Systematic Review Article

Recent Advancements in Targeted Breast Cancer Treatments: A Review of Clinical Trials

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ABSTRACT

Despite developing standard treatments, breast cancer remains a global challenge due to its high recurrence rates and treatment-resistant tumors, emphasizing a need for more targeted treatment strategies. Standard treatments such as chemotherapy, radiation therapy, and surgery are nonspecific and significantly reduce patient quality of life. This review presents recent clinical trial findings on both single-line and combination targeted therapies, focusing on their efficacy, safety, and how biomarkers help optimize patient outcomes. The four main results of this paper indicate: PARP and PD-L1 inhibitors significantly benefit certain subgroups, an antibody drug-conjugate (ADC) is effective regardless of Trop-2 expression, adoptive cell transfer (ACT) shows promise for extremely personalized treatment, and dietary restrictions further induce anti-tumor activity. While challenges such as increased toxicity and little improvement in overall survival (OS) were observed, targeted therapies are a significant step towards creating effective, personalized treatments for breast cancer.

Keywords: Breast cancer; Phase III breast cancer immunotherapies; PD-L1; breast cancer biomarkers; targeted therapies; clinical trials

INTRODUCTION

Breast cancer is one of the largest global health challenges today, representing approximately 30% of all cancers diagnosed in women and affecting about one in eight women during their lifetime (1). In the U.S alone, 316,950 cases are estimated to be diagnosed, with 42,170 predicted deaths (1). Despite advancements in cancer detection and standard treatments, high recurrence rates and the prevalence of treatment-resistant tumors indicate a need for more effective treatment strategies.

Though standard breast cancer treatments–chemotherapy, radiation, and surgery–are effective, they are limited by non-specificity. Chemotherapy targets all rapidly dividing cells, which also damages healthy tissues throughout the body. This results in severe side effects that significantly deteriorate patients' overall health and quality of life. Similarly, while radiation therapy is localized, it still damages surrounding healthy tissues. It also misses microscopic tumors, which can contribute to recurrence. Surgery carries risks (e.g., infection) and is challenging for tumors located in complex areas of the body (e.g., brain and spine metastasis). Additionally, any remaining cancer cells during surgery increase the likelihood of recurrence. These limitations highlight a critical need for more precise therapeutic strategies.

In recent years, there have been breakthroughs with immunotherapy and highly targeted agents (Figures 1 and 2). These therapies activate patients' immune

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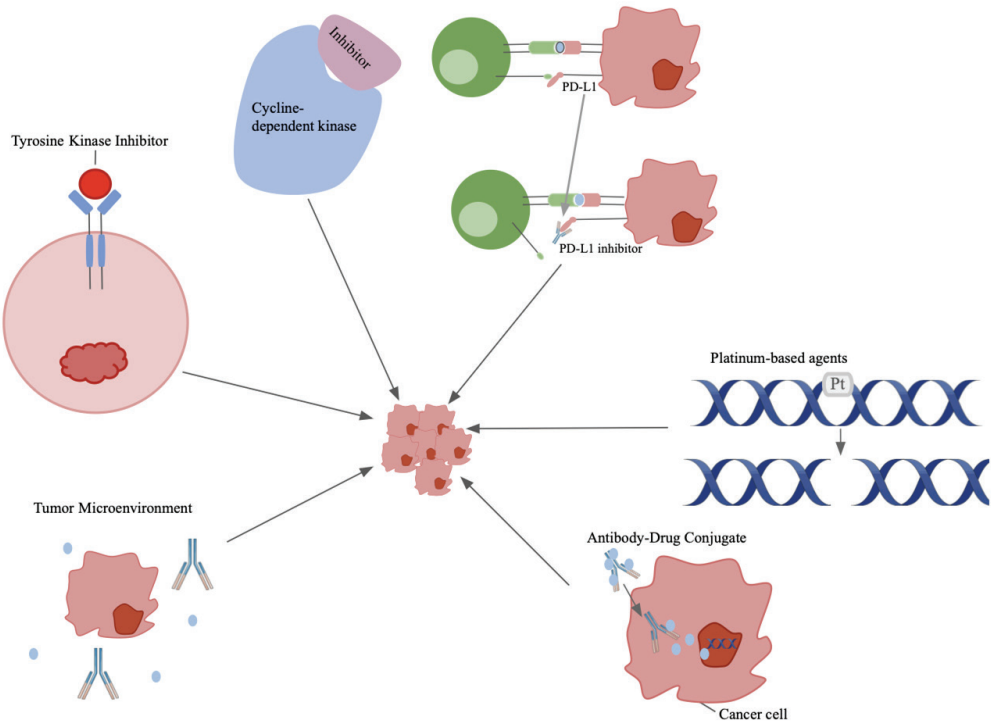

