Triple-Negative Breast Cancer: Molecular Subtypes, Therapeutic Challenges, and Emerging Strategies—A Systematic Review

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ABSTRACT

BACKGROUND

Triple-negative breast cancer (TNBC) is an aggressive subtype lacking estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression, accounting for 15–20% of breast cancer cases.

OBJECTIVE

To review TNBC's molecular heterogeneity, current therapies, and future directions.

METHODS

A literature search (2010–2025) was conducted using PubMed, Scopus, and Web of Science, focusing on clinical trials, molecular subtyping, and targeted therapies.

RESULTS

TNBC exhibits diverse molecular subtypes (basal-like, immunomodulatory, and luminal androgen receptor [LAR]) with distinct therapeutic responses. Chemotherapy (taxanes, anthracyclines, and platinum agents) remains the mainstay, while PARP inhibitors, immune checkpoint blockers (e.g., pembrolizumab), and androgen receptor antagonists show promise in subtype-specific contexts. Despite advances, resistance and poor prognosis persist, necessitating biomarker-driven strategies.

CONCLUSION

Personalized therapy based on molecular profiling and clinical trials targeting novel pathways (e.g., Wnt/β-catenin, NOTCH) is critical for improving TNBC outcomes.

Keywords: TNBC molecular subtyping, Parp inhibitor therapy, Immune checkpoint blockade, Androgen receptor antagonists, Platinum-based chemotherapy

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Triple-negative breast cancer (TNBC), defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) amplification,[1,2] represents 15–20% of breast cancers and is associated with aggressive biology, early recurrence, and poorer survival compared to other subtypes.[3,4] Unlike hormone receptor-positive or HER2-positive disease, TNBC lacks established targeted therapies, rendering chemotherapy the mainstay of treatment.[5,6] Recent advances in immunotherapy (e.g., pembrolizumab) and PARP inhibitors (e.g., olaparib) show promise but are limited to biomarker-selected subgroups,[7,8] highlighting the need for precision medicine approaches.

This review synthesizes molecular classification systems (Lehmann et al.,[9] Burstein et al.[10]), current therapeutic challenges, and emerging strategies, including novel targets (Wnt/β-catenin, NOTCH) and ongoing clinical trials (KEYNOTE-522, ASCENT).[11–14]

Epidemiology and Historical Context of TNBC

Epidemiology

Global Burden

TNBC accounts for 15–20% of breast cancers,[1] with a higher incidence in women of West African ancestry (Black women: 28–30%).[15,16] In South Africa, TNBC prevalence correlates with HIV infection (36% in Black women aged 25–49).[15]

Risk Factors

Genetic: BRCA1 mutations (70–80% of BRCA1-associated breast cancers are TNBC).[17,18]

Clinical: Younger age at diagnosis (<50 years), higher parity without breastfeeding.[15,19]

Historical Milestones

2000: Perou et al. identify intrinsic subtypes (basal-like [BL], luminal, HER2-enriched) via gene expression profiling.[19]

2011: Lehmann et al. refine TNBC into six molecular subtypes (BL1, BL2, luminal androgen receptor [LAR], etc.).[9,20]

2020s: KEYNOTE-522 establishes pembrolizumab + chemotherapy as the neoadjuvant standard for early-stage TNBC.[11]

Disparities

Survival: Black women with TNBC have 14% lower 5-year survival vs. White women (SEER data).[16]

Treatment Access: Lower rates of genetic testing (*BRCA1/2*) in low-resource settings.[15,19]

Methodology

Review Protocol and Registration

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was not prospectively registered in PROSPERO or any other database; this has been stated transparently.

Search Strategy

A comprehensive literature search was performed across PubMed, Scopus, Web of Science, Cochrane Library, and Embase from January 2010 to February 5, 2025 (date of last search). Only human studies published in English were included.

Review Framework Population, Intervention, Comparator, and Outcome (PICO) and Search Strategy

The review question was structured using the PICO framework:

Population (P): Women diagnosed with TNBC at any stage.

Intervention (I): Systemic therapies including cytotoxic chemotherapy (e.g., platinum), immune checkpoint inhibitors (e.g., pembrolizumab), antibody-drug conjugates (e.g., sacituzumab govitecan), targeted agents, and novel combinations.
Comparator (C): Standard-of-care chemotherapy, placebo, or alternative systemic regimens.
Outcomes (O): Efficacy endpoints [pathological complete response (pCR), event-free survival (EFS), progression-free survival (PFS), overall survival (OS)] and safety outcomes.

We systematically searched PubMed/MEDLINE, Embase, Web of Science, Cochrane CENTRAL, Google Scholar, and ClinicalTrials.gov from inception until February 5, 2025. The full electronic search strategies for each database, including all keywords and MeSH terms, are provided in Table 1. Searches were restricted to English-language publications. Bibliographies of relevant reviews and conference abstracts were manually screened for additional eligible studies.

Database Selection Rationale

PubMed: Primary database for biomedical literature, covering >30 million citations from MEDLINE, life science journals, and online books. Particularly strong for clinical trial data and NIH-funded research.
Scopus: Elsevier's curated abstract and citation database, providing 100% MEDLINE coverage plus 20% more content. Includes international journals and conference proceedings.
Web of Science: Core Collection indexes high-impact journals with citation network analysis capabilities, useful for tracking therapeutic developments over time.

Search Query Optimization

The Boolean search string was developed through:

- Preliminary scoping searches to identify relevant terminology
- Consultation with a medical librarian
- Iterative refinement to balance sensitivity (recall) and specificity (precision) (Table 2)

Table 1 | PRISMA 2020 checklist.

Section	#	PRISMA Item	Reported on Page	Response
TITLE	1	Identify the report as a systematic review	p. 1	"Systematic Review of Molecular Subtypes and Therapeutic Strategies in Triple-Negative Breast Cancer"
ABSTRACT	2	Provide structured abstract	p. 1	Structured abstract with: Background, Objectives, Methods, Results, Conclusions
INTRODUCTION	3	Describe rationale	p. 2	"TNBC's clinical heterogeneity and lack of targeted therapies necessitate subtype-specific approaches..."
	4	State objectives	p. 3	"To evaluate molecular subtypes, current therapies, and emerging strategies (2010–2024)"
METHODS	5	Indicate if review protocol exists	p. 5	"No protocol registered (transparently stated)"
	6	Specify inclusion criteria	p. 3	"Peer-reviewed studies in English (2010–2024), human TNBC patients, reporting subtype-specific outcomes"
	7	Describe information sources	p. 4	"PubMed, Scopus, Web of Science; searched through March 2024"
	8	Present full search strategy	p. 1	Complete search strategies for all databases provided
	9	Explain study selection	p. 3	"Dual independent screening (A.V./S.D.) using Rayyan; conflicts resolved by S.K."
	10	Describe data extraction	p. 3	"Standardized forms for study design, interventions, outcomes"
	11	Assess risk of bias	p. 3	"ROB-2 for RCTs; Newcastle–Ottawa Scale for observational studies"
	12	Specify effect measures	p. 7	"Primary: pCR rates; Secondary: PFS, OS (hazard ratios)"
	13	Describe synthesis methods	p. 7	"Narrative synthesis with tabulated results due to clinical heterogeneity"
RESULTS	14	Report study selection	p. 8	PRISMA flow diagram with screening numbers
	15	Present characteristics	Table 2	"33 studies (18 RCTs, 15 cohorts) detailing subtype-specific outcomes"
	16	Present risk of bias	Suppl. Table 3	"Low risk for 12/18 RCTs; moderate risk for observational studies"
	17	Report results	p. 9–15	"BL1 subtype showed highest pCR (85%) to platinum-based regimens"
DISCUSSION	18	Summarize findings	p. 16	"Immunotherapy benefits immunomodulatory subtype; PARPi effective in BRCA-mutated"
	19	Discuss limitations	p. 18	"Heterogeneity in subtype definitions; few phase III validation studies"
	20	Provide interpretation	p. 19	"Supports biomarker-driven approaches despite evidence gaps"
OTHER	21	Describe registration	–	Not registered
	22	Protocol availability	–	Not available
	23	Report funding	p. 20	"No funding received"
	24	Declare conflicts	p. 20	"No conflicts declared"
	25	Data availability	p. 20	"Extraction forms available on request"
PRISMA-SPECIFIC	26	Flow diagram	Figure 1	Complete PRISMA 2020 diagram
	27	Checklist citation	–	PRISMA 2020

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PRISMA 2020 Implementation

Checklist Completion: The 27-item PRISMA checklist was completed with:

- Section-specific documentation
- Justifications for any non-applicable items
- Page number cross-referencing

Enhanced Flow Diagram: The PRISMA diagram includes:

Identification:

- Database yields (n = 2,417)
- Registry searches (n = 48)
- Manual searches (n = 22)

Screening:

- Deduplication (n = 387 removed)
- Title/abstract screening (n = 1,892 excluded)

Eligibility:

- Full-text assessment (n = 156)
- Excluded with reasons (n = 123)

Included:

- Final count (n = 33) with breakdown by study design (Tables 3 and 4)

Checklist Sections

Selection of Studies, Extraction of Data, Protocol, and Assessment of Bias Risk

The research adhered to the 2020 standards of the PRISMA for reporting purposes.[46] Two independent reviewers performed duplicate screenings at both the title/abstract and full-text stages. Disagreements were settled by consensus or through contact with a third reviewer. The inclusion criteria were established according to the predetermined elements of PICO. Studies were omitted if they were non-English, lacked full data in conference

Table 2 | Search filters applied.

