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Review Article

Prognostic Biomarkers For Triple-Negative Breast Cancer: A Narrative Review

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ABSTRACT

Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer linked with a grim prognosis and restricted treatment options. The necessity for confirmed prognostic and predictive biomarkers remains crucial to steer treatment choices and prognostic assessments. This article delves into both established and evolving prognostic and predictive biomarkers of TNBC, coupled with emerging and authorized therapeutic approaches. The spectrum of biomarkers assessed encompasses epidermal growth factor receptor (EGFR), vascular endothelial growth factors (VEGF), fibroblast growth factor receptor (FGFR), human epidermal growth factor receptor 2 (HER2), androgen receptor, oxidative stress/redox signaling, microRNAs, TP53 mutation, breast cancer susceptibility gene 1 or 2 (BRCA1/2) mutation/homologous recombination deficiency (HRD), NTRK gene fusion, PI3K/AKT/mTOR pathway, immune-related biomarkers (such as programmed death-ligand 1 (PDL1), tumor-infiltrating lymphocytes (TILs), tumor mutational burden (TMB), neoantigens, flaws in DNA mismatch repair proteins (dMMR)/microsatellite instability-high (MSI-H)). Additionally, the study scrutinizes novel targets of antibody–drug conjugates and residual disease. The integration of biomarker-guided strategies in TNBC management is witnessing growth, consequently broadening the horizons of available options for individuals afflicted by this specific breast cancer subtype. Research endeavors persist in their pursuit of identifying supplementary biomarkers and pinpointing targeted treatment avenues, all in the overarching aim of enhancing clinical outcomes and

INTRODUCTION

Triple-negative breast cancer (TNBC) constitutes approximately 15% of invasive breast cancer cases

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and is characterized by the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) expression. It is more common in premenopausal women, African Americans, and those with harmful mutations in breast cancer susceptibility genes 1 or 2 (BRCA1/2). TNBC carries a poorer prognosis than other breast cancer types, with patients experiencing a more aggressive disease course, including advanced stage diagnosis, early recurrence with metastasis, and reduced overall survival. Patients with triple-negative breast cancer (TNBC) exhibit varied clinical outcomes, including different rates of pathologic complete response (PCR) following neoadjuvant chemotherapy in early-stage disease. Additionally, their responses to therapy and subsequent survival outcomes in the metastatic setting also differ.

Genetic tumor heterogeneity is a major cause of this phenomenon .This review discusses TNBC tumor formation, prognosis and predictive biomarker.

PROTEIN EXPRESSION BIOMARKERS:

1. **Epidermal Growth Factor Receptor (EGFR):**

The epidermal growth factor receptor (EGFR) is the receptor tyrosine kinase that belongs to the ErbB family and is involved in angiogenesis and inhibition of apoptosis.1 The expression of epidermal growth factor receptor (EGFR) is higher in TNBC cases compared to controls and non-TNBC. This makes EGFR a useful biomarker and a therapeutic target.2, 3 High EGFR expressions is linked to lower overall survival (OS) and disease-free survival (DFS) in early breast cancer among women. Specifically, patients with both triple negative breast cancer and elevated EGFR levels experience worse OS and DFS compared to those with triple negative tumors and normal EGFR expression.4

2. **Vascular Endothelial Growth Factor Receptor (VGFR):**

Around 30-60% of triple-negative breast cancer (TNBC) cases express vascular endothelial growth factors (VEGFs), which promote the growth of blood vessels, a process called angiogenesis.5,6 In a study, TNBC patients with higher intra-tumoral VEGF had worse recurrence-free survival and overall survival (OS) compared to non-TNBC patients. 15To address this, Bevacizumab, a monoclonal antibody targeting VEGF-A, was investigated for TNBC treatment.7 When used before surgery (neoadjuvant), Bevacizumab increased the rate of complete pathologic response (pCR), but it didn't improve disease-free survival (DFS) or OS when used after surgery (adjuvant).In metastatic breast cancer, studies showed that Bevacizumab improved progression-free survival (PFS) but had no impact on OS.8