Figure 1. Breast cancer treatment strategies and their mechanisms. This includes: tumor microenvironment adjustments (Fast-mimicking and serine-glycerine free diets), Tyrosine kinase inhibitors (Tucatinib plus monoclonal antibody Trastuzumab), CDK inhibitor (Palbociclib), PD-L1 inhibitor (nivolumab, spartalizumab-LAG3 blockade, PARP inhibitor (Veliparib-Cisplatin), and antibody-drug conjugates (Sacituzumab Govitecan). Each strategy has its own mechanism–diets modify tumor microenvironments to be unsuitable for tumor growth, inhibitors block immune checkpoints, cell signaling pathways, and DNA repair, and ADCs release molecules that prevent DNA replication. Figure created with images adapted from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

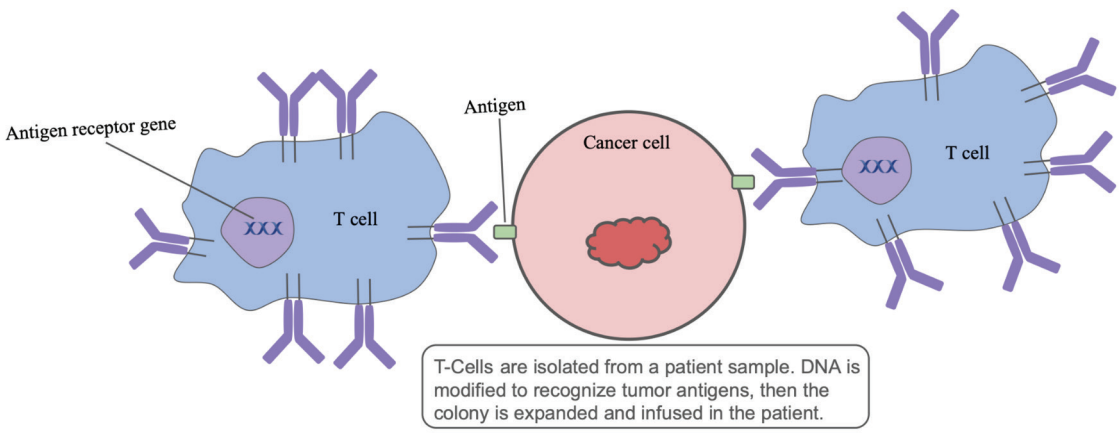

Figure 2. Adoptive Cell Transfer. T-cells are retrieved from patients, modified to recognize and target tumor antigens, expanded ex vivo, and infused back into the patient to attack tumor cells. The patient's T-cells are modified to identify distinct neoantigens based on the patient's tumor profile. This strategy reduced tumors and allowed for complete tumor removal in three out of six patients. Figure created with elements adapted from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

systems or inhibit cellular pathways to fight cancer cells. With molecules like antibodies and inhibitors only targeting specific substrates, disease control can be achieved with more precision. Combining these therapies with standard treatments also results in a higher chance of response through anti-tumor effects and overcoming resistance mechanisms. However, the multiple molecular subtypes of cancer cells have unique characteristics, making it difficult for all patients to achieve a long-term response. By profiling a tumor's genomic profile, researchers can identify mutations, gene expression patterns, and biomarkers that allow for optimized treatment regimens with minimized toxicities. While individual treatment advancements have been recorded, direct comparisons of different drug classes remain crucial for future clinical research. Ultimately, this review seeks to answer the question: How can the use of targeted therapies as individual treatments or in combination with standard treatment, guided by the genetic profile of a breast cancer tumor, impact patient outcomes and the development of personalized treatments?

METHODS AND MATERIALS

A systematic literature search was conducted with sources from PubMed using the keywords: "immunotherapy", "cancer vaccine", "Phase III breast cancer immunotherapies", "breast cancer antibodies", "PD-L1", and "antibody cancer treatment". Data from Phase II and Phase III clinical trials were prioritized, as they provided large patient cohorts and statistically significant data on efficacy across different demographics. Phase I studies were included only if they had significant findings relevant to this review or offered additional therapies not studied in later-stage trials. Two Phase I trials investigating the impact of diet on tumor microenvironment were included as they could potentially enhance existing therapies. In total, 11 papers were reviewed. All papers were peer-reviewed and published in scientific journals. Abstracts from conferences were not included to ensure a high level of detail was included in the studies. Clinical trials were selected if the trial included one or more breast cancer genetic subtypes. Publications within the past five years were selected to ensure the most relevant and advanced treatment strategies. The main outcomes analyzed included progression-free survival (PFS), overall survival (OS), pathological complete response (pCR), and objective response rate (ORR).