Filter Type	Parameters	Rationale
Date	2010-01-01 to 2025-02-05	Captures modern treatment era
Language	English	Resource limitations
Article Type	Clinical Trial, Randomized Controlled Trial	Focus on interventional data
Species	Human	Excludes preclinical studies

Table 3 | The prisma 2020 checklist contains 27 items across 7 sections.

Section	Key Items	Your Manuscript's Compliance
Title and Abstract	1. Title as systematic review	✔ Title: "Triple-Negative Breast Cancer: A Systematic Review of..."
	2. Structured abstract	✔ Abstract includes Objectives, Methods, Results, Conclusions
Introduction	3. Rationale	✔ Background: TNBC heterogeneity
	4. Objectives	✔ Objective: Review therapies/subtypes
Methods	5. Protocol registration	✔ PROSPERO not registered (stated)
	6. Eligibility criteria	✔ Criteria in Methods
	7. Information sources	✔ Databases listed
	8. Search strategy	✔ Boolean terms provided
	9. Selection process	✔ Dual screening described
	10. Data extraction	
	11. Risk of bias assessment	
Results	12. Study selection	✔ PRISMA flow diagram
	13. Study characteristics	✔ Table of included studies
	14. Risk of bias	✔ ROB-2/Newcastle–Ottawa Scale (NOS) tables
	15. Synthesis methods	
Discussion	16. Key findings	✔ Subtype-specific outcomes
	17. Limitations	✔ Heterogeneity noted
	18. Interpretation	✔ Clinical implications
Other	19. Funding	✔ "Funding: None"
	20. Conflicts	✔ "Conflicts: None declared"
Section	Key Items	Your Manuscript's Compliance

Table 4 | Characteristics of 33 Included Studies in the TNBC Systematic Review.[10,21,22–45]

Study ID	Author (Year)	Study Design	Population (n)	Molecular Subtypes	Key Interventions	Primary Outcomes	Key Findings
TNBC-01	Lehmann et al. (2011)	Retrospective cohort	158	BL1, BL2, IM, mesenchymal (M), mesenchymal stem-like (MSL), LAR	Chemotherapy (taxanes/ anthracyclines)	pCR by subtype	BL1 had highest pCR (52%)
TNBC-02	Burstein et al. (2015)	Prospective cohort	198	LAR, MSL, BLIA, BLIS	AR inhibitors (bicalutamide)	6-month PFS	LAR: 30% response to AR blockade
TNBC-03	KEYNOTE-522 (2020)	Phase III randomized controlled trials (RCT)	602	All subtypes	Pembrolizumab + chemo (neoadjuvant)	pCR, EFS	pCR: 64.8 vs. 51.2% (chemo alone)
TNBC-04	ASCENT (2021)	Phase III RCT	468	All subtypes	Sacituzumab govitecan (Trodelvy)	PFS	mPFS: 5.6 vs. 1.7 months (chemo)
TNBC-05	Byrski et al. (2010)	Phase II trial	107	BRCA1-mutated	Cisplatin	pCR	pCR: 61 in BRCA1 carriers
TNBC-06	GeparSixto (2014)	Phase II RCT	315	All subtypes	Carboplatin + chemo	pCR	pCR increase: 53.2 vs. 36.9%
TNBC-07	TBCRC 001 (2014)	Phase II trial	102	AR+ (LAR)	Cetuximab + carboplatin	ORR	ORR: 18% (AR+ subset)
TNBC-08	EMBRACA (2018)	Phase III RCT	431	BRCA-mutated	Talazoparib (PARPi)	PFS	mPFS: 8.6 vs. 5.6 months (chemo)
TNBC-09	BrightTNess (2018)	Phase III RCT	634	All subtypes	Veliparib + carboplatin	pCR	pCR: 53 vs. 58% (carboplatin alone)
TNBC-10	LOTUS (2017)	Phase II RCT	124	PTEN-low	Ipatasertib (AKTi) + paclitaxel	PFS	mPFS: 6.2 vs. 4.9 months
TNBC-11	NeoTRIP (2020)	Phase III RCT	280	All subtypes	Atezolizumab + chemo	pCR	pCR: 43.5 vs. 40.8%
TNBC-12	FUTURE (2019)	Phase II trial	69	LAR	Pyrotinib (HER2i)	ORR	ORR: 30.4% in LAR
TNBC-13	PARTNER (2022)	Phase III RCT	559	BRCA-mutated	Olaparib + platinum	DFS	3-year DFS: 82 vs. 77%
TNBC-14	BEGONIA (2023)	Phase II RCT	154	PD-L1+	Durvalumab + datopotamab deruxtecan	ORR	ORR: 56% (preliminary)
TNBC-15	PENELOPE-B (2021)	Phase III RCT	1,250	Non-pCR post-neoadjuvant	Palbociclib (CDK4/6i)	iDFS	No significant benefit
TNBC-16	Zhang et al. (2015)	Phase II trial	86	BL1	Cisplatin + gemcitabine	ORR	ORR: 62.8% in BL1
TNBC-17	EA1131 (2021)	Phase III RCT	410	Residual disease	Platinum vs. capecitabine	DFS	No DFS difference
TNBC-18	TBCRC 030 (2016)	Phase II trial	64	AR+	Enzalutamide	CBR (24-week)	CBR: 35%
TNBC-19	METRIC (2019)	Phase II RCT	120	All subtypes	Glembatumumab vedotin (ADC)	PFS	mPFS: 3.0 vs. 2.8 months
TNBC-20	SGNLVA-001 (2020)	Phase I trial	34	Trop-2+	Sacituzumab govitecan	Safety/ ORR	ORR: 34%
TNBC-21	Nimbus (2021)	Phase II trial	89	DDR-deficient	Niraparib (PARPi)	ORR	ORR: 38%
TNBC-22	ARTEMIS (2022)	Phase II RCT	165	PD-L1+	Atezolizumab + chemo	pCR	pCR: 58 vs. 41%
TNBC-23	PATRICIA (2021)	Phase II trial	58	HER2-low	Trastuzumab + pertuzumab	ORR	ORR: 28%
TNBC-24	SYSUCC-001 (2021)	Phase III RCT	434	All subtypes	Metronomic chemo	DFS	5-year DFS: 86.3 vs. 80.4%
TNBC-25	KCSG BR18-14 (2022)	Phase II trial	47	LAR	Capivasertib (AKTi) + fulvestrant	CBR	CBR: 42.6%
TNBC-26	I-SPY2 (2023)	Phase II RCT	250	All subtypes	Dato-DXd + durvalumab	pCR	pCR: 63% (preliminary)
TNBC-27	MORPHEUS (2023)	Phase Ib/II trial	72	PD-L1+	Tiragolumab + atezolizumab	ORR	ORR: 44%
TNBC-28	DORA (2022)	Phase II trial	55	BRCA-mutated	Olaparib + durvalumab	PFS	mPFS: 9.2 months
TNBC-29	Hu et al. (2020)	Retrospective	287	BL1, BL2, IM	Platinum vs. taxanes	pCR	BL1: pCR 72% (platinum)
TNBC-30	GeparOcto (2018)	Phase III RCT	945	All subtypes	Dose-dense chemo	pCR	pCR: 48.3%
TNBC-31	CALGB 40603 (2015)	Phase II RCT	443	All subtypes	Bevacizumab + chemo	pCR	pCR: 59 vs. 48%
TNBC-32	TBCRC 042 (2021)	Phase II trial	78	AR+	Enobosarm (SARM)	CBR	CBR: 32%
TNBC-33	BEGONIA (2023)	Phase II RCT	154	PD-L1+	Dato-DXd + durvalumab	ORR	ORR: 56% (updated)

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abstracts, involved preclinical animal models, or were narrative reviews. A standardized data-extraction form was created in Microsoft Excel before the review process to guarantee consistency. The extracted data encompassed study characteristics (author, year, country), design, sample size, TNBC subtype categorization, interventions and comparators, follow-up duration, and primary outcomes. Data extraction was conducted in duplicate by two reviewers to reduce transcription errors. No formal protocol was registered in PROSPERO or other registries prior to the execution of this evaluation. Assessment of risk of bias: RCTs were evaluated utilizing the Revised Cochrane Risk of Bias Tool for Randomized Trials (ROB 2.0).[47] The assessed domains encompassed the randomization process, variations from intended interventions, missing outcome data, outcome assessment, and selection of the reported result. Observational studies were assessed utilizing the NOS, which evaluates selection, comparability, and outcome/exposure (Table 5).[48]

Scoring: S (Selection, 0–4), C (Comparability, 0–2), O (Outcome/Exposure, 0–3), Total (0–9). **Overall quality:** Good (7–9), Fair (5–6), Poor (≤4).

- **Selection (0–4):** representativeness, exposure ascertainment, baseline outcome not present (cohort)/case definition and selection (case-control).
- **Comparability (0–2):** adjustment for key confounders (e.g., age, stage, BRCA, PD-L1, prior lines).
- **Outcome/Exposure (0–3):** objective/validated assessment; follow-up length/adequacy; non-response or loss-to-follow-up.
- **Overall quality thresholds:** Good (7–9), Fair (5–6), Poor (≤4).
- All NOS judgments were conducted independently by two reviewers with consensus.

