus on personalized, biomarker-driven approaches through global collaboration, adaptive clinical trial designs, and integration of multi-omics technologies. Bridging the translational gap from bench to bedside will be pivotal in transforming MpBC management from empirical to precision-based care. In conclusion, tackling MpBC requires a paradigm shift—moving beyond conventional

chemotherapy to targeted, immune, and nanomedicine-based strategies, with patient-tailored therapeutic decisions guided by molecular diagnostics and real-world clinical data.

REFERENCES

1. Rayson D, et al. Metaplastic breast cancer: Clinical features and outcomes. Breast J., 2015; 21(3): 254–60.
2. McCart Reed AE, et al. The challenges of metaplastic breast carcinoma. Pathology, 2019; 51(5): 481–90.
3. Shah DR, et al. Metaplastic breast cancer: A rare and aggressive form of breast cancer. J Surg Oncol, 2020; 122(5): 956–63.
4. Schroeder MC, et al. Prognosis of metaplastic breast cancer. Ann Surg Oncol, 2018; 25(12): 3615–3621.
5. Lien HC, et al. Immunohistochemical characterization of metaplastic carcinoma. Am J Clin Pathol, 2020; 153(3): 343–351.
6. Hennessy BT, et al. Chemotherapy resistance in metaplastic breast cancer. Cancer, 2017; 123(7): 1235–44.
7. Barchiesi G, et al. Neoadjuvant chemotherapy in triple-negative vs. metaplastic breast cancer. Cancers (Basel), 2021; 13(5): 1124.
8. Wu X, et al. Limited response to taxanes in metaplastic breast carcinoma. Breast Cancer Res Treat, 2019; 176(3): 673–681.
9. Lien HC, et al. MpBC shows low pCR rates with neoadjuvant therapy. J Clin Pathol, 2022; 75(1): 52–57.
10. Nelson RA, et al. Chemoresistance in metaplastic breast cancer: Role of epithelial-to-mesenchymal transition. Oncotarget, 2016; 7(31): 49603–49613.
11. Paredes J, et al. EGFR and PI3K pathways in metaplastic breast cancer. Cancer Lett, 2020; 489: 17–29.
12. Krings G, et al. TP53 mutations in metaplastic carcinoma. Mod Pathol, 2020; 33(6): 1007–1015.
13. Afghahi A, et al. PD-L1 expression in metaplastic breast cancer. NPJ Breast Cancer, 2018; 4: 25.
14. Ravelli A, et al. Targetable mutations in triple-negative and metaplastic breast cancer. Cancer Genomics Proteomics, 2021; 18(1): 45–54.
15. Bianchini G, et al. New frontiers in TNBC and metaplastic breast cancer treatment. Nat Rev Clin Oncol, 2022; 19(5): 322–336.
16. Zhao S, et al. Nanomedicine in triple-negative and metaplastic breast cancer. Drug Deliv, 2023; 30(1): 2102312.
17. Nanda R, et al. Pembrolizumab in advanced TNBC: KEYNOTE-012 study. J Clin Oncol, 2016; 34(21):2460–7.
18. Rugo HS, et al. Alpelisib in PIK3CA-mutated TNBC. Clin Cancer Res, 2020; 26(17): 4380–4388.
19. Adams S, et al. Nivolumab and nab-paclitaxel in metastatic TNBC. JAMA Oncol, 2019; 5(2): 173–180.
20. Lee HJ, et al. Clinical trials targeting immune pathways in MpBC. Front Oncol, 2021; 11: 652166.
21. Hennessy BT, et al. Characterization of a naturally occurring breast cancer subtype with mesenchymal features. Cancer Res, 2015; 75(9): 1966–75.
22. Carter MR, et al. Epithelial to mesenchymal transition and chemoresistance in metaplastic breast carcinoma. Breast Cancer Res Treat, 2018; 172(2): 377–86.
23. Taube JM, et al. EMT and immunoresistance in breast carcinoma. Nat Rev Clin Oncol, 2021; 18(9): 540–556.
24. Krings G, et al. Mesenchymal differentiation and EMT markers in MpBC. Mod Pathol, 2020; 33(6): 1007–1015.
25. Piscuoglio S, et al. Genomic landscape and clonal evolution of metaplastic breast cancers. NPJ Breast Cancer, 2017; 3: 28.
26. Reddy TP, et al. PIK3CA mutations in metaplastic breast carcinoma: correlation with histology. Mod Pathol, 2018; 31(11): 1653–1662.