RESULTS AND DISCUSSION

The results section is separated into drug classes (e.g., PD-L1 Inhibitors, Antibody-Drug Conjugates, Adoptive Cell Transfer, Diets). Each category presents a summary of critical clinical trials, followed by a discussion of the findings. A full summary of all the reviewed studies is provided in Table 1.

Nivolumab in Clinical Trials

Phase 3 study NCT04109066 analyzed the addition of nivolumab (PD-L1 inhibitor) to neoadjuvant anthracycline- and taxane-based chemotherapy in 510 patients with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer (2). This subtype has low pCR rates to neoadjuvant therapy, likely because these tumors are less immunogenic and have low proliferative activity. However, some ER+/HER2- tumors with high lymphocytic infiltration–similar to triple-negative breast cancer (TNBC)–may still respond to PD-L1 inhibitors. Nivolumab significantly improved pCR: 63 out of 257 nivolumab patients versus 35 out of 253 placebo patients ($P = 0.0021$) achieved pCR. Event-free survival (EFS) rates were limited due to an early study end (18 months), and were similar in both arms (89.1% vs. 91.7%). Both cohorts experienced adverse events (AEs, 98.5% vs. 98.4%), with alopecia, nausea, anemia, and fatigue being the most frequent. Grade 3 or 4 treatment-related AEs occurred in 35.1% (nivolumab) versus 32.5% (placebo) of patients, indicating tolerable safety. Patients with tumors expressing PD-L1 and high levels of stromal tumor-infiltrating lymphocytes (sTILs) had the highest pCR rates with nivolumab. Similarly, higher pCR and residual cancer burden (RCB) 0 or 1 rates occurred in tumors with ER levels of <50% and progesterone receptor expression of <10%.

Long-Term Response to PD-1 and LAG-3 Blockade

In one case, a metastatic TNBC patient achieved long-term complete response (CR, ongoing at 50 months) to PD-1 (spartalizumab) and LAG-3 blockade (LAG525), which activated cytotoxic T and NK cells and reduced immunosuppressive cells (3). Initial molecular and immunological profiles of cancer and stromal cells showed no PD-L1expression and only moderate T cell infiltration (5%-30% of cells). At week 9, skin involvement largely regressed, and lymph nodal metastases showed a near CR, and by week 20, the lymph nodal tumor regressed entirely. Profiling of

Table 1. Summary of clinical trials discussed in the paper.

Study Id	Mechanism	Phase	Number of Patients	Follow-up	Outcome
NCT04109066	PD-L1 inhibitor (nivolumab), CTX	3	510	19 mth	+10.7% pCR, similar 18-month EFS, safe
NCT02460224	PD-1 blockade (spartalizumab), LAG-3 blockade (LAG525)	1/2	1	50+ mth (Ongoing)	Durable CR, -MDSCs, +effector-memory T cell phenotype
NCT01864746	CDK4/6 inhibitor (Palbociclib), ET	3	1031	43 mth (med)	No iDFS or OS improvement, +Grade 3/4 AEs
NCT02595905	PARP inhibitor (Veliparib), Pt CTX (Cisplatin)	2	320	11.1 mth (med)	+1.7 mth PFS for BRCA-like, no OS benefit, +AEs
NCT03901339	Anti-Trop-2 ADC (Sacituzumab Govitecan)	3	521	12.5 mth (med)	+OS, +ORR, Trop-2 expression-independent, safe
NCT02574455 (analysis of NCT0390133)	Anti-Trop-2 ADC (Sacituzumab Govitecan)	3	235	Not specified	+PFS, +OS, Trop-2 and gBRCA1/2-independent, safe
NCT04579380	HER2 Tyrosine Kinase Inhibitor (Tucatinib), Monoclonal Antibody (Trastuzumab), HR inhibitor (fulvestrant)	2	31	15 mth (med)	cORR: 41.9%, HER2 mutation-independent, med response duration 12.6 months, safe
NCT00542451	CTX (Paclitaxel), HER2-targeted Monoclonal Antibody (Trastuzumab)	2	406	10.8 years (med)	91.3% iDFS, 94.3% OS, HER2DX score predicts recurrence
NCT01174121	ACT of mutation-reactive TILs	1/2	3	Not specified	1 CR, 2 PR, HLA loss as immune escape
ChiCTR2300067929	SG-free diet	1	40	Daily, 9 weeks	-tumor growth; + CD8+ T cells, induced PD-L1 lactylation, safe
FMD analysis of NCT03454282	FMD	1	22 BC	Not specified	-glucose, -IGF1, -immunosuppressive MDSCs, +ketones, activated: CD8+ T cells, NK cells