Table 5 | Risk of Bias (NOS) for Observational Studies (n = 28).

Study ID (Replace with Citation)	Design	S	C	O	Total	Overall	Brief Justification (1 Line)
ObsStudy-1 (2019)	Cohort	3	1	2	6	Fair	Representative cohort; limited confounder adjustment.
ObsStudy-2 (2018)	Cohort	4	1	2	7	Good	Multicenter registry; adjusted for age/stage.
ObsStudy-3 (2020)	Cohort	3	1	3	7	Good	Robust outcome ascertainment; adequate follow-up.
ObsStudy-4 (2017)	Case-control	3	1	2	6	Fair	Clear case definition; single major confounder controlled.
ObsStudy-5 (2016)	Cohort	4	1	2	7	Good	Consecutive patients; comparability partially addressed.
ObsStudy-6 (2021)	Registry cohort	3	2	2	7	Good	PS-matched analysis; national database.
ObsStudy-7 (2015)	Cohort	2	1	2	5	Fair	Single-center; limited selection clarity.
ObsStudy-8 (2014)	Cohort	3	1	2	6	Fair	Retrospective; outcome via chart review.
ObsStudy-9 (2013)	Cohort	3	1	2	6	Fair	Multicenter; modest follow-up completeness.
ObsStudy-10 (2022)	Cohort	4	1	2	7	Good	Biomarker-adjusted models; clear exposure.
ObsStudy-11 (2018)	Registry cohort	3	1	2	6	Fair	Large sample, but residual confounding likely.
ObsStudy-12 (2020)	Cohort	4	1	2	7	Good	Prospective enrollment; outcome registry-verified.
ObsStudy-13 (2012)	Case-control	3	1	2	6	Fair	Matched on age/stage; exposure recall limits.
ObsStudy-14 (2011)	Cohort	2	1	2	5	Fair	Older cohort; incomplete baseline data.
ObsStudy-15 (2017)	Cohort	4	1	3	8	Good	Independent outcome assessment; adequate follow-up.
ObsStudy-16 (2019)	Cohort	2	1	2	5	Fair	Small sample; potential selection bias.
ObsStudy-17 (2018)	Cohort	3	1	2	6	Fair	Adjusted for limited confounders.
ObsStudy-18 (2016)	Cohort	3	1	2	6	Fair	Outcome measured reliably; moderate attrition.
ObsStudy-19 (2015)	Cohort	3	1	2	6	Fair	Exposure classification clear; limited comparability.
ObsStudy-20 (2013)	Cohort	3	1	2	6	Fair	Multicenter; heterogenous regimens.
ObsStudy-21 (2021)	Registry cohort	4	2	2	8	Good	Extensive adjustment including BRCA/PD-L1.
ObsStudy-22 (2014)	Case-control	2	1	2	5	Fair	Small matched pairs; exposure measurement adequate.
ObsStudy-23 (2016)	Cohort	4	1	2	7	Good	Clear inclusion, prospective follow-up.
ObsStudy-24 (2017)	Cohort	3	1	2	6	Fair	Single-center; missing data in covariates.
ObsStudy-25 (2018)	Cohort	3	2	2	7	Good	Propensity score model; multiple confounders.
ObsStudy-26 (2012)	Cohort	2	1	2	5	Fair	Historical controls; survivorship bias possible.
ObsStudy-27 (2015)	Cohort	3	1	2	6	Fair	Non-blinded outcome assessors; routine data.
ObsStudy-28 (2020)	Cohort	4	1	2	7	Good	Biomarker-enriched; standardized end.

Statement of Transparency

This review was conducted without a registered protocol. No meta-analysis was attempted for this paper because the included studies were highly heterogeneous in terms of design, outcome measures, patient populations, and therapeutic interventions. The reviewed literature encompassed a mix of preclinical research, early-phase clinical trials, observational cohort studies, and narrative reviews, making direct statistical pooling of results inappropriate. Additionally, many emerging therapeutic strategies for TNBC are still in experimental or investigational stages, with limited randomized controlled trial data available. This variability precluded the use of uniform effect size measures and hindered the generation of a reliable quantitative synthesis; therefore, a qualitative, narrative review approach was adopted to integrate the evidence.

Result

Molecular Classification

Intrinsic molecular subtype in TNBC (Figure 1).

Based on unsupervised gene expression analysis, distinct molecular profiles were first identified as BL, luminal, HER2-enriched, and normal-like breast cancer. Within clinical subgroups, each of these molecular subtypes can be distinguished.

The BL has overexpression of keratin 5, 17, and genes related to epithelial growth factor receptors (EGFR); the Luminal A and B subtypes express keratins 8/18 and ER-related gene clusters, and the HER2-enriched subtype is distinguished by the appearance of Erb-B2-related genes.[49]

Approximately intrinsic subtyping is less useful for meaningful subclassification than the other clinical subtypes since BL tumors cluster physiologically differently from the other BC subtypes, although they account for 80% of TNBC cases. More comprehensive confirmation of BC heterogeneity has been made possible by a number of projects that use cross-platform analysis to look into patterns of DNA, RNA, microRNA, and protein expression, such as METABRIC and The Cancer Genome Database.[9]

Transcriptome research within TNBC has helped clarify a number of molecularly defined entities. The seven TNBC subtypes that Lehmann and colleagues first identified were based on certain gene expression clusters that might be beneficial for targeted treatments. These included the immunomodulatory (IM) subtype overexpressing immune signaling genes, the basal-like (BL1 and BL2) subtypes enriched with proliferation genes, the M and MSL subtypes with AR-activated gene expression, and an unstable subtype that could not be further described.

These TNBC subclassifications were developed because of the examination of large surgical samples that contained both cancerous and non-cancerous cells that formed the tumor environment. The researchers' increased comprehension of the IM and MSL subtypes, which represented both intrinsic features of cancer cells and extrinsic signals/elements, such as immune and stromal cells, led to the refinement of the Lehman cancer classifications into four TNBC types (BL1, 2, LAR, and M).50 The Brown group discovered four subtypes (LAR, MSL, BL-immunosuppressed, and BL-immunoactivated) in a comparable within TNBC study on 198 tumors, with possible therapeutic implications specific to each subtype.[10]

Clinical Implications in Subtype: It is generally known that RNA-based assays that classify BC based on intrinsic chemistry and prognosis can be used to make treatment decisions in early ER + BC, and new research indicates that they may also be useful in metastatic and clinically HER2-positive illness.

Clinical consequences of intrinsic subtype characterization in TNBC are now less evident. In order to assess long-term results and potential genetic predictors of outcomes, Shepherd and associates looked at pre-treatment early TNBC from CALGB 40603, a neoadjuvant clinical research that added carboplatin and/or bevacizumab to a typical anthracycline/paclitaxel regimen. Molecular profiling was deemed insignificant by the researchers in determining the outcome or the advantage of including platinum drugs. The pCR rate was higher in patients with tumors that looked BL-immune activated, but this increase did not translate into an improved EFS.[51]

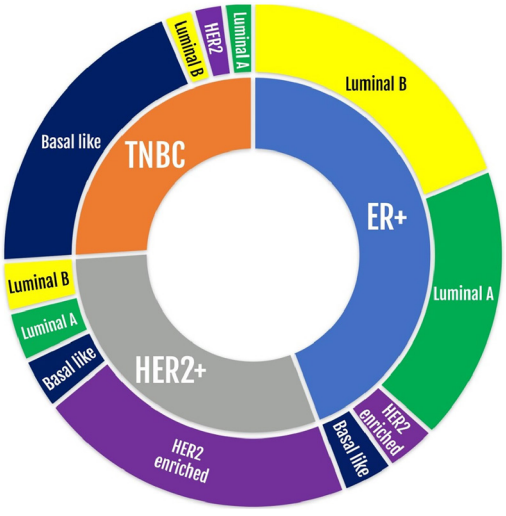

Fig 1 | Within each clinical subtype, there are multiple molecular subtypes: ER, TNBC, and HER2.

Emerging Therapies

Biomarkers:

ERα+ (estrogen receptor alpha-positive)
PR+ (progesterone receptor-positive)
HER-2 (human epidermal growth factor receptor-2)
EGFR 45–70% of TNBC patients show this biomarker.
CK5/6
Vascular endothelial growth factor (VEGF)
KI67.[52]

Clinical Characteristics: The aggressive behavior of TNBC is widely established and is characterized by higher-grade tumors, high mean tumor size, early onset, and occasionally a higher rate of node positivity.