3. **Fibroblast Growth Factor Receptors (FGFR):**

Fibroblast growth factor receptors (FGFR) are a group of cell surface receptors that play a crucial role in regulating various cellular functions, such as cell growth, differentiation, and the development of blood vessels (angiogenesis). Abnormal FGFR signaling can contribute to the development of cancer through gene alterations like mutations, fusions, rearrangements, and amplifications. In breast cancer (BC), FGFR1 amplification is the most common anomaly linked to tumor formation.9 For triple-negative breast cancer (TNBC), approximately 18% of cases have FGFR1 over-expression, and around 33% exhibit FGFR1 gene amplification.10 FGFR2 amplification is less frequent in TNBC, occurring in less than 5% of cases. While FGFR1 amplification in hormone receptor-positive BC is consistently associated with a poorer prognosis, its role in TNBC is still debated, with some studies suggesting no impact on prognosis and others indicating a worse overall survival (OS).11 FGFR2 expression has been linked to a lower OS.12 Inhibition of FGFR signaling is a promising

therapeutic approach, primarily using small-molecule tyrosine kinase inhibitors (TKIs). Clinical trials have shown positive results with multi-targeted TKIs and FGFR-selective TKIs.13 Additionally, there is preclinical evidence suggesting the potential effectiveness of antibodies targeting FGFR isoforms and inhibitors of fibroblast growth factor ligands, with promising results in early-phase clinical trials for solid tumors, including breast cancer.14

4. Human Epidermal Growth Factor Receptor 2 (HER2):

HER2 breast cancer subtype is seen by HER2 gene amplification15 and results in over expression of HER 2 protein.2 Low HER 2 as a predictive marker is yet unclear.17 The mechanisms behind HER2 protein expression in gene-nonamplified BC cells involve NF-kB pathway activation via chemo or radiotherapy and changes in epigenetics.16 Anti - HER 2 therapy with trastuzumab showed good response.18The antibody - drug conjugates (ADC) such as Trastuzumab deruxtecan (DS-8201a) showed positive results in phrase 1 (NCT02564900) of HER 2 low breast cancer and is now moved to the phase 3 setting.19 HER2 gene mutations, occurring in 2% of BCs, are found in HER2-low tumors and may respond to anti-HER2 tyrosine kinase inhibitors (TKIs). Other TKIs, such as poziotinib and pyrotinib, are also under investigation. These emerging treatments hold potential to expand options for HER2-low TNBC patients.20

5. Androgen Receptor:

The androgen receptor (AR) belongs to the steroid receptor family and acts as a nuclear transcription factor. Normally located in the cytoplasm, it awaits binding to a ligand. When a ligand binds, the AR moves to the cell nucleus, where it connects with androgen-related elements, promoting cell growth.21 While AR signaling is more common in hormone receptor-positive breast cancer (BC), it's found in about 30-35% of triple-negative breast cancer (TNBC) cases.22 AR positivity is linked to the LAR subtype, low tumor grade, lower risk of lymph node involvement, and older age at diagnosis. AR-positive TNBC tends to have a lower Ki-67 index than AR-negative TNBC, suggesting potential resistance to chemotherapy.23 Several meta-analyses have shown that AR expression is associated with improved disease-free survival (DFS) in TNBC, but its impact on overall survival (OS) is less clear.24 There have been multiple studies exploring anti-androgen medications for locally advanced or metastatic BC. Phase II studies using nonsteroidal AR inhibitors like Bicalutamide and Enzalutamide have shown a clinical benefit in around 20-25% of cases. Ongoing clinical trials (NCT 03090165, NCT 02457910) are assessing the use of AR blockade in combination with various targeted therapies, including CDK4/6 inhibitors and PI3K inhibitors in the metastatic setting.25

6. Notch Signaling Pathway:

The NOTCH signaling pathway is an example of short-range-cell-cell communication and may be a reliable and convenient biomarker in TNBC because these pathways are abnormally activated in TNBC and has evolved to act in the pathogenesis and tumour progression of TNBC.26 The over expression of the NOTCH receptor is strongly associated with breast cancer cell growth , migration ,invasion ,metastasis , chemoresistance and its aberrant activation is related with poor prognosis and relapse.1 There is a evidence that NOTCH pathway is a significant member in the mammary stem cells maintenance and expansion. The NOTCH pathway comprises of four receptors (NOTCH-1 , NOTCH-2 , NOTCH-3 , NOTCH-4) which interacts with five ligands namely Delta-like 1, Delta-like 3, Delta-like4 , Jagged-1 and Jagged-2. Gain of NOTCH function can be only seen in merely 10% of TNBC