The table is organized by treatment strategy and includes relevant expression changes after the strategy was implemented. Median follow-up time was included for clinical trials that provided it.
Abbreviations: Chemotherapy (CTX), median (med), months (mth), eval (evaluated), Pt (platinum), partial response (PR), Antibody-drug conjugates (ADC), Adoptive cell transfer (ACT), breast cancer (BC), increased (+), decreased (-).

peripheral blood mononuclear cells showed that PD-1 was expressed in CD4+T cells (23%) and Treg cells (17%), and CD8+ T cells (3%). LAG-3 was present in Tregs (26%), a subset of CD8+ T (4%), CD56high (8%), and CD56dim (19%). The treatment increased proliferation and activation of Tregs and NK cells, with Tregs significantly increasing throughout treatment. Therapy also rapidly decreased immunosuppressive monocytic myeloid-derived suppressor cells (MDSC), but the overall CD14+ monocytic population did not significantly change. Furthermore, memory T cells shifted to an "effector-memory" phenotype, indicating a long-term immune response against tumor antigen NY-ESO-1. This study suggests that dual PD-1 and LAG-3 blockade may reactivate T cells and NK cells to fight tumor cells, overcoming immune suppression mechanisms.

Effect of Palbociclib on Invasive Disease

The phase III PENELOPE-B trial evaluated the addition of CDK4/6 inhibitor palbociclib to standard endocrine therapy (ET) in high-risk hormone receptor-positive (HR+)/HER2- breast cancer patients with residual disease after neoadjuvant chemotherapy (4). At follow-up, invasive disease-free survival (iDFS) events occurred in 152 palbociclib patients and 156 placebo patients. At 3 years, iDFS was 81.2% with the palbociclib group versus 77.7% with the placebo group ($p = 0.525$), making the difference insignificant. Overall survival was also insignificant for both groups ($HR = 0.87$, $p = 0.420$). Grades 3 and 4 AEs were more common in the palbociclib group, with 301 patients in the palbociclib arm versus 11 in the placebo arm given dose reductions. Therefore, the addition of palbociclib to ET did not improve iDFS for HR+/HER2- breast cancer patients, but instead resulted in higher toxicities.

Cisplatin and Veliparib in BRCA patients

In the phase II trial S1416, 320 eligible patients were randomized to cisplatin (platinum-based chemotherapy) with either placebo or veliparib (PARP inhibitor) to determine its efficacy in three biomarker groups: germline BRCA (gBRCA) mutated, BRCA-like, and non-BRCA-like (5). Only the BRCA-like group showed significant improvement in PFS events with veliparib (median of 5.9 months vs. 4.2 months). No PFS benefit was observed in the gBRCA (6.2 vs 6.4 months) or non-BRCA-like group (4.0 vs 3.0 months). No significant improvement in OS was seen in any group. However, all three veliparib groups experienced more AEs (e.g., neutropenia, anaemia, thrombocytopenia), leading to 30% of veliparib patients and 17% placebo patients withdrawing. If the toxicity can be minimized, PARP inhibitors can potentially improve PFS in BRCA-like patients by inhibiting tumor DNA repair.

These clinical trials describe specific immune and DNA repair pathways that can be targeted for certain subgroups. The nivolumab study identified that patients with high tumor immunogenicity (high TIL and PD-L1expression) improved the most (2). The much higher pCR rates suggest that immunotherapy may be effective in this typically less immunogenic subset if patients are selected by these biomarkers. Although longer follow-ups are needed to determine if pCR improvement translates to overall survival (study ended early), these results show that immunotherapy can benefit early-stage ER+ breast cancer patients based on biomarker status. Further investigation is needed to validate biomarkers and standardize assay methods to identify which patients are likely to benefit. Similarly, the long-term response of patients treated with PD-L1 and LAG3 blockade emphasizes the potential of checkpoint inhibition (3). PD-1 blockades alone may be insufficient for TNBC tumors, but combining PD-1 and LAG-3 inhibitors may reactivate T and NK cells by decreasing MDSCs, and LAG-3 ligands may also serve as biomarkers. This study's statistical significance was limited by its single-patient design, but the immune reactivation observed suggests that combined PD-1/LAG-3 blockade could be effective in PD-L1–negative tumors, warranting evaluation in larger studies.

In contrast, palbociclib did not improve iDFS for HR+/HER2- breast cancer patients and instead resulted in increased toxicity (4). However, palbociclib may delay relapses rather than sustaining a long-term effect, which needs long-term follow-up of other CDK4/6 inhibitor trials to investigate. Similarly, the cisplatin/veliparib trial increased toxicity, but the addition of PARP inhibitors showed significant potential to improve PFS in BRCA-like patients (5). More research is needed to find the optimal PARP inhibitor-cisplatin combination to avoid high toxicities. This may include exploring PARP inhibitors other than PARP 1/2 and adjusting dosage during the treatment course.

