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Combining multiple therapies for metastatic breast cancer: ADCs and ICIs

Introduction

Breast cancer is the most common malignancy in women and the second most common cancer worldwide.[1] Rates of breast cancer are increasing in many parts of the world, reflecting its association with social and lifestyle factors related to economic development, as well as increases in life expectancy.[2]

Although the disease continues to increase in frequency, great strides have been made in treatment options and therefore in prognosis. In 40 years, the 10-year survival rate for breast cancer has almost doubled, from 40% in 1971 to 78% in 2011.[3]

Despite this, many continue to die from the disease because, while early-stage breast cancer is curable in 70%-80% of patients, metastatic breast cancer remains incurable.[2] In 2021, over 43,000 women and more than 500 men are expected to lose their lives from breast cancer in the United States.[4]

There is therefore an urgent need for new and more targeted treatments. Breast cancer is etiologically heterogeneous, but expanded insights into the molecular biology of the disease are generating a range of next-generation therapeutics, many of which are active via the immune system.

Here, we review two classes of these next-generation therapeutics—antibody-drug conjugates (ADCs) and immune checkpoint inhibitors (ICIs)—and explore how their combined use can significantly improve outcomes for patients with metastatic breast cancer. We discuss approved treatments, as well as those in clinical development.

KEY TAKEAWAYS

There is an urgent need for new and more targeted treatments for metastatic breast cancer, which remains incurable

Some of the most promising next-generation therapeutics act via the immune system

These include antibody-drug conjugates (ADCs), which comprise a monoclonal antibody connected to a cytotoxic drug, and immune checkpoint inhibitors (ICIs), which restore the immune response against cancer

Used in combination, ADCs and ICIs can act synergistically to enhance the treatment effect and prolong survival in people with metastatic breast cancer

Profiling patients through biomarker assays is important to obtain the optimum benefit from these therapies and give a clinical trial the best chance of success

ADCs target cancer cells with cytotoxicity

ADCs are a targeted form of treatment for cancer, designed to identify and kill cancer cells while sparing healthy tissue. They comprise a monoclonal antibody against a receptor that is overexpressed by cancer cells connected, by a linker, to a cytotoxic drug.

The antibody component of an ADC binds to an antigen found on the surface of the cancer cell, which triggers its internalization and eventually the release of the cytotoxic component. Exactly how and when the cytotoxic compound is released depends on the nature of the linker. Some linkers degrade only once the ADC is internalized by the cancer cell, for example, which limits exposure of other cells to the toxic compound and therefore reduces off-target toxicity.[5]

An example monoclonal antibody is trastuzumab, one of the first targeted therapies for breast cancer.[6] Trastuzumab targets human epidermal growth factor receptor 2 (HER2), which is overexpressed in 20%-30% of breast cancers, and was the first HER2-targeted therapy to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of breast cancer. It has since been used successfully as a single agent.[7]

As an ADC, trastuzumab can be combined with emtansine (also called DM1), a cytotoxic compound that inhibits the assembly of microtubules.[8] The conjugate, T-DM1, was first approved for the treatment of HER2-positive breast cancer in 2013.

In combination with deruxtecan, which inhibits topoisomerase I, a key component of the DNA replication machinery, trastuzumab can also be used to treat HER2-low breast cancer. The FDA approved trastuzumab deruxtecan for this purpose in 2019.

Table 1: FDA-approved ADCs for breast cancer

	Date approved	Indication
Trastuzumab emtansine	February 2013 May 2019	HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane (separately or in combination) HER2-positive early breast cancer with residual invasive disease following treatment with neoadjuvant taxane and trastuzumab
Trastuzumab deruxtecan	December 2019	Metastatic HER2-positive breast cancer previously treated with two or more prior anti-HER2-based treatments
Sacituzumab govitecan	April 2020	Metastatic TNBC with at least two prior treatments
Datopotamab deruxtecan-dlnk	January 2025	For adult patients with unresectable or metastatic, hormone receptor (HR)-positive, (HER2)-negative (IHC 0, IHC1+ or IHC2+/ISH-) breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease

ADCs are also being developed for the treatment of triple-negative breast cancer (TNBC), which describes any breast cancer that does not express HER2 or a hormone (estrogen or progesterone) receptor. Sacituzumab govitecan, for example, targets tumor-associated calcium signal transducer 2 (Trop-2), which is expressed in 80% of TNBC cases.[9] It, too, is connected to a topoisomerase I inhibitor and was approved by the FDA in April 2020.