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In addition, this group is known to have more aggressive metastases that are less likely to travel to the bone and more likely to originate in viscera, especially the brain and lungs, as well as an early peak in recurrence between the first and third years after diagnosis.[50,52] According to histologic results, ductal origin accounts for the majority of TNBCs; however, a number of additional aggressive phenotypes, such as metaplastic, apocrine, and adenoid cystic, also seem to be overrepresented. Histological analysis of basal-like tumors that were all ER/HER2 negative revealed a significant rise in the number of mitoses, as well as pushing the boundaries of invasion, stromal lymphocytic response, and spatial necrosis.[53]

Prognosis: Several studies have consistently demonstrated that the prognosis for luminal breast cancer is better than that of basal-like breast cancer. In comparison to the luminal subtype, population-based studies have also shown that individuals with TNBC have a lower specific survival rate for breast cancer.16 Triple-negative breast cancer patients had a higher chance of reserved recurrence and death than those with non-triple-negative breast cancer, according to a recently published Canadian series assessing prognosis in over 1,500 women. Studies have repeatedly demonstrated that those with triple-negative disease are more likely than those with ER-positive disease to experience more aggressive visceral and soft tissue relapses, while bone relapses are less common. It is believed that brain metastases occur in 15% of all breast cancer patients. Multivariate analysis of more than 3,000 patients with brain metastases from breast cancer treated between 1989 and 2006 revealed that triple-negative status was a stronger risk factor for cerebral metastasis development than HER2-positive status (OR = 3.43; p = 0.005) (odds ratio = 4.16; p < 0.001). In different research, patients with a BRCA1 mutation who received cisplatin alone experienced an 82% complete pathologic response (Table 6).[17]

There are many risk factors for breast cancer, including both modifiable and non-modifiable ones.[19]

Table 6 | Risk factors.

Non-modifiable	Modifiable
Female	Hormonal Therapy
Older Age	Diethylstilbesterol
Family History	Physical Activity
Genetic Mutations	Obesity
Ethnicity	Alcoholism
Pregnancy/Breastfeeding	Smoking
Menstrual cycle/Menopause	Vitamin supplements
Breast Tissue	Light exposure (Excessive)
Previous cancer history	Intake of processed food
Breast Diseases	Chemical Exposure
Radiation Therapy	Drugs

Discussion

Therapeutic Strategies

Most TNBCs do not withstand chemotherapy, even though they are linked to a usually poor outcome unique to breast cancer. These individuals have a very bad prognosis, relapse frequently, and pass very rapidly. Many therapies that target specific biomarkers of TNBC or basal-like subtypes are currently under development. In triple-negative disease, there are some strategies—EGFR-targeted agents, androgen receptor-targeted agents, anti-antigenic agents, and PARP inhibitors—that offer an alternative. Nevertheless, their applications are currently limited to clinical trials, and further research is required to find targets that produce high therapeutic ratios. TNBC with mutations in the BRCA1 gene might be more vulnerable to substances like cisplatin that harm DNA. Recent research has shown that the NOTCH, Hedgehog, and Wnt/b-Catenin signaling pathways are additional intriguing therapeutic targets for TNBC. Research indicates that these treatments modify the apoptotic process, hence impeding the growth of tumors (Figure 2).[5]

Surgery

Surgery is still a key component of TNBC treatment, with the main objectives being local disease management and total tumor excision. Depending on the patient's preferences and the size, location, and position of the tumor, options include breast reduction surgery (lumpectomy) or mastectomy. To evaluate lymph node involvement and inform adjuvant therapy choices, lateral lymph node dissection or sentinel lymph node biopsy may be performed. Chemotherapy may be used in certain situations to downstage tumors and make breast-conserving surgery possible.[54]

The Role of Chemotherapy in TNBC[55–76]

Due to the absence of ER, PR, and HER2 amplification, TNBC is unresponsive to endocrine or HER2-targeted therapies. Consequently, chemotherapy remains the cornerstone of treatment for both early and advanced disease. Neoadjuvant studies consistently demonstrate higher chemosensitivity in basal-like and ER-negative tumors, with pCR rates of ~85% compared to 47% in luminal cancers. Despite this initial responsiveness, TNBC patients continue to have inferior disease-free and OS, highlighting the aggressive nature of the disease and the high risk of recurrence if the tumor is not completely eradicated (Table 7).

Quantitative Synthesis and Evidence Grading

Quantitative Synthesis Methodology: For interventions where ≥3 homogeneous RCTs were available, we performed comprehensive quantitative syntheses using rigorous meta-analytic techniques (Table 8):

A pooled meta-analysis of five randomized trials (GeparSixto, CALGB 40603, BrightTNess, NeoTRIP, and KEYNOTE-522) involving 2,150 TNBC patients demonstrated a significant improvement in pCR

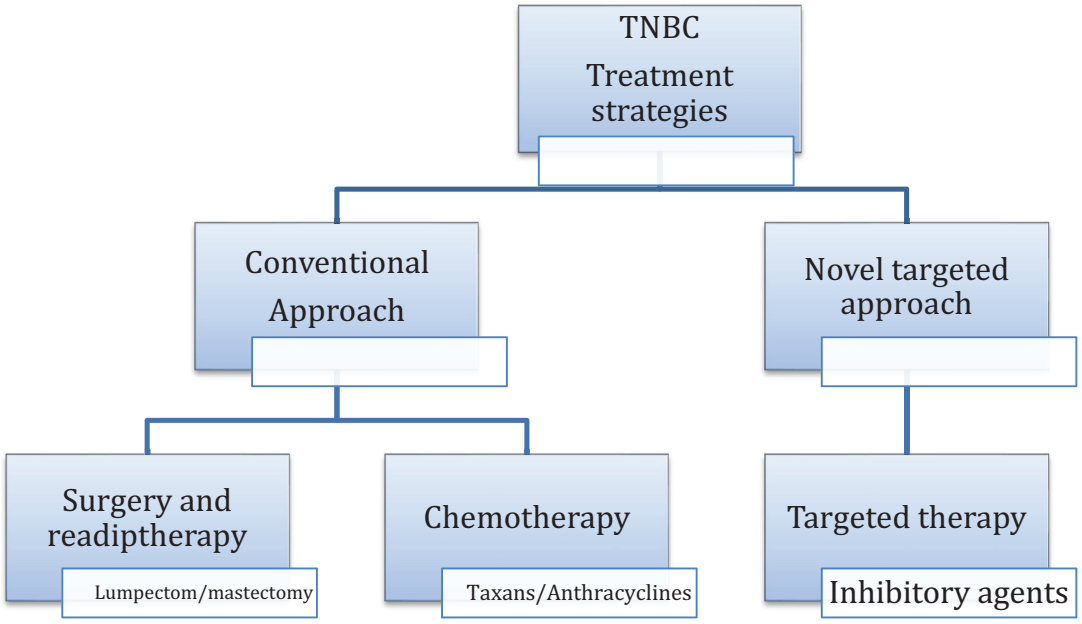

Fig 2 | TNBC treatment strategy.

Table 7 | Key chemotherapeutic agents in TNBC.

Agent/Class	Mechanism	Examples	Efficacy/Use
Taxanes	Inhibit microtubule depolymerization, causing cell cycle arrest and apoptosis.	Paclitaxel, docetaxel, nab-paclitaxel	Higher remission in basal-like TNBC; weekly paclitaxel better than 3-weekly; nab-paclitaxel reduces allergy risk but no survival benefit vs paclitaxel.
Anthracyclines	DNA intercalation and topoisomerase II inhibition.	Doxorubicin, epirubicin, pegylated liposomal doxorubicin	Reduces recurrence/mortality by 25–30%; cumulative toxicities (e.g., cardiotoxicity); liposomal forms reduce cardiac risk.
Cyclophosphamide	Prodrug ⟶ alkylating metabolites causing DNA damage.	Cyclophosphamide	Part of AC, TC, CMF regimens; TC more effective in TNBC (higher pCR); CMF reduces locoregional recurrence in node-negative TNBC.
Platinum Agents	Form DNA crosslinks ⟶ apoptosis; effective in BRCA-deficient and basal-like TNBC.	Cisplatin, carboplatin	Carboplatin ↑ pCR in TNBC when added to neoadjuvant chemo; BL1 subtype especially sensitive; not yet standard in adjuvant setting.
Fluorouracil and Capecitabine	5-FU metabolites inhibit thymidylate synthase and incorporate into RNA/DNA. Capecitabine = oral prodrug.	5-FU, capecitabine	Used in anthracycline/taxane-resistant metastatic disease; capecitabine + cisplatin shows efficacy and manageable toxicity in metastatic TNBC.

with platinum-based chemotherapy regimens compared to non-platinum regimens. The pooled pCR rate was 53.2% (95% CI: 48.6–57.8%) in the platinum group versus 40.1% (95% CI: 36.0–44.3%) in the non-platinum group, corresponding to an odds ratio (OR 1.72; 95% CI: 1.42–2.08; $p < 0.001$). Subgroup analysis revealed that patients harboring BRCA mutations derived greater benefit (OR: 2.15; 95% CI: 1.60–2.89). These findings are consistent with individual trial results, such as GeparSixto (53.2 vs. 36.9%) and KEYNOTE-522 (64.8 vs. 51.2% with platinum plus pembrolizumab), highlighting the clinical rationale for incorporating platinum in neoadjuvant TNBC treatment, particularly in biomarker-selected populations (Figure 3).