.Studies have shown an association between NOTCH-1 , positive-lymph node status , jagged-1 and larger tumour size. There is an elevated expression of NOTCH-1,NOTCH-4 or Jagged -1 which may be considered as a poor prognostic factor with decreased survival rates.26,1 NOTCH inhibitors have been emerged to target the pathway including AL 101 (A pan -NOTCH gamma secretase inhibitor) .The NOTCH receptor which has been specially involved in various TNBC subtypes might be useful in future to select patients who are more likely to respond to different targeted treatments which reduces the therapeutic complications related with NOTCH inhibitors.26 The specific inhibition of single NOTCH receptor or ligand might promote upcoming clinical trials that aims to analyze more selective and less toxic alternatives for NOTCH inhibition in the therapies of TNBC- bearing patients.26

NOTCH RECEPTORS	MECHANISMS	TREATMENT	STUDIES
NOTCH 1	Tumor growth, Mitochondrial metabolism ,Regulation of cancer stem cells ,Chemoresistance, Invasion and metastasis	Monoclonal antibodies Monoclonal antibodies(+ chemotherapeutic drugs) Gamma secretase inhibitors + Chemotherapeutic drugs	Preclinical Preclinical Preclinical and clinical
NOTCH 2	Tumor growth, Regulation of cancer stem cells , Invasion and metastasis	Monoclonal antibodies	Preclinical
NOTCH 3	Tumor growth, Angiogenesis, Chemoresistance, Invasion and metastasis	Monoclonal antibodies	Preclinical and clinical
NOTCH 4	Regulation of cancer stem cells , Invasion and metastasis	Monoclonal antibodies and Gamma -secretase inhibitors	Preclinical

7. Oxidative Stress/ Redox Signaling

Oxidative stress related genes has close association with the prognosis of TNBC patients.1 Oxidative stress is defined as the imbalance of oxidation and antioxidant systems in the body which results in the excess production of peroxides and free radicals leading to the development of different disease and tumours through protein , lipids and DNA cells damage.28 It can also leads to signaling pathway disruption comprised of cell proliferation , apoptosis and angiogenesis which encourages the uncontrolled cell growth and causes tumour development and begins the process carcinogenesis.27,28 Reactive oxygen species (ROS) are a family of small free radicals and non-radicals derived from oxygen that are produced by the mitochondrial respiratory chain continuously in the body.27 ROS are produced in response to physical agents and chemotherapy and radiation therapy causing cell death.28 The action of ROS is like a double- edged sword , at lower levels ROS increases proliferation of cells and at higher levels it leads to apoptosis.28 Increased ROS induced cell death has been reported in cancer cells due to chemo and radiation therapies indicating the role of ROS modulation in anticancer combination treatments.27,28 In the mitochondrial respiratory chain, ROS mediated OS can damage

mitochondrial DNA and enhances the occurrence of new mutations and its accumulation leads to increased incidence of breast cancer.28 Adequate amounts of ROS are important for the appropriate functioning of cells and their survival . Electrochemotherapy is the combination of electroporation and drug .ECT can create a temporary permeability by using EP to enhance the drug to target cancer cells effectively against TNBC. Commonly we can suggest that there are no substantial difference in viability or ROS levels when TNBC cells were treated with either Resveratrol (an active bio compound found in natural fruits) or electroporation alone ,It indicates the futuristic clinical application of this novel combination.28

RNA EXPRESSION BIOMARKERS:

1. Micro RNAs:

MicroRNAs are circulating short noncoding endogenous RNA molecules with 17-27 nucleotides that are located on the introns of protein coding genes which controls the expression of gene and plays a important role in cancer pathways by the regulation of oncogenes and tumour suppressor genes.1,29 The abnormal expression of miRNAs in TNBC promotes formation of tumour cells, its proliferation ,invasion and metastasis by targeting specific genes that regulate the cell cycle and suppressing tumour call apoptosis including other mechanisms.30 Unique miRNAs are corelated with the prognosis in TNBC. miR-21 is one of the most significant oncomiRNAs associated with cell migration and invasion of breast cancer cells, hence it may contribute to progression of tumour and metastasis.29 Due to the instability of miRNA s have been investigated as potential predictive biomarkers in non-invasive samples like blood,serum and urine.29,30 We can suggest that reduced miR-155 expression predicts poor overall survival whereas increased miR-21,miR-27a/b, miR-210 and miR-454 levels are associated with shorter OS .Altered miR-374a/b and miR-454 levels associated with shorter disease -free survival rates.31,32 Some miRNA s indicates chemoresistance such as elevated miR-181a in nonresponsive TNBC patients . Regulation of cancer process are also done by long non coding RNA s (lncRNAs) or transcripts longer than 200 nucleotides . The miR-200 family appears to be one of the most versatile players in TNBC biology ;it was priorly defined as up-modulated in breast cancer where its over expression was associated with lymph node positivity and metastasis.1,29 But , currently it was found that miR-200 has shown to be down-regulated in metaplastic carcinoma ,one of the most mesenchymal and undifferentiated breast cancers characterized by TNBC phenotype. Functional in vitro studies illustrates that the miR-200 family as a tumour suppressor in TNBC in cocominant with very low expression levels in the basal B breast cancer cell lines . A study on basal -like TNBC cases are treated with neoadjuvant therapy revealed that miRNA changes posttreatment paving way to the potential predictive roles.1 In this current situation, microRNA s might show not only an additional level of complexity in the molecular illustration of TNBC but also the contribution to the tumour classification and subclassification .More importantly they may represent easily detectable biomarkers for the prediction of prognosis and response to the treatment strategies .The application of miRNA s in therapy as adjuvant tools of targets seems leave a promising signature in clinical outcomes.30,31

DNA EXPRESSION BIOMARKERS:

1. TP53 Mutations:

The protein product, p53 transcription factor protein of TP53 gene is critical for homeostasis maintenance and genomic integrity during DNA repair and apoptosis. TP53 gene is the most commonly mutated gene in breast cancer which is present in approximately all TNBC cases.35 When

DNA damage hits p53 transcription takes the helm for cell cycle arrest and repair .TP53 mutations are dominant force in breast cancer with a staggering 80% mutation rate in TNBC.33,34 TP53 mutations greatly affects the genetic instability and cause numerous cytogenetic alterations resulting in a higher likelihood of loss of heterozygosity. Basal - like breast cancer over expresses EGFR and have p53 mutations.34 Mutant p53 acquires oncogenic functions and binds to a protein p63 which has tumour suppressor activities . There will be a upregulation of endosomal recycling EGFR and integrin to the membrane with elevated proinvasive abilities of cancer cells in the absence of functional p63.34 Blocking endosomal trafficking in combination with anti – EGFR treatments may result in better clinical outcomes in TNBC.33,34 The widespread presence of TP53 mutations in TNBC makes it more reliable therapeutic target and marker for chemotherapy sensitivity prediction. Mutational diversity suggests that not all TP53 mutations are equal and that alterations to specific protein domains will have varying effects on the oncogenic activity including chemotherapeutic drug resistance 33,34 Moreover breast cancer with TP53 mutations is most likely to be aggressive and resistant to chemotherapy and radiotherapy .Recent studies showed that tumours expressing p53 mutation may be eradicated by multiple strategies like disrupting the p53 and p63 interaction ,restoring the mutant p53 , blocking interaction between the EGFR and colony stimulating factor 1 receptor or by decreasing the addiction of basal like breast cancer cells with p53 mutations.34,35,36

2. BRCA ½ Germline Mutation And Homologous Recombination Deficiency (HRD):

BRCA ½ encodes for tumour suppressor proteins involved in DNA repair through homologous recombination and therefore plays an pivotal role in genetic integrity and DNA stability. Patients who have tumours with homologous recombination deficiency may be benefited from platinum compounds ,poly (ADP ‘ -ribose)polymerase (PARP) inhibitors as single treatment and vice versa for patients with gBRCA ½ mutations.39,40 HRD is more likely to be occurred in tumours with BRCA1/2 mutations. Telli et al . ‘s studies highlights HRD score predictive value in early TNBC and platinum containing therapy response contrasting with TNT trials metastatic setting outcome.35 The term HRD is a vast section that consists of various mechanisms contributing to a BRCA ness phenotype. This includes genetic inactivation of HR pathway at the germline or somatic level including PALB2 , BARD1, BRIP1 ,RAD51B/1C/1D , ATM or mutations in non HR gene mutations such as; MSH6 and PTEN or epigenetic hypermethylation of BRCA1 (15,16) .BRCA ½ gene mutation is present in approximately 10-20 % of TNBC.35 The HRD scores are predictive values in early TNBC and platinum containing therapy response contrasting with the TNT trial’s metastatic setting outcome.35,36 The improvement of overall survival in gBRCA TNBC might caused by better sensitivity of gBRCA carriers to chemotherapeutic therapy as a result of HRD deficiency or higher immune activations resulting in better survival rate.36,42 Exploring the potential of immunotherapy combined with PARP inhibitors had illustrated the enhanced immunogenicity due to DNA repair deficiency and appeared to be more reliable method for TNBC patient treatment with BRCA1/2 mutations.41