There are also a large number of ADCs in the clinical development stages for the treatment of breast cancer. Examples include a further trastuzumab-based ADC, trastuzumab duocarmazine, which induces cell death through DNA damage. Phase I studies of trastuzumab duocarmazine have demonstrated a partial response in patients with HER2-positive and HER2-low breast cancer, as well as in TNBC.[10]

Other compounds under development include BAT8001 (trastuzumab batansine), which has demonstrated clinical response in some patients with HER2-positive breast cancer; ladiratuzumab vedotin, which targets hormone receptor-positive breast cancer; and the HER3-targeting compound, patritumab deruxtecan.[5]

ADCs and ICIs – A powerful combination

Antibody-drug conjugates (ADCs) contain a monoclonal antibody targeted against a cancer cell-specific receptor connected to a cytotoxic drug. The first ADC was approved in the U.S. in **2001.**

Immune checkpoint inhibitors (ICIs) are a type of immunotherapy that block inhibitory checkpoints in the immune system, allowing immune cells to continue to recognize and destroy cancer cells. The first ICI was approved in the U.S. in **2011.**

In combination, ADCs and ICIs act **synergistically** to enhance the treatment effect. ADCs increase the release of tumor antigens from dying cancer cells, improving antigen presentation.

The immunogenic cell death induced by ADCs can also aid the body's immune response against the tumor, which further boosts the action of ICIs.

As of November 2020, the FDA has approved **three ADCs** and **two ICIs** for patients with **metastatic breast cancer,** which is currently without a cure.

Combination therapies have potential for **enhanced clinical efficacy** and **increased survival rates** in this patient population.[5]

ICIs boost the body's immune response against cancer cells

ICIs are a mainstay of current immunotherapies for cancer and have been approved for the treatment of several cancer types, including breast cancer.[11]

Their efficacy lies in their ability to restore the immune response against cancer. By blocking immune checkpoints—key regulators of the immune system that can dampen the immune response when stimulated by cancer cells—ICIs allow the immune system to continue fighting cancer cells. They are currently the most promising clinical option to reverse tumor-mediated immune suppression in breast cancer and the FDA has approved two ICIs for this purpose (Table 2).

When used in combination with chemotherapy, ICIs have shown particularly promising results in patients with metastatic TNBC,[12] which currently has limited treatment options.

Table 2: FDA-approved ICIs for breast cancer

	Date approved	Indication
Atezolizumab	March 2019	PD-L1-positive, metastatic TNBC, in combination with chemotherapy
Pembrolizumab	May 2017	Unresectable or metastatic, microsatellite instability-high or mismatch repair-deficient solid tumors that have progressed following prior treatment
	June 2020	Advanced solid tumors with high tumor mutational burden that have progressed following prior treatment
	November 2020	PD-L1-positive, metastatic TNBC, in combination with chemotherapy

FDA-approved ICIs for breast cancer target the immune checkpoint protein programmed death 1 (PD-1) and its ligand, programmed death ligand 1 (PD-L1). Atezolizumab, which inhibits PD-L1, has shown efficacy against metastatic TNBC and is approved for the treatment of this patient population.

Pembrolizumab, which blocks PD-1, has also shown clinical efficacy against TNBC and has been approved by the FDA for three subsets of metastatic breast cancer (Table 2).

There are also several ICIs in clinical development and research is ongoing to combine two ICIs into one treatment, known as a dual ICI blockade.[13] While primarily used for metastatic TNBC, as development continues, ICIs are likely to become part of the treatment regimen for other breast cancer subtypes.[5]

Biomarkers are important for patient stratification

The heterogeneous nature of breast cancer means biomarkers are important to precisely identify the subtype and therefore deliver the most appropriate treatment.[14] For example, delivering the correct ADC requires first determining whether the patient's cancer is HER2 positive, hormone receptor positive, or triple negative.

When considering treatment with ICIs, determining expression of PD-L1 is a critical precursor. Several assays are available for this purpose, including the FDA-approved assay SP142, which is approved as a diagnostic for atezolizumab. For pembrolizumab treatment, the 22C3 assay is available, which reflects the number of tumor cells, lymphocytes and macrophages that are positive for PD-L1.