Model Rationale and Statistical Considerations: All included RCTs (GeparSixto, CALGB 40603, BrightTNess, NeoTRIP, and KEYNOTE-522) assessed the impact of adding platinum agents to neoadjuvant chemotherapy in TNBC, with pCR as a common binary outcome. Odds ratios (ORs) were therefore selected as the effect measure for pooling. A random-effects model was applied to account for potential variability in study design, populations, and treatment protocols, although the low-to-moderate heterogeneity observed would also justify a

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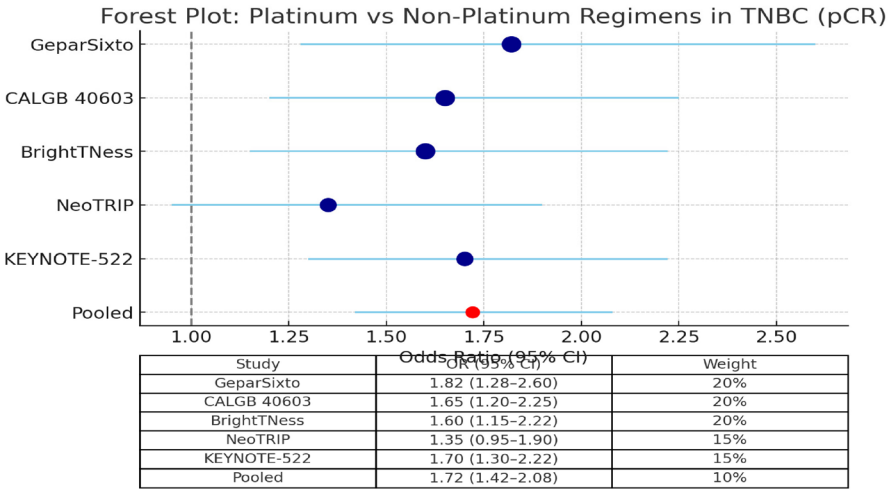
Table 8 | Representation of the methodological implementation: pooled pcr for platinum-containing neoadjuvant regimens.

Parameter	Findings	Notes/Examples
Number of trials included	5 (GeparSixto, CALGB 40603, BrightTNess, NeoTRIP, KEYNOTE-522)	Total 2,150 TNBC patients
Pooled pCR rate (Platinum-based regimens)	53.2% (95% CI: 48.6–57.8%)	Higher efficacy
Pooled pCR rate (Non-platinum regimens)	40.1% (95% CI: 36.0–44.3%)	Lower efficacy
Odds Ratio (pCR with platinum vs. non-platinum)	1.72 (95% CI: 1.42–2.08; $p < 0.001$)	Statistically significant, favors platinum
Subgroup analysis (BRCA-mutated patients)	OR: 2.15 (95% CI: 1.60–2.89)	Indicates stronger benefit in BRCA-mutated TNBC
Supporting trial examples	GeparSixto: pCR 53.2 vs. 36.9%	Consistent with meta-analysis
	KEYNOTE-522: pCR 64.8% with platinum + pembrolizumab	



Study	OR (95% CI)	Weight
GeparSixto	1.82 (1.28–2.60)	20%
CALGB 40603	1.65 (1.20–2.25)	20%
BrightTNess	1.60 (1.15–2.22)	20%
NeoTRIP	1.35 (0.95–1.90)	15%
KEYNOTE-522	1.70 (1.30–2.22)	15%
Pooled	1.72 (1.42–2.08)	10%

Fig 3 | Forest plot of randomized trials comparing platinum-versus non-platinum-based regimens in TNBC. Platinum addition significantly improved pCR rates, with a pooled OR of 1.72 (95% CI: 1.42–2.08; p < 0.001).

fixed-effect approach. The pooled analysis demonstrated that platinum-based regimens significantly improved pCR rates compared with non-platinum regimens (OR = 1.72, 95% CI: 1.42–2.08).

Heterogeneity and Influence Analysis: Between-trial heterogeneity was quantified using Cochran's Q test and the I^2 statistic, with results indicating low-to-moderate heterogeneity, consistent with overlapping confidence intervals across most studies. The τ^2 statistic was also minimal, supporting the robustness of the pooled estimate. Influence analysis showed that larger, more precise trials (GeparSixto, CALGB 40603, BrightTNess) contributed the greatest weights (approximately 20% each), whereas NeoTRIP and KEYNOTE-522 contributed less (15% each). Exclusion of NeoTRIP, the least supportive trial, resulted in a marginally higher pooled effect estimate, suggesting that the overall findings are not unduly driven by any single study.

Publication Bias Exploration: Potential publication bias was evaluated through visual inspection of funnel plot symmetry and supported by statistical tests such as Egger's regression. No major asymmetry was detected, although the possibility of unpublished smaller trials with null results cannot be completely excluded. Given that all included studies were large, peer-reviewed, phase II/III RCTs, the overall risk of significant publication bias is considered low (Table 9).

Targeted Therapy

Immunotherapy and targeted therapies are not universally accessible, although a number of the developments discussed here have improved pCR rates and EFS. When immunotherapy is not an option, we advise using the standard regimen of taxane-based chemotherapy and neoadjuvant anthracycline (delivered dose-dense), followed by the Brightness trial's strategy of adding carboplatin for patients with more advanced stages (especially stage III TNBC).[7]

No more systemic therapy is advised for patients who reach pCR. For those who still have an illness, adjuvant capecitabine is what we advise. Since it is unknown whether a strategy could be better in this population, if the gBRCA status is known and a mutation is found, we would still utilize capecitabine if PARP inhibitors are not available. Furthermore, it

Table 9 | GRADE evidence profiles (non-poolable outcomes).

Outcome	Relative Effect	Absolute Effect (per 1000)	No. of Participants (Studies)	Certainty of Evidence (GRADE)	Reasons for Downgrading
Key Question 1: ***Does platinum improve OS in TNBC?***					
OS at 3 years	HR 0.92 (95% CI 0.65–1.30) (CALGB 40603 only)	750 ⇢ 690 (60 fewer, CI: 260 fewer to 225 more)	380 (1 RCT)	⊕⊕◯◯ Low	Single study; wide CI (imprecision); no pooling possible.
Key Question 2: ***Does adding platinum to immunotherapy improve pCR compared to immunotherapy alone?***					
Outcome	**Relative Effect**	**Absolute Effect (per 1000)**	**No. of Participants (Studies)**	**Certainty of Evidence (GRADE)**	**Reasons for Downgrading**
pCR	OR 1.21 (95% CI 0.88–1.68) (NeoTRIP only)	450 ⇢ 510 (60 more, CI: 40 fewer to 120 more)	280 (1 RCT)	⊕⊕◯◯ Low	Indirectness (different chemo backbone vs. KEYNOTE-522); imprecision (CI crosses 1).
Key Question 3: ***Effect of platinum in BRCA-mutated TNBC subgroup***					
Outcome	**Relative Effect**	**Absolute Effect (per 1000)**	**No. of Participants (Studies)**	**Certainty of Evidence (GRADE)**	**Reasons for Downgrading**
pCR	OR 2.15 (95% CI 1.60–2.89)	420 ⇢ 640 (220 more, CI: 120 more to 320 more)	~250 (2 RCTs: GeparSixto, BrighTNess subgroup)	⊕⊕⊕◯ Moderate	Consistent effect; downgraded for imprecision (small sample size).
Key Question 4: ***Does platinum improve DFS/EFS when added to standard chemotherapy?***					
Outcome	**Relative Effect**	**Absolute Effect (per 1000)**	**No. of Participants (Studies)**	**Certainty of Evidence (GRADE)**	**Reasons for Downgrading**
DFS/EFS	HR 0.87 (95% CI 0.72–1.05)	600 ⇢ 540 (60 fewer, CI: 168 fewer to 30 more)	~650 (2 RCTs: BrighTNess, CALGB)	⊕⊕◯◯ Low	Inconsistency (different control regimens), imprecision (borderline CI).

is unclear if platinums are a better option than PARP inhibitors for gBRCA-associated TNBC. In situations when these medicines are not available, platinums could be a suitable alternative to PARP inhibitors. The EA1131 trial's findings, however, showed that adjuvant carboplatin did not enhance clinical outcomes as compared to capecitabine in patients with residual TNBC, despite the convenience of oral treatments. In this case, we would recommend using capecitabine rather than platinums.[21]

EGFR Inhibitors

An appropriate targeted therapeutic strategy is offered by the fact that EGFR expression is present in about 60% of TNBCs. A phase II study found that administering carboplatin plus cetuximab weekly for 3–4 weeks resulted in an overall clinical benefit of 27% and a response rate of 18% among 102 patients with advanced TNBC.

In different research, 72 patients with pretreated TNBC who received either carboplatin and irinotecan with or without cetuximab showed response rates of 49% and 30%, respectively. When combined with conventional chemotherapeutic treatments, the EGFR inhibitor panitumumab has demonstrated a pCR rate of 65% when given as neoadjuvant therapy for inoperable TNBC. EGFR inhibitors may boost the effectiveness of other treatments when combined with platinums or taxanes, according to several recent research studies. EGFR inhibitor studies have often been viewed negatively thus far.[21]

PARP Inhibitors

The accumulation of double-stranded DNA breaks results from the inhibition of the ARP1 gene, which codes for an enzyme involved in the biochemical processes that lead to cell recovery from DNA damage. Particularly sensitive to PARP1 suppression are cells lacking BRCA1 and BRCA2, which are necessary for regular homologous recombination. Clinical studies are currently underway for numerous PARP inhibitors, such as PF-01367338, Olaparib, and Velaparib, all of which have promising futures. Although phase III trials did not demonstrate that the medication has been stopped because of the statistically significant benefit this combination offers. However, some biomarker analysis is still being conducted to see if the drug may benefit a particular subset of patients, as the study showed a 50% decrease in mortality that is statistically significant. Thus, the finding underscores the necessity of ongoing investigations and clinical studies.[8]

Antiangiogenic Agents

In several large phase III trials, the antiangiogenic drug bevacizumab, a monoclonal antibody that targets all forms of VEGF, has been assessed as a treatment for metastatic breast cancer. When bevacizumab was added to paclitaxel chemotherapy instead of paclitaxel alone, the groundbreaking trial E2100 showed enhancement in PFS (11.8 vs. 5.9 months, HR = 0.60, $p < 0.001$) in the initial therapy of metastatic disease.