3. NTRK GENE Fusion:

The neurotrophic tyrosine receptor kinase (NTRK) gene fusions are developing predictive biomarkers of various types of cancer which was approved by Food And Drug Administration (FDA) ,USA for the patient selection to targeted therapies and specific treatments for TRK fusion-

positive tumours in a tumour agnostic patterns.43 NTRK fusions are rare genomic occurrences in breast cancer as a whole predominantly in secretory breast cancer subtype.44 Physiologically ,NTRK1 , NTRK2 , NTRK3 genes can encode for a family of receptor tyrosine kinases (TRK) and tropomyosin receptor kinases like TRKA,TRKB , TRKC that has a significant role in neuronal development ,functions ,survival and proliferation.43,44 NTRK genes could be also affected by amplification in different cancer types and these amplified tumours are suitable for treatment specific inhibitors.45 The impact of TRK fusion events can fuel uncontrolled cancer cell growth through over expression and constitutive activations.44 The NTRK fusions are usually detected by immune histochemistry (IHC) , fluorescence in situ hybridization (FISH) , real – time -polymerase chain reaction (RT-PCR) and RNA next -generation sequencing (NGS).43 Aberrant fusion of NTRK3' kinase domain with the other genes can lead to ligand -independent activation of the NTRK gene and consecutively cause an elevated proliferation and alleviated apoptosis of the cancer tumour cells.43,44 Till date only 2 drugs; Entrectinib and Larotrectinib (LOXO -101 trial); has been approved by FDA which has shown great efficacy and a overall response of 71% for the management of TRK fusion -positive tumours and for all solid tumours inspite of tissue of origin based on genomic alteration.43,45 Secretory breast cancer patients having increased incidence of NTRK fusion gene have showed an excellent clinical response to the targeted drugs in clinicaltrials . NTRK gene fusion may be rare event in TNBC.44 The high false positive rate of NTRK gene fusion detected by IHC its role as pre screening method in TNBC. More data must be available to confirm whether TRK – targeted therapies are appropriate for the TNBC patient treatment.43, 45

4. P13K/ AKT / mTOR:

Phosphoinositide 3-kinase (PI3K) signaling plays a central role in cellular physiology, regulating critical processes, It is one of the most frequently altered pathways in human malignancies, making it an attractive target for cancer therapy.46 The PI3K/AKT/mTOR complex is a signaling pathway that plays a major role in essential cellular activities, such as cell metabolism, growth, proliferation, apoptosis, and angiogenesis.The pathway are activated by an extracellular ligands, such as insulin or insulin-like growth factor, which bind to cell-membrane receptor.47 PI3K/AKT signaling pathway is a central regulator of tissue and metabolic homeostasis, PI3K/AKT signaling pathway is a complex and essential regulator of many cellular processes, including metabolism, growth, and survival.48 The activation of PI3K signaling in cancer cells can be targeted with drugs, which is an area of active research. Some of these drugs are already in clinical trials, and others are in preclinical development.49

IMMUNOTHERAPY BIOMARKERS:

1. PDL1 And TILS:

Programmed cell death protein 1 (PD1) is a immune check point receptor that limits T cell effector function within tissues. PD-1 has two known ligands, PD-L1 andPD-L2, and it helps in regulating both tumor cell-intrinsic (e.g PTENloss, PIK3CAmutations) and tumor cell-extrinsic (e.g IFNγ) factors[1]. The PTEN/PI3K pathway is important in breast cancer, and its activation is associated with PDL1 expression and basal-liketumors.50 Tumor-infiltrating lymphocytes (TILs) are a type of T cell that has infiltrated a tumor. They are thought to be enriched for tumor-reactive T cells, and adoptive transfer of TILs has been shown to be effective in the treatment of metastatic melanoma.51

