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Breast Cancer Immunotherapy: A Clinical Review for the Plastic Surgeon

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Background: Immunotherapy has transformed breast cancer management. However, it can be challenging to remain familiar with the adverse events, contraindications, and perioperative recommendations for each agent.
Methods: We used FDALabel to identify all Food and Drug Administration–approved immunotherapies indicated for the treatment of breast cancer. We extracted details regarding warnings and precautions, indications, and adverse events from each package insert.
Results: We identified nine immunotherapies belonging to three classes: anti-human epidermal growth factor receptor 2 (HER2) agents, anti-programmed cell death protein 1 (PD-1) agents, and anti-trophoblast cell-surface antigen 2 (TROP-2) agents. Cardiotoxicity, including heart failure and cardiomyopathy, was common among those receiving anti-HER2 agents, and hypothyroidism was common among patients receiving the anti-PD-1 agent. The anti-TROP-2 agent was associated with diarrhea and neutropenia. Given the adverse event profile for each drug, we recommend preoperative evaluation components, including transthoracic echocardiography, liver function tests, and thyroid panels. We also indicate here which immunotherapies raise concern for venous thromboembolism, hematoma, and infection.
Conclusions: Using data from clinical trials, we recommend a preoperative evaluation tailored to the immunotherapeutic regimen of individual patients. *(Plast Reconstr Surg Glob Open 2024; 12:e5915; doi: 10.1097/GOX.0000000000005915; Published online 18 June 2024.)*

INTRODUCTION

Immunotherapy has transformed the landscape of breast cancer management. Since its US Food and Drug Administration (FDA) approval in 1998, immunotherapy has shown effectiveness against an array of breast cancers, including those once considered nonresponsive to medical management. The power of these agents, however, is shrouded by mystery regarding their adverse effects and potential complications in the perioperative setting. Surgeons have decades of experience working around radiation and chemotherapy.[1–5] In contrast, immunotherapy is rapidly evolving, and it can be a challenge for surgeons to remain familiar with the myriad of adverse events, contraindications, and perioperative recommendations for these agents. Nevertheless, the effectiveness of immunotherapies means that reconstructive surgery will be an option for patients whose survival would have been unlikely several years ago. Therefore, plastic surgeons have begun to operate on patients undergoing immunotherapy and must be aware of the perioperative safety profile of these drugs.

Immunotherapy refers to the clinical use of genetically engineered immunoglobulins (ie, antibodies) for the management of malignancies and other diseases. Immunotherapy drugs have a shared nomenclature that makes them easy to recognize and describes their mechanism of action **(See table, Supplemental Digital Content 1**, which displays the nomenclature scheme for immunoglobulins. **http://links.lww.com/PRSGO/D305**.)

Generally, these antibodies work by binding to target proteins and preventing the activation of cell growth and signaling pathways that are pathologically altered

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in the setting of cancer. By blocking these pathways, immunotherapies induce an antineoplastic blockade within tumors. Simultaneously, immunotherapies weaponize the innate immune system against opsonized targets, thereby enhancing their cytotoxic effect. Many of these pathways are shared with nonpathologic tissues. Therefore, immunotherapies, like chemotherapy and radiation therapy (RT), also have off-target effects. This article aims to review the immunotherapies indicated for breast cancer, describe the mechanisms of each broad class, and present evidence regarding adverse reactions and key perioperative risks that plastic surgeons should know and consider in the setting of oncologic reconstruction.

METHODS

We used FDALabel, an online repository of prescription package inserts, to identify all immunotherapies approved by the FDA for the treatment of breast cancer. We included agents with active FDA approval on June 10, 2023, and excluded agents with withdrawn or pending breast cancer indications. Two investigators reviewed the package insert for each medication and extracted details regarding warnings and precautions, indications, and adverse events.

RESULTS

Our search identified nine immunotherapies belonging to three major classes. This section reviews these classes, identifies the agents within each class, and summarizes their indications and supporting evidence. Key warnings and perioperative recommendations are summarized in Table 1. Additional information regarding adverse events, their incidence rates, and clinical trial data is included in Supplemental Digital Content 2. (**See table, Supplemental Digital Content 2**, which displays the FDA-approved immunotherapies for the treatment of breast cancer. **http://links.lww.com/PRSGO/D306**.) Mechanisms of action for each immunotherapy are depicted in Figure 1 and described in greater detail in Supplemental Digital Content 3. (**See table, Supplemental Digital Content 3**, which displays the detailed mechanisms of action of FDA-approved breast cancer immunotherapies. **http://links.lww.com/PRSGO/D307**.)

ANTI-HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2

The human epidermal growth factor receptor 2 (HER2) is a co-receptor for several ligands and is often overexpressed in malignancy. Activation of HER2 occurs upon dimerization of HER2 with a member of the ERBB family of receptor tyrosine kinases (eg, HER1, HER2, HER3, HER4). Once activated, HER2 induces the Ras and phosphoinositide 3-kinase (PI3K) intracellular pathways, promoting cell survival and proliferation. Dysregulation of this pathway causes uncontrolled cell proliferation and survival and is the inciting incident in several cancers. Anti-HER2 agents bind HER2 and prevent its dimerization and subsequent downstream signaling cascade. As a result, anti-HER2 immunotherapies effectively inhibit uncontrolled cancer cell proliferation. Besides tumors, HER2 is also expressed by cardiac myocytes and in the epithelia of the lung, bladder, and pancreas, predisposing these tissues to off-target effects.

Takeaways

Question: What adverse events and contraindications to reconstructive surgery are associated with the immunotherapy agents used to treat breast cancer?