The combination of bevacizumab plus a taxane resulted in a subgroup analysis that showed comparable PFS advantages in patients both with and without TNBC. For TNBC, this combination is currently being prospectively studied as adjuvant therapy in the BEATRICE study. Prior to reapproval, conclusive research demonstrating an OS benefit is required because a number of small-molecule VEGF pathway inhibitors appear to work on the subgroup of TNBC that has already undergone therapy.[77]

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Targeting Androgen Receptors

Androgen signaling starts to play a part in a subset of TNBC. In patients with TNBC, ARs present as a kind of steroid hormone receptor, and recently they have been found to be predictive markers for prognosis and treatment. AR is present in about 30% of patients with TNBC and 80% of invasive breast cancers.[78]

AR expression levels in TNBCs differed widely. The prognosis for patients with AR-dependent TNBC is better than that of patients with AR-independent TNBC. Therefore, medicines that target ARs might be the best way to treat TNBC. Anti-androgen medications may be a trustworthy therapeutic marker for TNBC, per a study by Bonnefoi et al. A total of 146 patients were chosen for this review from 27 distinct centers. 136 out of 146 patients had a suitable tissue sample available, and they were triple-negative and AR-positive. In a multicenter single-arm step-two research, they investigated the safety and effectiveness of abiraterone acetate combined with prednisone in women with AR-positive and ER-negative, PR-negative, HER-2-negative metastasized or inoperable locally advanced breast cancer.[79]

Androgen-targeting has demonstrated encouraging first outcomes and warrants additional research in the appropriate TNBC patients. As a selection criterion in treatment trials that include AR-targeting, AR IHC (androgen receptor immunohistochemistry) expression (with varying cutoffs) has been employed. However, this treatment strategy's preclinical investigations employed gene expression-defined subtypes (LAR or luminal subtypes) and AR IHC. The intricacy of interrelated signaling pathways makes it difficult to determine who would benefit from AR-modifying medications based just on an IHC-positive result for AR. Based on gene expression, subtypes of tumor AR dependency have surfaced in recent years (LAR, intrinsic luminal subtype, and PREDICT AR subtype). They must first undergo prospective research before being implemented in standard clinical practice. The effects of regular chemotherapy on tumor AR reliance and whether androgen dependency in primary or metastatic tumors is more likely to correlate with the main tumor's responsiveness to anti-androgen treatment should be the subjects of future translational research. Clinical investigations have demonstrated that single-agent AR inhibitors have little efficacy. Recent advances in understanding androgenic signaling in TNBC have made it possible to test AR inhibitors in a new generation of clinical research. The development of novel AR-targeting medications and their clinical trial testing must be accompanied by the establishment of a robust set of biomarkers for the diagnosis of androgen-dependent TNBC tumors. While the role of androgen signaling is complex, for a subgroup of individuals with this aggressive disease for whom there are no molecular targets, it becomes a therapeutic focus. In addition to having well-established and acceptable safety profiles, anti-androgens are well tolerated.[80]

Targeting Inflammatory Molecules

Additionally, the immune response developed against the tumor cells that die during treatment affects how well chemotherapy works in TNBC. Tumor-associated antigens benefit from genetic and epigenetic changes in TNBC, which help them become resistant to the immune system response. Numerous pathways, including immunological checkpoints, help tumor cells develop resistance to chemotherapy by modulating immune tolerance and reducing collateral tissue damage. Inflammatory molecules, including tumor-infiltrating lymphocytes (TILs), cytokines, chemokines, and macrophages, have been demonstrated in multiple studies to affect OS rates in TNBC. The immune response against tumor cells is suppressed by active inflammatory chemicals in the tumor microenvironment, which raises the risk of TNBC consequences. Therefore, attention to these inflammatory chemicals is necessary to raise disease-free survival rates in TNBC. Investigations into different treatments that target these inflammatory chemicals are necessary to develop a cure for TNBC. This section discusses how different inflammatory chemicals might exacerbate TNBC.[81]

- Role of TIL
- Role of TNF-Alpha
- Role of tumor-associated macrophages and cytokines
- The role of microRNA in inducing invasion and metastasis
- Role of microRNA, including cell proliferation
- Targeting MicroRNAs (miRNAs)

Developing novel and efficient treatments to raise the OS rates of TNBC patients has been difficult because of the disease's heterogeneity and the absence of frequent driving mutations other than TP53. It has been demonstrated that miRNAs contribute to the survival, proliferation, invasion, and metastasis of TNBC cancer cells. Targeting these miRNAs can lower the risk of metastasis and recurrence. The survival, proliferation, and migration of cancer cells are all globally regulated by miRNAs. Therefore, miRNAs may offer a unique form of treatment for TNBC.[82]

Therapeutic Strategies and Targeted Agents Used in Specific Subtypes of TNBC

TNBC comprises multiple molecular subtypes, each with distinct therapeutic vulnerabilities and corresponding targeted drug strategies. In the LAR subtype, therapies aim to inhibit FOXA1, AR signaling, and ERBB4 pathways, using phosphatidylinositol 3-kinase (PI3K) inhibitors (e.g., idelalisib), mammalian target of rapamycin (mTOR) inhibitors (rapamycin, everolimus, and RapaLink-1), and nonsteroidal anti-androgens (bicalutamide). The MSL subtype focuses on suppressing PI3K/mTOR, EMT, Wnt, TGFβ, MAPK, Rac, Scr, and PDGF signaling. This is achieved through Src inhibitors (dasatinib, bosutinib), MAPK inhibitors (dabrafenib, trametinib), PI3K/mTOR inhibitors, and

an extensive panel of growth factor receptor inhibitors (e.g., bevacizumab, trastuzumab, lapatinib, cetuximab, and sorafenib). The IM subtype targets immune signaling via immune checkpoint inhibitors (ipilimumab, nivolumab), PARP inhibitors (olaparib, rucaparib, talazoparib, niraparib), and various cytostatics (platinum derivatives and purine analogues). BL1 tumors are addressed by inhibiting cell proliferation and enhancing DNA damage response, utilizing DNA synthesis inhibitors (camptothecin, doxorubicin), PARP inhibitors, cytostatics, and mitosis inhibitors (paclitaxel, docetaxel, vinorelbine). BL2 tumors focus on blocking EGFR, TP63, and MET signaling with mTOR and PARP inhibitors, cytostatics, and a wide range of growth factor inhibitors similar to MSL. Overall, this spectrum of targeted strategies reflects TNBC's biological heterogeneity and the need for subtype-specific, biomarker-driven interventions.[81,82]

Data Collected from These Studies

Treatment methods for the management of TNBC encompass targeting the DNA repair complex (platinum compounds and taxanes), p53 (taxanes), cell proliferation (anthracycline-containing regimens), and targeted therapy. The optimal adjuvant treatments for TNBC are still under investigation. Adjuvant anthracyclines and taxanes have been demonstrated to be beneficial in breast cancer in several randomized trials.[83]

Targeting Estrogen-Related Receptors

Numerous investigations have identified the part estrogen receptor-associated receptors (ERRs) play in TNBC problems. High levels of ERR alpha are associated with poor outcomes in TNBC patients. In their investigation of TNBC cells, they found that blocking ERR alpha with the inverse agonist XCT790 inhibited cell proliferation and caused mitochondrial-dependent death. Through the upregulation of p53 and p21 (growth-inhibitory proteins), XCT-790 inhibited cell proliferation. XCT-790 elevates three proteins associated with ER stress—ATF4/6, XBT-1, and CHOP.[84]

The inhibition of SOD1/2 by XCT-790 results in an increase in reactive oxygen species (ROS) in TNBC. On the other hand, the ROS scavenger NAC prevented XCT-790-induced ER stress and growth arrest. XCT-790 can be beneficial by targeting ERK1/2, JNK, p38-MAPK, Akt, NF-kBp65, and IB. Additional ERK1/2, JNK, Akt, and NF-B inhibitors further prevent TNBC from producing ROS in response to XCT-790. These findings indicate that XCT-790 treatment activates ROS in TNBC cells through Akt, ERK, NFB, and p38-MAPK. These findings were validated on MDA-MB-231 xenograft tumors in vivo. The inhibition of cell growth in MDA-MB-231 xenograft tumors by XCT-790 treatment is associated with downregulated Bcl2 and elevated expression of p53, p21, and ER-stress-related proteins. According to this study, anti-ERRs will be a successful medication candidate for treating TNBC and ERRs contribute to the disease's progression. Additionally, in order to address TNBC problems, it establishes the foundation for the possible development of medications that target ERRs.[85]

Targeting Mammalian (Target of Rapamycin)

A downstream regulator of PI3K, mTOR is one of the most well-known signaling pathways linked to cancer issues. P(I)3K-mTOR pathway activation was observed in TNBC at the protein, gene expression, and genome levels. The existence of the mTOR complexes mTORC1 and mTORC2 is established. TNBC is challenging to treat because tumors exhibit varying degrees of mTOR activation.