Ultimately, the varying outcomes of these combination treatments emphasize the importance of selecting patients through biomarkers to maximize benefit and minimize unnecessary toxicities.

Effect of Trop-2 on Sacituzumab Govitecan

Sacituzumab Govitecan (SG) is an antibody-drug conjugate (ADC) targeting humanised anti-Trophoblast cell-surface antigen 2 (-Trop-2) and delivering SN-38 (topoisomerase inhibitor) (6). Trop-2, linked to tumor progression, is highly expressed in ~80% of breast cancers. In a Phase III study, 268 patients received SG and 249 received chemotherapy. Patients had HR+/HER2- tumors and had one previous ET, CDK4/6 inhibitor, and two to four chemotherapy regimens. Trop-2 expression was analyzed by immunohistochemistry (IHC), and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) genotype was collected via blood for safety assessment. SG improved median OS by 3.2 months. At 12 months, OS was 61% in the SG arm and 37% with chemotherapy. Similar rates were observed at 18 and 24 months. OS benefit was observed regardless of Trop-2 expression. SG also improved ORR for patients, with 57 SG patients compared to 38

chemotherapy patients achieving a partial response, and delayed deterioration and fatigue. 268 SG and 249 chemotherapy patients experienced >Grade 3 TEAEs. Homozygous UGT1A1 patients, who have less SN-38 metabolism, experienced higher rates of severe AEs. However, UGT1A1 interpretation was limited due to the small subgroup. Overall, SG improved responses in endocrine-resistant, post CDK4/6 inhibitor settings and was even more effective than trastuzumab deruxtecan in the subset of HER2-low patients. Overall, SG is an extremely effective therapy for breast cancer, especially after finding that the therapy works across various Trop 2 levels.

Sacituzumab Govitecan Trop-2 Biomarker Study

An evaluation of the SG biomarker study ASCENT confirms Trop-2 non-association and examines the impact of the gBRCA1/2 mutation on SG efficacy (7). 235 TNBC patients received SG, 151 had tumors evaluated for Trop-2 expression using IHC. Trop-2 expression was categorized by histochemical scores: low (0 - <100), medium (100-200), and high (>200 - 300). If applicable, gBRCA1/2 mutation status was collected at baseline. Trop-2 levels in SG-treated patients were 56% high, 26% medium, and 18% low (similar distribution in the chemotherapy arm, +/- 5%). SG significantly improved overall outcomes compared to chemotherapy alone–regardless of gBRCA1/2 mutation status. PFS rates were 6.9 months (high), 5.6 months (medium), and 2.7 months (low) for SG versus 2.5 months (high), 2.2 months (medium), and 1.6 months (low) for chemotherapy. Median OS was 14.2 months (high), 14.9 months (medium), and 9.3 months (low) for SG versus 6.9 months (high), 6.9 months (medium), and 7.6 months (low) for chemotherapy. ORR with high, medium, and low Trop-2 H-scores were 44%, 38%, and 22% for SG versus 1%, 11%, and 6% for chemotherapy. Like TROPiCS-02, significant benefits of SG in TNBC were observed regardless of Trop-2 expression.

Both TROPiCS-02 and ASCENT showed that SG is more effective than chemotherapy in pretreated breast cancer, increasing PFS, OS, and ORR (6, 7). Importantly, SG efficacy is independent of Trop-2 expression levels, countering the prior belief that high Trop-2 levels were required for anti-Trop-2 monoclonal antibodies to be effective (6). This may be due to the SG bystander effect, where the release of SN-38 kills nearby tumor cells. The high ratio of SN-38 released to Trop-2 required for binding allows for tumor cell proliferation despite low Trop-2 levels. While tumor heterogeneity and Trop-2 plasticity may lead to the failure of Trop-2 detection, the lack of correlation of Trop-2 levels and SG benefit suggests that Trop-2 tests may be unnecessary, simplifying patient selection. It also means that SG may benefit patients who have exhausted other treatment options, since even low-Trop-2 can be targeted. Still, further research is needed to confirm the effect of low Trop-2 levels and germline BRCA1/2 mutations, as the sample sizes were limited. Additionally, other SG biomarkers (such as those enhancing SN-38 effects), along with more combinations of ADCs, should be explored to maximize patient benefit.