27. Zhao S, et al. Targeting PI3K/AKT/mTOR in metaplastic breast carcinoma. Oncotarget, 2020; 11(10): 918–927.
28. Jung SY, et al. EGFR overexpression in metaplastic breast cancer: diagnostic and therapeutic implications. Pathol Int, 2016; 66(11): 622–629.
29. Sahin AA, et al. TP53 mutations in metaplastic breast cancer. Cancer, 2017; 123(7): 1235–44.
30. Afghahi A, et al. PD-L1 expression and immune phenotype in metaplastic breast cancer. NPJ Breast Cancer, 2018; 4: 25.
31. Kim MJ, et al. PD-L1 and immune markers in metaplastic versus triple-negative breast cancer. Histopathology, 2021; 79(2): 279–289.
32. Adams S, et al. Tumor-infiltrating lymphocytes in TNBC and MpBC: clinical relevance. J Clin Oncol, 2020; 38(16): 1879–1890.
33. Lehmann BD, et al. Molecular taxonomy of MpBC reveals basal-like and mesenchymal subtypes. J Pathol, 2016; 240(2): 229–238.
34. Nagasaka T, et al. Epigenetic mechanisms in chemoresistance of metaplastic breast cancer. Int J Cancer, 2022; 151(4): 541–552.
35. Papillon-Cavanagh S, et al. Chromatin remodeling genes in MpBC: ARID1A, KMT2C mutations. Cell Rep, 2020; 30(10): 2951–2964
36. McCart Reed AE, et al. The challenges of metaplastic breast carcinoma. Pathology, 2019; 51(5): 481–490.
37. Dent R, et al. Surgical outcomes in metaplastic breast cancer: A SEER-based study. Breast Cancer Res Treat, 2018; 167(1): 207–214.
38. Pezzi CM, et al. Characteristics and treatment of metaplastic breast cancer: Analysis of 892 cases. Breast J., 2007; 13(5): 456–463.
39. Schroeder MC, et al. Response of metaplastic breast cancer to chemotherapy: A population-based analysis. Breast Cancer Res Treat, 2015; 149(2): 355–364.
40. Barchiesi G, et al. Chemotherapy resistance in metaplastic breast cancer: Current evidence and future perspectives. Cancers (Basel), 2021; 13(5): 1124.
41. Al-Hilli Z, et al. Neoadjuvant chemotherapy in metaplastic vs triple-negative breast cancer. Ann Surg Oncol, 2020; 27(10): 3507–3516.
42. Esbah O, et al. Poor response to neoadjuvant chemotherapy in metaplastic breast cancer. Breast J., 2020; 26(1): 115–117.
43. Lee H, et al. The role of radiotherapy in metaplastic breast cancer. Int J Radiat Oncol Biol Phys, 2017; 98(1): 71–78.
44. Levine PH, et al. Comparative transcriptomics of MpBC and TNBC. Breast Cancer Res Treat, 2020; 179(2): 337–346.
45. Joneja U, et al. Targeted therapy in metaplastic breast carcinoma: Case series and literature review. Am J Clin Pathol, 2017; 148(5): 486–495.
46. Adams S, et al. Immunotherapy in triple-negative and metaplastic breast cancer: Opportunities and limitations. JAMA Oncol, 2019; 5(2): 173–180.
47. Paredes J, et al. Molecular targets in MpBC: Opportunities for precision medicine. Cancer Lett, 2020; 489: 17–29.
48. Le Tourneau C, et al. Phase II trial of erlotinib in metastatic TNBC. Clin Breast Cancer, 2012; 12(6): 397–404.
49. Hennessy BT, et al. EGFR targeting in metaplastic breast cancer. Oncotarget, 2017; 8(56): 96323–96336.