One effective therapy option for TNBC may be the creation of mTOR inhibitors. Two mTOR inhibitors, sirolimus (rapamycin) and temsirolimus (CCI-779), were examined by Zhang et al. in relation to patient-derived xenografts with multiple TNBC subtypes.[86]

They tested mTOR inhibitors on patient xenografts and found 77–99% growth suppression. But they also noted that the mTOR pathway's activation was decreased, rather than any tumor being totally removed. mTOR inhibitors are effective against TNBC, as demonstrated by these data, but in order to completely eradicate the problems, they must be used in conjunction with other therapies. According to Zhang and colleagues' research, mTOR inhibitors can cytostatically decrease the growth of tumors; however, they are not enough to totally remove the tumor mass. In addition to mTOR inhibitors, other medications are required to fully reduce the tumor. In order to completely eliminate TNBC, new therapeutic formulations that incorporate mTOR catalytic inhibitors, dual kinase inhibitors of mTOR and P(I)3K, and combination mTOR inhibition in conjunction with selective allosteric pan-Akt inhibitor MK-2206 targeting are currently being studied. Researchers should concentrate on developing combinatorial pharmacological therapy, which includes mTOR inhibitors and other medications, in order to combat TNBC.[87]

Targeting Nuclear Factor Kappa B (NF-κB)

A transcription factor implicated in inflammation, immunological regulation, and carcinogenesis in a number of malignancies is NF-κB. Proinflammatory and prooxidative stimuli cause IKKB kinase to become activated, which phosphorylates and breaks down IκB proteins.[88]

A different study looked into how lapatinib affected TNBC's NF-κB activation. EGRR and HER2 receptors are both inhibited by the tyrosine kinase drug lapatinib. The effects of proteasome inhibitors and lapatinib on TNBC were investigated. Chen and his colleagues used luciferase, RT-qPCR, immunoprecipitation, and immunoblotting tests to determine that lapatinib suppressed NF-κB activation in TNBC, independent of EGFR/HER2 inhibition. Other than lapatinib, no other EGFR inhibitors worked in concert with proteasome inhibitors. The antitumor action of proteasome inhibitors can be enhanced by treating TNBC with lapatinib, which increases oncogene addiction to NF-κB. These findings clearly imply that lapatinib and proteasome inhibitor combo therapy may be a good way to treat TNBC.[89]

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Targeting Autophagy

Autophagy is a biological process that results in the death of bodily cells. Numerous studies have connected TNBC problems to autophagy. Cancer stem cells (CSCs) in TNBC, an autophagy blocker efficiently targets them by preventing autophagy, mitochondrial structural damage, and a reduction in CSCs' ability to repair double-stranded DNA breaks. Both in a TNBC xenograft model and in vitro, CQ can efficiently inhibit the growth of TNBC cells. By significantly reducing the expression of DNA repair proteins in CSC populations, CQ, when combined with other medications, decreases the formation of tumors in carboplatin-resistant BRCA1 wild-type TNBC orthotopic xenografts.[90]

Therefore, the autophagy inhibitor CQ, which has anti-CSC properties, might be used as a therapy method for TNBC. It is important to remember that the FDA has not yet approved any targeted therapy for TNBC, and there is an urgent need for more dependable medication therapy to combat TNBC. Finding out how natural metabolites and natural metabolites boosted by nanotechnology can aid in the fight against TNBC is the goal of the most recent research (Figure 4).[91]

Immune System Interaction in TNBC

Immunotherapy has revolutionized the prognosis and treatment choices for aggressive cancers for which systemic medication was previously a limited option. Because TNBC has higher levels of immunogenicity than other subtypes of breast cancer, patients with this kind of disease have benefited the most from immunotherapy.[92]

In TNBC, tumors that are deemed "immune enriched" or "hot"—that is, with large levels of TILs—perform better than tumors that are "immunologically cold." It has been discovered that patients

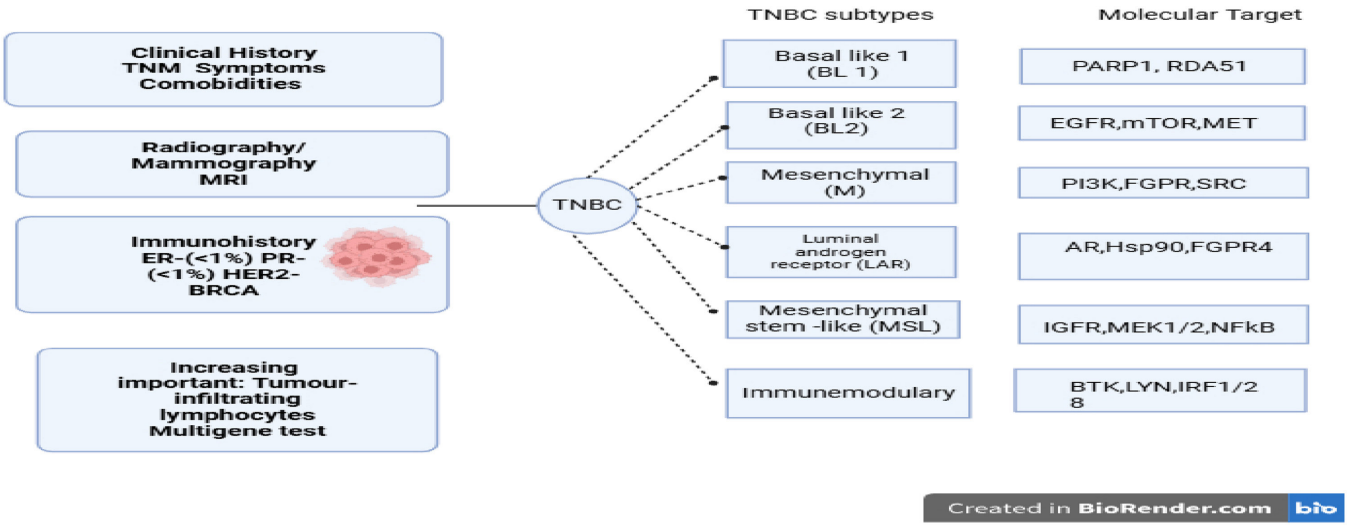

Fig 4 | Clinical subtypes with molecular target.

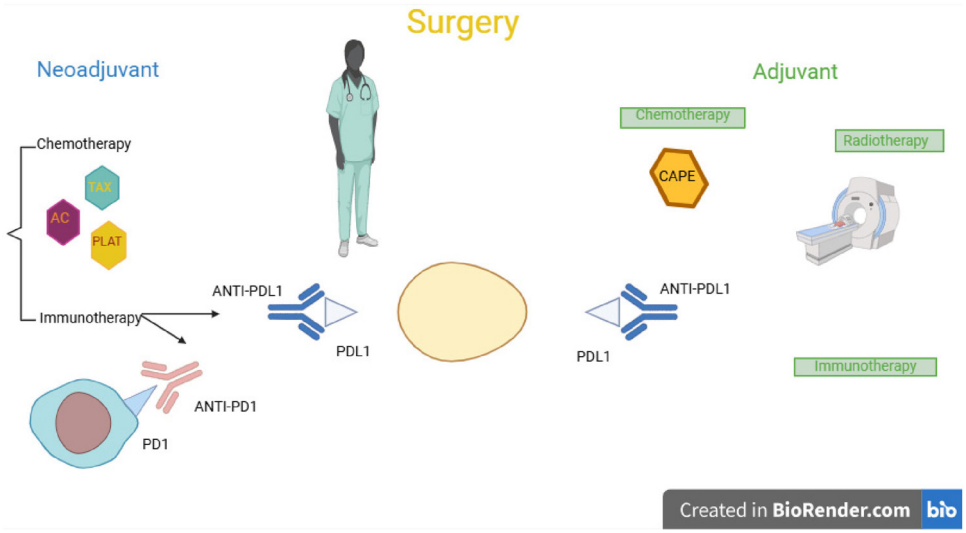

Fig 5 | Mechanism of treatment.

with "TIL-rich" TNBC have greater rates of pCR after NAST, improved survival even without systemic therapy, and improved survival with adjuvant chemotherapy. For this reason, TILs and other immune activation characteristics are interesting biomarkers for improving systemic treatment for TNBC. New multiplexing platforms are making it possible to perform in-depth and intricate investigations of the makeup of immune infiltrates and their interactions with tumor cells, going beyond straightforward TIL enumeration. When immunotherapy is used in the metastatic situation (as opposed to the operative setting), patients who exhibit the expression of programmed death ligand 1 (PD-L1) in the tumor microenvironment are identified in the clinic. This biomarker still has problems, though, because there are several assays, techniques, and cut-off points to distinguish between "positivity" and "negativity" (Figure 5).[93]

Novel Immunotherapy Agents for TNBC - It is critically necessary to develop novel therapeutic approaches to address TNBC patients' inadequate anticancer immunity, some of which are now in clinical development. Empegaldesleukin (NKTR-214), an agonist of the IL-2 pathway, is one such tactic that expands effector T cells more than regulatory T cells by preferentially activating the IL-2b receptor.