While biomarkers remain important for specifying ADC targets, their benefit across broader breast cancer biomarker levels suggests it could be used as an alternative to inhibitors. Inhibitors such as nivolumab improved pCR in only PD-L1–positive ER+/HER2– patients, and veliparib improved PFS in only BRCA-like subgroups; patients outside of those subtypes experienced increased toxicity in both trials. In comparison, SG increased OS across all Trop-2 expression levels, along with manageable toxicity at all expression levels. This comparison emphasizes the potential of ADCs as an alternative option for breast cancer patients who do not meet biomarker-specific requirements for inhibitors or who have not responded to inhibitor-based treatment.

Trastuzumab and Tucatinib in Pretreated Patients

Phase II basket study SGNTUC-019 explored the use of HER2-targeted tyrosine kinase inhibitor tucatinib with monoclonal antibody trastuzumab (8). 31 patients with heavily pretreated HER2-mutated metastatic breast cancer were included. HR+ patients also received fulvestrant to block hormone receptors. Median PFS was 9.5 months, and median OS was 20.1 months. The confirmed objective response rate (cORR) was 41.9%, with 2 complete responses. Responses were durable (median: 12.6 months) and fast (median time to response: 1.4 months). Disease control was achieved in 80.6% of the patients, with 73% of patients experiencing tumor reductions. Responses occurred across a range of HER2 mutations, including those in both tyrosine kinase (Leu755) and extracellular (Ser310) domains, and were found in all patients with and without CDH1 and PIK3CA mutations. Consistent responses across HER2 mutations indicate they may be oncogenic drivers, highlighting the need to target HER2 mutations. Three patients had serious TEAEs to tucatinib; two discontinued tucatinib, and seven

required dose reductions. One patient also had a dose reduction of fulvestrant due to TAEAs. No TAEA-related deaths occurred. The chemotherapy-free combination of tucatinib and trastuzumab showed high clinical response and safety threshold for patients.

10-year Outcome of Paclitaxel and Trastuzumab

A ten-year analysis of a single-arm Phase II study examined long-term outcomes of adjuvant paclitaxel and trastuzumab in 406 patients with small (<3cm), node-negative, HER2+ breast cancer (9). Patients received intravenous trastuzumab weekly for 12 weeks, followed by trastuzumab weekly or every 3 weeks for 40 weeks. The outcomes were positive: 10-year invasive disease-free survival rate was 91.3%, 10-year breast cancer-specific survival interval was 98.8%, OS was 94.3%, and 10-year recurrence-free interval was 96.3%. There were only 31 iDFS events and 6 cases of distant recurrences. The study also evaluated the HER2X risk score, which uses 27 genes with patient characteristics to predict long-term relapse risk. It found that every 10-point increase in the score increased the risk of recurrence by ~24% for iDFS recurrence, and 45% for any recurrence. Overall, adjuvant paclitaxel and trastuzumab achieve long-term cancer control in low-risk HER2+ patients, and the HER2X risk score is a useful predictor of recurrence risk for breast cancer patients.

These two studies highlight the importance of genetic profiles in predicting and treating breast cancer. The tucatinib/trastuzumab trial shows that HER2 activating mutations, drivers of tumor growth, can be effectively targeted (8, 9). Since heavily pretreated MBC patients still showed clinical activity, HER2 mutations could also be targets in MBC (8). The effectiveness of this combination may be from blocking HER2 signaling domains: trastuzumab binds to the extracellular tyrosine kinase domain, and tucatinib inhibits the intracellular domain. By inhibiting both extracellular and intracellular domains, more resistance mechanisms and mutations are overcome. However, this was a small, single-arm basket trial lacking a control group, making the findings exploratory. Larger randomized Phase III trials are needed to confirm these results. Meanwhile, adjuvant paclitaxel and trastuzumab were effective in achieving long-term cancer control in early, node-negative, HER2+ breast cancer (9). More importantly, the trial showed that the HER2X risk score is reliable for identifying breast cancer patients at high risk for recurrence. This advancement allows for better risk mitigation, such as extensive follow-up or additional treatments for high-risk score patients. Together, these findings are a promising start to personalized, HER2-targeted approaches tailored for HER2 mutations and individual risk profiles.

Adoptive Transfer of Mutation-Reactive Autologous Lymphocytes

A Phase I/II pilot trial explored the efficacy, feasibility, and safety of adoptive cell transfer (ACT) in breast cancer (Figure 2), focusing on the efficacy of mutation-reactive tumor-infiltrating lymphocytes (TILs) (10). TILs were successfully grown from 42 patients after in vitro expansion for 24 days. Immunogenic mutations increased significantly ($P < 0.001$) with mutation number, but were only identified in 2.3% of mutations. The majority of mutated variants were nonsynonymous single-nucleotide variants (SNVs, median: 61% per patient). 28 patients had TILs recognizing at least one neoantigen, with TP53 as the only mutated gene recognized by more than one patient. 76% of neoantigens were recognized by CD4+ T lymphocytes; fewer were recognized by CD8+ T cells. gBRCA mutation tumors had more neoantigens, while fewer neoantigens were identified in HR+/HER2- patients.