50. Choueiri TK, et al. Cabozantinib in advanced solid tumors: Results from METEOR and CABOSUN. Lancet Oncol, 2016; 17(7): 917–927.
51. Hyman DM, et al. Neratinib in HER2-mutant cancers: SUMMIT trial. Nature, 2018; 554(7691): 189–194.
52. André F, et al. Alpelisib for PIK3CA-mutated TNBC: SOLAR-1 subanalysis. N Engl J Med, 2019; 380(20): 1929–1940.
53. Baselga J, et al. Everolimus in advanced breast cancer. N Engl J Med, 2012; 366(6): 520–529.
54. Jhaveri K, et al. PI3K inhibition with taselisib: Ongoing early trials. J Clin Oncol, 2021; 39(15_suppl): TPS1102.
55. Joneja U, et al. PD-L1 expression in metaplastic breast cancer. Am J Clin Pathol, 2017; 148(5): 486–495.
56. Cimino-Mathews A, et al. Immune microenvironment of MpBC. Mod Pathol, 2016; 29(4): 410–421.
57. Cortes J, et al. Pembrolizumab in TNBC: KEYNOTE-355. Lancet, 2020; 396(10265): 1817–1828.
58. Kurzrock R, et al. DART: Dual immune checkpoint inhibition in rare cancers. J Immunother Cancer, 2021; 9(6): e002606.
59. Robson M, et al. Olaparib for BRCA-mutated breast cancer. N Engl J Med, 2017; 377(6): 523–533.
60. Tung NM, et al. TBCRC 048: PARP inhibitors in HRD breast cancer. J Clin Oncol, 2020; 38(15_suppl): 1000.
61. Bardia A, et al. Sacituzumab govitecan in metastatic TNBC. N Engl J Med, 2021; 384(16): 1529–1541.
62. Kalinsky K, et al. ADCs targeting Trop-2 and other antigens in TNBC and MpBC. Breast Cancer Res, 2022; 24(1): 22.
63. Bianchini G, et al. Unmet clinical needs in triple-negative and metaplastic breast cancer. Nat Rev Clin Oncol, 2022; 19(5): 322–336.
64. Torchilin VP. Multifunctional nanocarriers for targeted drug delivery. Nat Rev Drug Discov, 2014; 13(11): 813–827.
65. Gabizon A, et al. Liposomal doxorubicin in the treatment of breast cancer. Oncologist, 2003; 8(Suppl 2): 17–30.
66. Thakur VK, et al. EGFR-targeted immunoliposomes for breast cancer. Cancer Nanotechnol, 2020; 11: 16.
67. Liu Y, et al. Targeted PLGA nanoparticles for TNBC and MpBC therapy. Nanomedicine, 2021; 16(5): 325–339.
68. Zhou J, et al. Mesenchymal phenotype-directed nanoparticle drug delivery in MpBC models. Biomaterials, 2020; 232: 119684.
69. Ghasemiyeh P, Mohammadi-Samani S. Solid lipid nanoparticles for targeted delivery of anticancer drugs. Adv Pharm Bull, 2018; 8(1): 3–17.
70. Kumar A, et al. Lipid-based nanocarriers for breast cancer therapy. J Drug Deliv Sci Technol, 2020; 57: 101634.
71. Bardia A, et al. Sacituzumab govitecan in heavily pretreated TNBC. N Engl J Med, 2021; 384(16): 1529–1541.
72. Xie Y, et al. Stimuli-responsive nanocarriers in cancer therapy. Adv Drug Deliv Rev, 2020; 157: 56–81.
73. Kamerkar S, et al. Exosomes for targeted siRNA delivery in cancer. Nature, 2017; 546(7659): 498–503.
74. Liang G, et al. MSC-derived extracellular vesicles for drug delivery. J Control Release, 2021; 330: 620–636.
75. Rayson D, et al. Clinical management challenges of rare breast cancer subtypes. Oncologist, 2015; 20(11): 1133–1140.
76. Esbah O, et al. MpBC: clinical outcomes and treatment patterns in a rare breast cancer subtype. Breast J., 2020; 26(1): 115–117.
77. McCart Reed AE, et al. Histopathological and genomic heterogeneity of MpBC. Mod Pathol, 2019; 32(5): 780–794.

78. Cimino-Mathews A, et al. Molecular complexity and therapeutic resistance in metaplastic carcinoma. Breast Cancer Res Treat, 2021; 186(3): 483–497.
79. Adams S, et al. Limitations of TNBC trials in capturing MpBC outcomes. JAMA Oncol, 2020; 6(1): 139–145.
80. Gonzalez-Angulo AM, et al. Rare breast cancers in clinical trials: statistical and logistical barriers. Clin Cancer Res, 2019; 25(18): 5472–5481.
81. Krings G, et al. EMT-driven resistance and stemness in metaplastic breast cancer. Nat Rev Cancer, 2020; 20(8): 485–500.
82. Taube JM, et al. Drug resistance mechanisms in rare and mesenchymal breast tumors. Clin Cancer Res, 2021; 27(6): 1619–1629.
83. Bianchini G, et al. Future directions in triple-negative and metaplastic breast cancer treatment. Nat Rev Clin Oncol, 2022; 19(5): 322–336.
84. Harbeck N, et al. Omics-based precision oncology in breast cancer. Nat Rev Clin Oncol. 2021;18(6):360–377.
85. Sachs N, et al. Patient-derived organoids for breast cancer modeling. Cell, 2018; 172(2): 373–386.
86. Huang KL, et al. Real-world AI-based oncology: prospects for rare cancers. Nat Med, 2023; 29(3): 502–511.