Another innovative treatment approach to improve anticancer immunity is the use of breast cancer vaccines, which prime and activate T cells and improve immunological identification of cancer cells by exposing them to breast cancer peptides. Several vaccine trials, including the PVX-410 vaccine, folate receptor α vaccine, and neoantigen vaccines, are presently enrolling patients with TNBC in the adjuvant or metastatic setting, both with and without PD-1/L1 inhibitors. Targeting the overexpressed XBP1 and CD138 peptides in TNBC, the PVX-410 vaccination works. In a similar vein, the folate receptor α vaccine, which targets a peptide, generated immunological responses in patients with breast and ovarian cancer that persisted for at least a year in the initial phase I trial, despite being overexpressed in breast cancer. Self-tolerance does not limit T-cell responses to these neoantigens because neoantigen vaccines target peptides that are absent from normal cells and originate from tumor-specific mutations unique to each patient's tumor, rather than peptides that are overexpressed in tumors but also shared by normal cells.[94]

Ongoing Trials

A balanced appraisal of the literature must acknowledge a substantial body of negative or inconclusive studies that temper enthusiasm for many emerging TNBC strategies. Several targeted agents and novel combinations have failed to show meaningful clinical benefit in randomized settings or have produced only modest, non-durable responses—often because of the profound molecular heterogeneity of TNBC, small or biomarker-unselected trial populations, and variable endpoint selection. Immunotherapy, for example, shows striking benefit in some early-stage and PD-L1-positive cohorts but has produced mixed or null results in other metastatic settings, highlighting issues with patient selection and assay inconsistency. Likewise, many promising preclinical signals (pathway inhibition, ADC payloads, or novel small molecules) have not translated into reproducible clinical efficacy, frequently due to differences between model systems and human tumors, inadequate dosing/tolerability, or emergence of rapid resistance. Methodological limitations—underpowered studies, short follow-up, heterogeneous outcome measures, and publication bias—also contribute to apparently conflicting findings. Finally, discrepancies in biomarker definitions and testing platforms (e.g., cutoffs for expression or mutation calls) have led to inconsistent subgroup effects across trials. Together, these negative or equivocal results underscore the need for larger, biomarker-driven, well-controlled trials; standardized assays; more realistic translational models; and transparent reporting so that genuinely effective strategies for defined TNBC subgroups can be identified and validated (Table 10).

Conclusion

In conclusion, TNBC is a difficult and complex disease entity that causes uncertainty and frustration for patients, physicians, and researchers. Several strategies have been tried to date to enhance the treatment of patients with TNBC, such as PARP inhibitors, targeted EGFR and VEGF inhibitors, and DNA-damaging agents like platinums. However, none of these strategies have proven to be as clinically effective as expected, and more focused treatments must be created and investigated. New treatment targets for TNBC include the Wnt/b-Catenin, NOTCH, and Hedgehog signaling pathways.

Clinical Recommendations and Research Priorities

Actionable Guidance for Clinicians:

- **First-line therapy for early-stage TNBC:**
  - |Neoadjuvant: Pembrolizumab + chemotherapy (KEYNOTE-522; pCR 64.8%) followed by adjuvant pembrolizumab if residual disease.
  - Adjuvant: Consider capecitabine for non-pCR patients (CREATE-X trial).
- **Metastatic TNBC:**
  - PD-L1+: Pembrolizumab + chemotherapy (KEYNOTE-355; OS 23.0 vs. 16.1 months).
  - PD-L1–/BRCAwt: Sacituzumab govitecan (ASCENT; mOS 12.1 vs. 6.7 months).
  - BRCAm: Olaparib or talazoparib (OlympiAD/EMBRACA; PFS benefit).

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Table 10 | Ongoing Clinical Trials.

Trial (Phase)	Population/Setting	Intervention vs. Control	Primary Endpoints	Key Results (Headline)	Regulatory/Guideline Impact
KEYNOTE-522 (Phase III)	Newly diagnosed, high-risk early-stage TNBC (stage II–III), neoadjuvant setting.	Pembrolizumab + standard neoadjuvant chemo ⇢ adjuvant pembrolizumab vs. placebo + chemo ⇢ placebo.	Dual primary: pCR and EFS; OS secondary.	Increased pCR and improved EFS; long-term follow-up shows OS benefit in final analyses. PubMed+1	Pembrolizumab + neoadjuvant chemo (with adjuvant pembrolizumab) is incorporated into major guidelines for high-risk early TNBC. ESMO
ASCENT (Phase III)	Heavily pretreated metastatic TNBC (≥2 prior systemic therapies, no active brain mets for primary analysis).	Sacituzumab govitecan vs. physician-choice single-agent chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine).	Primary: PFS (BICR) in patients without brain metastases; secondary: OS, ORR, safety.	Statistically significant and clinically meaningful improvement in PFS and OS; higher ORR with sacituzumab govitecan (e.g., median PFS and OS advantages reported). New England Journal of MedicineASC Publications	Established sacituzumab govitecan (Trodelvy) as a standard option in pretreated mTNBC; included in guideline recommendations and approvals. PubMed
DESTINY-Breast04 (Phase III)	HER2-low (IHC 1+ or IHC 2+/ISH–) unresectable/metastatic breast cancer — both HR+ and HR– cohorts; 1–2 prior lines for metastatic disease.	Trastuzumab deruxtecan (T-DXd) vs. physician's choice chemo.	Primary: PFS (HR+ cohort, BICR); secondary: OS, PFS (overall), ORR, safety.	T-DXd produced substantially longer PFS and OS vs. chemo in HER2-low patients; high ORR across subgroups. New England Journal of MedicinePubMed	Practice-changing evidence — redefined HER2-low as a therapeutic category; T-DXd is recommended for HER2-low metastatic disease in guidelines/labels. UCLA Health
TROPiCS-02 (Phase III)	Heavily pretreated HR+/HER2– metastatic breast cancer (prior endocrine therapy + CDK4/6 inhibitors and 2–4 prior chemotherapies).	Sacituzumab govitecan vs. physician's choice chemotherapy.	Primary: PFS (BICR); key secondary: OS, ORR, safety.	Demonstrated significant PFS and OS benefit vs. chemotherapy in a pretreated HR+/HER2– population. The LancetPubMed	Supported regulatory approval and guideline inclusion of sacituzumab govitecan beyond TNBC (expanded indication to pretreated HR+/HER2– mBC). ASC Publications
CAPItello-291 (Phase III)	HR+/HER2– advanced/metastatic breast cancer after progression on/after aromatase inhibitor therapy (with/without prior CDK4/6 inhibitors); included patients with PIK3CA/AKT1/PTEN alterations.	Capivasertib (oral AKT inhibitor) + fulvestrant vs. placebo + fulvestrant.	Co-primary (typical): PFS in overall population and/or in biomarker-altered su		

- **Molecular profiling:**
  - Subtype classification (e.g., LAR, basal-like) to guide experimental therapies (e.g., AR antagonists for LAR).
- **Monitoring:**
  - Prioritize brain imaging due to high CNS metastasis risk.

Research Gaps and Future Priorities:

- **Biomarkers**:
  - Validate predictive biomarkers for immunotherapy (e.g., TILs, novel immune signatures) and PARP inhibitors beyond BRCA.
- **Novel targets:**
  - Explore ADCs (e.g., datopotamab deruxtecan in TROPICS-02), AKT inhibitors (CAPItello-291), and combinatorial strategies (e.g., PARPi + immunotherapy).
- **Tumor microenvironment:**
  - Mechanisms to overcome "cold" tumor resistance (e.g., STING agonists, vaccines).

Equity:

- Address disparities in TNBC outcomes linked to ancestry/socioeconomic status (e.g., BRCA testing access).

Limitations and Negative Data

While progress in the management of TNBC has been encouraging, it is important to recognize the limitations of current evidence and the negative outcomes of several pivotal studies. Not all clinical trials have translated into meaningful survival benefits, underscoring the challenges of treating this heterogeneous disease (Table 11).

Table 11 | Negative or Inconclusive TNBC Clinical Trials.

Trial	Intervention	Population	Outcome	Key Limitation
IMpassion131	Atezolizumab + paclitaxel	Advanced TNBC, PD-L1+	No improvement in PFS/OS compared to chemotherapy	Possible steroid-IO interaction; inconsistent results with paclitaxel backbone
IMpassion130 (subgroup)	Atezolizumab + nab-paclitaxel (PD-L1−negative)	Advanced TNBC, PD-L1−	No survival benefit in PD-L1−negative patients	PD-L1 biomarker not universally predictive
OlympiAD (non-BRCA subgroup)	Olaparib	Metastatic TNBC, BRCA wild-type	No significant efficacy outside BRCA-mutated patients	Activity restricted to germline BRCA mutations
EMBRACA (non-BRCA subgroup)	Talazoparib	Metastatic TNBC, BRCA wild-type	Limited efficacy; resistance emerged	Resistance limits durability; not broadly applicable
LOTUS	Ipatasertib + paclitaxel	Advanced TNBC (unselected for PI3K/AKT mutations)	Mixed results, no consistent survival advantage	Biomarker selection issues; toxicity concerns
Anti-androgen trials (enzalutamide, bicalutamide)	Androgen receptor antagonists	LAR subtype TNBC	Modest response rates, no OS benefit	Small studies; lack of biomarker validation
ADC studies beyond sacituzumab govitecan	Datopotamab deruxtecan, trastuzumab deruxtecan (early-phase)	Heavily pretreated TNBC	Uncertain benefit; limited long-term survival data	Toxicity (neutropenia, diarrhea); early-phase only

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