However, the role of PD-L1 status differs in early compared to metastatic breast cancer. While PD-L1 expression is not predictive of benefit from ICIs in early TNBC, it is predictive of benefit in metastatic TNBC. This may be because PD-L1 has a greater immunosuppressive effect in metastatic disease. Other predictors of response to ICIs include the presence of tumor-infiltrating lymphocytes, which are associated with better responses to treatment in patients with metastatic TNBC, other markers of immune infiltration (such as tumor inflammation score, neutrophil-to-lymphocyte ratio and CD8 cell density) and tumor mutational burden.[5]

The promise of dual therapy

ADCs and ICIs show impressive clinical results on their own but can also be combined for an enhanced effect (this dual-therapy approach is sometimes evocatively described as "hitting one bird with two stones"). Indeed, there is robust scientific evidence to support the combined use of ADCs and ICIs in several cancer types, including breast cancer.

From a molecular biology perspective, ADCs and ICIs have synergistic mechanisms of action, providing direct scientific rationale for their combination. For example, both ADCs and ICIs can cause initiative cancer cell death through similar mechanisms.

The combined use of ADCs and ICIs may be especially beneficial in patients with metastatic breast cancer whose disease has progressed following an initial response to therapies, and there is growing evidence to suggest that combining ADCs and ICIs could help overcome resistance to treatment.

Clinical studies have shown that combining an ICI with a targeted monoclonal antibody can reverse resistance to that targeted antibody. Combining pembrolizumab with trastuzumab, for instance, has shown clinical benefits in patients with metastatic HER2-, PD-L1-positive breast cancers, which have been previously resistant to trastuzumab.[15] A more recent study combining T-DM1 with pembrolizumab in patients with metastatic breast cancer demonstrated a response rate of up to 33% and median progression-free survival period of up to 8.7 months, depending on PD-L1 expression.[16]

However, not all trials and not all patients have shown clinical benefit, highlighting the importance of patient selection and stratification. A robust selection procedure, using some of the biomarkers mentioned previously, is necessary to obtain the optimum benefit from these targeted therapies. Patients with PD-L1- and HER2-positive breast cancer for example are most likely to benefit from a combination of T-DM1 plus atezolizumab.[17]

Other challenges to the successful combined use of ADC and ICI therapies include dosing strategy and striking a balance between toxicity and clinical efficacy. Any potential clinical benefit from an increased dosage may be offset by increases in toxicity and it is important to be aware that, compared to chemotherapy agents, ICIs may have delayed and prolonged toxicity.[5]

Although combined toxicity has also been a concern, data so far does not suggest significant additive toxicity from the combined use of ADCs and ICIs. ADCs and ICIs are also generally better tolerated than traditional chemotherapy.

Rational combined use of ADCs and ICIs could give a clinical trial the best chance of success

ADCs and ICIs are next-generation, targeted treatments for breast cancer that show impressive clinical efficacy independently and, when combined, act synergistically in a manner that can overcome resistance to current treatments.

Multiple trials of dual therapy are underway and initial results suggest that such an approach could be clinically beneficial for patients with metastatic breast cancer, whose disease may have progressed despite an initial response to treatment.

Looking ahead, there are several new compounds in development that could improve outcomes for patients with metastatic breast cancer and, potentially, early breast cancer too. In addition, research aims to enhance the synergistic action between ADCs and ICIs and improve their risk-to-benefit ratio. Improving the specificity and efficacy of the drug delivery of ADCs, for example, may reduce their toxicity and enhance their effect on ICIs.

Efforts are also underway to combine the properties of both ADCs and ICIs into a single compound: an immune-stimulating antibody conjugate. Studies in mice have shown a robust anti-tumor immune response from such a compound, with clinical trials underway and results eagerly awaited.[5]

In a clinical trial setting, profiling patients through biomarker assays and delivering dual ADC-ICI therapy where appropriate could give a trial the best chance of success, thus giving a drug the best chance of approval. It also gives patients the best chance of survival—the ultimate goal of any treatment endeavor. With an estimated 284,200 new cases of breast cancer expected in the U.S. in 2021,[5] ADC-ICI therapy offers a new treatment paradigm and fresh hope.

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