Tumor responses were seen in three out of six analyzed patients: Patient 4136 achieved CR (ongoing at 66 months) of metastatic tumors, Patient 4355 achieved complete regression of breast/lymph node tumors and 69% reduction in a lung tumor (lasting 10 months), and Patient 4343 achieved a partial response (6-month, 52% reduction). A loss of heterozygosity on chromosome 6 (Human leukocyte antigen-(HLA-)DRB57:03 allele, which restricts mutated TTI2) was observed in Patient 4343's lymph node tumor. Additionally, anti-TTI2 and anti-p53 T cell receptors (TCRs) were very low (0.000%-0.058%) in both blood and tumor samples, suggesting poor antigen presentation (less expression of HLA allele). This pilot study shows that TILs can improve patient outcomes in breast cancer even when there is metastasis, and that T cells can be genetically modified to target tumor antigens.

The ACT trial demonstrates that using TILs to identify neoantigens is advantageous: the T cells have already survived thymic selection (minimizing toxicity), and TCRs responsible for neoantigen recognition can be isolated ex vivo (10). Most neoantigen-recognizing TILs were CD4+ T cells, suggesting that they drive significant tumor regression and long-term CR, and

potentially avoid certain immune escape mechanisms. This TIL therapy can especially benefit patients with tumors resistant to standard drugs, since TILs are tailored to attack each patient's treatment-resistant tumors. However, immune evasion (e.g., HLA loss) may still occur, so other strategies, such as immune checkpoint inhibitors, should be combined to overcome tumor resistance. Mutation-reactive TIL selection may be required for personalized ACT therapy, though the patient cohorts were too small to assess this potential correlation. Exploring reactivity against common mutations with high-frequency HLA could expand the use of T cell therapy. Furthermore, using TILs currently faces challenges, including the complexity and high cost of the identification and expansion process.

Serine-Glycine-Free Diet and Antitumor Effects

Tumor cells often rely on external serine and glycine for rapid proliferation. Preclinical mouse models and a Phase 1 study investigated the impact of serine/glycine-free (-SG) diet, which reduces amino acids, on colorectal cancer (CRC) growth and immunity (11). The -SG diet limited CRC growth and increased tumor cell death by preventing cell progression from G1 to S phase. Knocking down SG transporters also significantly reduced tumor growth, but combining this with the diet did not provide additional benefits. Larger lymphocyte clusters (T and B cells) and smaller macrophage clusters appeared in diet-treated mice tumors. Markers confirmed that there was an upregulation of lymphocyte differentiation and activation, including B cell-mediated immunity and T cell activation. CD8+ T cells increased in tumors, which induced antitumor effects but also increased the expression of PD-L1 in the tumor microenvironment. This suggests that an inhibitor must be used simultaneously to decrease PD-L1. The -SG diet group had significantly increased levels of lactylation, preventing lysosomal degradation of tumor PD-L1. This study demonstrated safety and feasibility: only low-level AEs occurred, quality of life was not impacted for 90% of patients, and the clinical benefit rate was 90%. These findings demonstrate that a -SG diet can modify tumor microenvironments to enhance antitumor activity and, potentially, the efficacy of other treatments.

Assistance of Fasting-Mimicking Diet in Cancer Treatment

Fasting-mimicking diets (FMD) have been well tolerated and induce systemic metabolic changes that can affect tumor immunity (12). Preclinical mouse studies found that FMD increased the activity of cancer treatments by modifying metabolism on top of antitumor responses to chemotherapy, immunotherapy, or ET. A Phase 1 trial investigated metabolic and immunomodulatory effects of FMD in 101 patients (22 breast cancer). Patients followed five-day calorie-restricted FMD cycles, followed by 16-23 days of refeeding, combined with standard treatments. Incidence of grade 3 or 4 FMD-related AEs was 12.9%, much lower than the initial threshold (20%). The most common side-effect experienced was fatigue (90.2%). FMD induced significant metabolic changes across 99 evaluable patients, including a decrease in plasma glucose concentration (-63.1% to +67.8%), serum insulin (-91.3% to +697%), and serum IGF1 (-72.3% to +139.8%). Average urinary ketones also increased from 0.18 mg/dL to 59.9 mg/dL. Similar metabolic changes occurred in 9 healthy volunteers on the same regimen, but not in 13 non-FMD advanced breast cancer patients. These changes were independent of cancer type, concomitant treatments, and tumor stage. FMD caused a significant decrease in monocytes, especially for those in the immunosuppressive $CD14^{+}HLA\text{-}DR^{-}$ subset (includes monocytic MDSC). The reduction of myeloid cells was followed by an increase of activated CD8+ T cells and cytolytic $CD3\text{-}CD16^{+}CD56^{dim}$ NK cells, triggering multiple antitumor immune pathways. However, growth-promoting signal IGF1, both its active form and total amount, decreased, meaning the benefits usually seen from FMD are likely reduced. Overall, FMD reshapes tumor microenvironments to a cytotoxic state by reducing growth factor and immunosuppressive cell levels–improving overall response to standard treatments and immunotherapy.