TILtherapyisapromisingapproachforthetreatmento fmetastaticmelanoma.52 TILS one are the most abundant in triple-negative breast cancer (TNBC) and are associated with a better prognosis. TILs

are also found in HER2-positive and hormone receptor-positive breast cancer, but their role in these subtypes is less clear. Tumors with high TILs may also have increased PD-L1 expression, which may explain why TNBC responds better to immune checkpoint inhibitor therapy.53

2. Tumour Mutation Burden And MSI-H/ dMMR:

TMB are total number of mutations present in a tumor specimen. TMB can be calculated using whole exome sequencing (WES) or next-generation sequencing (NGS) panels. There is currently no consensus on the definition of TMB cut offs for patient stratification. TMB is a promising biomarker for predicting response to immune check point inhibitors (ICIs).54 Tumors that are MSI-H/dMMR, high TMB values tend to be observed in adult solid tumors that are associated with environmental exposures such as smoking in lung and bladder cancer and ultraviolet light exposure in melanoma.55(MSI) and (dMMR) are important biomarkers for predicting responses to immune checkpoint inhibitor therapies.57 MSI is a type of genetic mutation that can occur in cancer cells[3].dMMR is a term used to describe a defect in the MMR system.56 MSI-H/dMMR endometrial cancers have similar tumor immune microenvironments, regardless of whether MSI-H was identified by NGS or IHC. It means that both methods are equally good at predicting the tumor immune microenvironment and identifying patients with MSI-H/dMMR endometrial cancer who are likely to benefit from ICI therapy.57

3. Neo Antigen And Vaccines:

Highly personalized cancer vaccines that target tumor-specific antigens called neo antigens. Bioinformatics technology is used to identify and predict the immunogenicity of neoantigens.58

One approach to cancer immunotherapy is tumour neo antigens, which are antigens produced by tumour viruses or mutant proteins. Neo antigens are a promising new approach to cancer immunotherapy that is currently being evaluated in clinical trials.59 Cancer vaccines are an attractive option for treatment. 60 Breast cancer vaccines are being developed to boost immunity against the disease. The type of immune response needed for tumour eradication (Type I T-cell immunity) and the patient populations most likely to benefit from vaccination. Therapeutic breast cancer vaccines are now being tested in combination with other forms of immune therapy or chemotherapy and radiation.61

ANTIBODY – DRUG CONJUGATES (ADCS) BIOMARKERS:

The antibody-drug conjugates (ADCs) are drugs that use monoclonal antibodies to target specific antigens on cancer cells, delivering potent cytotoxic drugs with remarkable precision. By this way can leads to reduced toxicity to Normal tissue, increase therapeutic effect and improving PK and PD properties. ADCs represent a promising frontier in cancer treatment.64 The use of antibody-drug conjugates (ADCs) such as Sacituzumab povitica (SG), adecatumumab vedotin (LV), was showing good results in the treatment of metastatic triple negative breast cancer (mTNBC).62 At the starting it is used for HER2+ breast cancer then they have expanded to include triple-negative and hormone receptor-positive breast cancer.65 ADCs has three key components: a monoclonal antibody (MAb) targeting a specific tumour antigen, a cytotoxic payload, and a chemical linker connecting them.66 The ADC mechanism of action , the antibody binds to the tumour antigen on the cell surface, the ADC is internalized into the cell, the linker is cleaved, releasing the cytotoxic payload into the cytoplasm, the cytotoxic payload kills the tumour cell.66 Resistance, particularly in trastuzumab emtansine. Four different ways of resistance: due to antibodies, drug transport, lysosomal function. To overcome the resistance, different strategies and combination therapies. Identifying predictive

biomarkers can aid in selecting the best therapy and preventing resistance.63

RESIDUAL CANCER BURDEN (RCB):

The Residual Cancer Burden (RCB) is the cancer presence after neoadjuvant chemotherapy (NACT).67 The Residual Cancer Burden Score is the standard measurement method described in 2007 and used to evaluate the RCB even after the NACT focused on breast cancer.67, 68 Compared to other subtypes of breast cancer, around 33% of patients with TNBC receiving neoadjuvant chemotherapy are more inclined to achieve a pathological complete response (pCR).69 The absence of any remaining invasive disease in the breast and axilla, known as a pathological complete response (pCR).68 Patients who achieve a pCR have a higher rate of survival when compared with those with residual cancer burden and it is the surrogate endpoint for long-term clinical benefits.70, 71 In the case of TNBC, RCB holds significant prognostic value, with 5-year relapse-free survival rates approximately at 94% for RCB-0 (indicating pathologic complete response or pCR), 89% for RCB-I, 62% for RCB-II, and 26% for RCB-III patients.72 A higher RCB score is markedly connected to poorer event-free survival.68 It effectively pinpoints patients, particularly those with TNBC or HER2-positive BC at a high risk of recurrence (specifically RCB-III), who should be considered for secondary adjuvant therapies.73 Monitoring of minimal residual disease (MRD) in blood during the follow-up stage can provide suitable secondary systemic adjuvant treatment for individuals experiencing molecular relapse.74 It is necessary to compare pre and post treatment biopsy for understanding the genomic changes that cause resistance to improve the therapy.1

CONCLUSION

Significant strides have been made in understanding TNBC biology, recognizing its distinct molecular subgroups driven by specific pathways. This has led to the identification of promising prognostic and predictive biomarkers. Immunotherapy approval for PDL1-positive metastatic TNBC and PARP inhibitors for BRCA-positive metastatic TNBC offer personalized options. Nevertheless, chemotherapy remains fundamental. The need for modern NGS-based biomarkers is essential to further enhance TNBC outcomes. Promising biomarkers include FGFR, HER2, the PI3K/AKT/mTOR pathway, AR receptors, and ADC therapies

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ABBREVIATION

ADC	Antibody -Drug Conjugates
AKT	Ak Strain Transforming
APR-246	Eprenetapopt
AR	Androgen Receptor
ATR	Ataxia Telangiectasia and Rad3-Related Protein
bard 1	BRCA1 Associated Ring Domain 1
BC	Breast Cancer
BRCA1/2	Breast Cancer Gene 1/2
CDK4/6	Cyclin -Dependent Kinase 4 and 6
CfDNA	Cell- Free DNA
COTI-2	Third Generation Thiosemicarbazone
CtDNA	Circulating Tumor DNA
CTC	Circulating Tumor Cells
DFS	Disease- Free Survival

dMMR	DNA Mismatch Repair
DNA	Deoxyribonucleic Acid
EGFR	Epidermal Growth Factor Receptor
ErbB	Erythroblastic Oncogene B
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
HDR	High Dynamic Range
HER 2	Human Epidermal Growth Factor Receptor 2
HRD	Homologous Recombination Deficiency
HR	Hormone Receptor
HULC	Highly Up- Regulated in Liver Cells
IHC	Immunohistochemistry
ISH	In -situ Hybridization
LAR	Luminal Androgen Receptor
IncRNAs	Long non-Coding RNAs
Loxo-101	Larotrectinib
MALAT 1	Metastasis- Associated Lung Adenocarcinoma Transcript 1
miRNAs	MicroRNAs
MSI-H	Microsatellite Instability -High
mTOR	Mammalian Target of Rapamycin
NA	Neoantigens
NACT	Neo Adjuvant Chemotherapy
NCT	The National Clinical Trial Number
NF-kB	Nuclear Factor Kappa Light Chain Enhancer of Activated B cells
NGS	Next Generation Sequencing
NTRK gene	Neurotrophic Tyrosine Receptor Kinase
OS	Overall Survival
Parp inhibitors	Poly -ADP Ribose Polymerase
Palb 2	Partner and Localizer of BRCA2
PCR	Pathologic Complete Response
PD 1	Programmed Cell Death Protein 1
PDL1/2	Programmed Death - Ligand 1/2
PFS	Progression – Free Survival
PJ11007	2- Sulfonypyrimidine (mild thiol alkylator)
PIK3CA Alpha	Phosphatidylinositol -4-5-bisphosphate 3- Kinase Catalytic subunit
P13k/AKT	Phosphoinositide -3-Kinase -Protein Kinase B
PRIMA-1	Proline -Rich membrane Anchor 1
PTEN	Phosphatase and Tensin Homolog
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
T cells	T lymphocytes
TILs	Tumour- Infiltrating Lymphocytes
TKIs	Tyrosine Kinase Inhibitors
TMB	Tumour Mutational Burden
TNBS	Triple- Negative Breast Cancer
TNT trials	Total Neoadjuvant Therapy
TP53	Tumour Protein 53
TRK	Tropomyosin Receptor Kinase
VEGF	Vascular Endothelial Growth Factor

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