These studies, though in early phases and conducted for colorectal cancer patients, show dietary changes as a promising addition to standard treatment that further enhances anti-tumor activity in breast cancer (11, 12). While the -SG diet was tested in a clinical trial focusing on colorectal cancer, the relationship between PD-L1 expression and diet patterns may be very relevant to breast cancer, as PD-L1 is a target for inhibitor treatments in breast cancer, and dietary restrictions are recognized for their potential to impact tumor control and treatment responses. The -SG diet affected the cell cycle and showed an increase in lymphocyte infiltration and activation within tumors, indicating that diet restrictions can directly influence tumor cell proliferation and immune cell levels (11). Identifying

PD-L1 lactylation connects metabolism and immune checkpoint regulation, suggesting that diet influences the efficacy of PD-L1 inhibitors and potentially overcomes resistance mechanisms. Ultimately, there should be larger investigations targeting PD-L1 lactylation in breast cancer patients.

Similarly, FMD induced significant metabolic changes, such as decreased IGF1, increased ketones, and significantly reduced MDSCs (known to block immune activity) (12). Since FMD targets immune-related molecules by reducing the substrates needed for expansion, it should be paired with T-cell therapy or targeted immunotherapies to maximize both the diet's and therapy's benefits. The results of this Phase 1 trial emphasize the need for Phase 2 and 3 trials to further test the efficacy of FMD.

These findings suggest that targeting nutrients in tumor microenvironments could serve as an effective, low-toxicity combination to standard treatment, including immunotherapies. By modifying the tumor microenvironment, these interventions could decrease the resistance of tumor cells to existing treatments, potentially improving overall patient outcomes. However, these diets result in nutrient deficiencies, which make patients physically weaker. Supplemental care must be used alongside these diets to ensure patient health and the ability to maintain the diet. Furthermore, there may be changes in antitumor molecule levels, which need to be observed in later-stage trials involving breast cancer patients.

CONCLUSION

This review evaluated how combining targeted therapies with standard treatments, guided by genomic and molecular profiles, can improve patient outcomes and personalize care. Breast cancer treatment is now more genetically guided and tailored to tumor molecular profiles. Biomarkers such as PD-L1, sTILs, and BRCA improved outcomes by targeting specific tumor characteristics. SG demonstrated efficacy across multiple subtypes, such as HR+/HER2- and TNBC. Since the initial correlation between Trop-2 expression and SG benefit was not observed, SG could benefit heavily pretreated patients resistant to other therapies. This expands eligibility for breast cancer patients, as Trop-2 expression levels do not determine the use of SG, and offers a potential alternative to inhibitors. Patients who are treated with inhibitors such as nivolumab and veliparib need specific biomarkers to achieve efficacy, while ADCs like SG show consistent improvements across biomarker statuses. Inhibitors also exhibited higher toxicities in patients outside of those specific subtypes, while ADCs had manageable toxicities across biomarker levels. As a result, ADCs may provide alternative treatment strategies for patients who do not meet molecular profile requirements for inhibitors or who become resistant to inhibitor-based strategies. It also highlights the need to identify additional biomarkers, like those affecting DNA replication inhibitors, to better predict SG efficacy.

ACT offers another personalized strategy, as it targets specific neoantigens based on individual tumor profiles. This bypasses many resistance mechanisms and can be tailored for each patient's molecular subtype and treatment history. However, high toxicities, complex expansion processes, and tumor escape mechanisms such as HLA loss may still limit patient benefit and widespread use. Addressing production and cost limitations will be critical for ACT to become widely used for breast cancer. Both SG and ACT demonstrate how genomic profiling and targeted therapies can overcome tumor resistance, enhancing overall efficacy. Future development will require identifying more biomarkers relevant to tumor pathways and immune responses, as well as expanding these therapies to more breast cancer subtypes. Ultimately, applications of biomarkers in targeted therapy have made breast cancer treatment more precise. Continued clinical investigation will be essential to ensure safety, effectiveness, and availability for future patients.

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CONFLICT OF INTERESTS

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