Findings: Our study reviewed the nine immunotherapies that are approved by the Food and Drug Administration to treat breast cancer. Cardiotoxicity was common among patients receiving anti-HER2 agents, and hypothyroidism was common among patients receiving anti-PD-1 agents. Patients receiving anti-TROP-2 agents were at an increased risk for neutropenia and severe diarrhea.

Meaning: Preoperative studies, including transthoracic echocardiography, liver function tests, and thyroid panels, including those not typically required for surgery, may be justified in the setting of immunotherapy treatment.

Trastuzumab

Trastuzumab (Herceptin) was introduced in 1998 as the first anti-HER2 immunotherapy.[6] It is indicated for HER2-overexpressing breast cancer but also carries indications for HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Trastuzumab has FDA black box warnings for cardiomyopathies, including congestive heart failure and heart failure with reduced ejection fraction.[6] The incidence of heart failure in patients receiving trastuzumab is approximately 1.9%; however, 7.5% of patients experience reductions in left ventricular ejection fraction.[7,8] Cardiotoxicity is more likely in patients 65 years or older and in patients with impaired renal function.[9] Trastuzumab has also been associated with an increased risk of deep vein thrombosis, amplifying concern for thromboembolic events in the postoperative setting.[6] In addition to routine laboratories, thorough preoperative evaluation of patients receiving trastuzumab includes transthoracic echocardiography for assessment of left ventricular ejection fraction, especially in patients of advanced age or with renal comorbidities. Postoperative deep vein thrombosis prophylaxis is also recommended.

Pertuzumab

Pertuzumab (Perjeta) followed trastuzumab as the second anti-HER2 immunotherapy when it was approved for the treatment of HER2-positive breast cancer in 2012. Pertuzumab is also indicated for neoadjuvant management of locally advanced, inflammatory, or early breast cancer, as well as the adjuvant management of patients at high risk of recurrence. Therefore, patients undergoing reconstructive surgery may reasonably also be undergoing

Table 1. FDA-approved Immunotherapies for the Treatment of Breast Cancer

					Preoperative			Postoperative
Mechanism	**Drug**	**Year**	**Indications***	**Warnings and Precautions†**	**TTE‡**	**LFT§**	**TSH¶**	**Expected Complications**
Anti-HER2	Trastuzumab (Herceptin)	1998	Adjuvant Rx of HER2(+) breast cancer; metastatic HER2(+) breast cancer	Cardiomyopathy†, infusion reactions†, pulmonary toxicity†, embryo-fetal toxicity†, exacerbation of chemotherapy-induced neutropenia	X	-	-	Venous thromboembolism
	Pertuzumab (Perjeta)	2012	HER2(+) mBC before other anti-HER2 therapies; neoadjuvant Rx of HER2(+), locally advanced, inflammatory, or early-stage breast cancer; adjuvant Rx of HER2(+) early breast cancer at high risk of recurrence	Embryo-fetal toxicity†, left ventricular dysfunction†, infusion-related reactions, hypersensitivity reactions/anaphylaxis	X	-	-	Surgical site infection
	Ado-trastuzumab emtansine (Kadcyla)	2013	Refractory or recurrent HER2(+) mBC HER2(+) early breast cancer with residual invasive disease after neoadjuvant taxanes and trastuzumab-based Rx	Hepatotoxicity†, left ventricular dysfunction†, embryo-fetal toxicity†, pulmonary toxicity, infusion-related reactions, hypersensitivity reactions, hemorrhage, thrombocytopenia, neurotoxicity, extravasation	X	X	-	Surgical site infection, hematoma
	Trastuzumab and hyaluronidase-oysk (Herceptin Hylecta)	2019	Adjuvant Rx of HER2(+) breast cancer; HER2(+) mBC	Cardiomyopathy†, pulmonary toxicity†, embryo-fetal toxicity†, exacerbation of chemotherapy-induced neutropenia, hypersensitivity reactions	X	-	-	Surgical site infection
	Fam-trastuzumab deruxtecan-nxki (Enhertu)	2019	Unresectable or HER2(+) mBC after ≥2 anti-HER2-based regimens for metastatic disease	Interstitial lung disease†, pneumonitis†, embryo-fetal toxicity†, neutropenia, left ventricular dysfunction	X	X	-	Postoperative pneumonia
	Pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo)	2020	HER2(+), locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence; HER2(+) mBC before other anti-HER2 therapies	Cardiomyopathy†, embryo-fetal toxicity†, pulmonary toxicity†, exacerbation of chemotherapy-induced neutropenia, hypersensitivity, and administration-related reactions	X	X	-	Surgical site infection
	Margetuximab-cmkb (Margenza)	2020	HER2(+) mBC after ≥2 anti-HER2 regimens, at least one of which was for metastatic disease	Left ventricular dysfunction†, embryo-fetal toxicity†, infusion-related reactions	X	X	-	Acute kidney injury
Anti-PD1	Pembrolizumab (Keytruda)	2014	Neoadjuvant Rx of high-risk early-stage TNBC, then continued as a single adjuvant Rx after surgery; locally recurrent unresectable or metastatic PD-L1(+) TNBC	Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, and other immune-mediated adverse reactions, Hepatotoxicity, infusion-related reactions, complications of allogeneic HSCT, increased mortality in patients with multiple myeloma when pembrolizumab is added to a thalidomide analogue and dexamethasone, embryo-fetal toxicity	-	X	X	Venous thromboembolism, surgical site infection
Anti-TROP-2	Sacituzumab govitecan-hziy (Trodelvy)	2020	Unresectable locally advanced or metastatic TNBC after ≥2 prior therapies for metastatic disease; unresectable locally advanced or HR(+), HER2(-) mBC after ≥2 prior therapies for metastatic disease	Neutropenia†, diarrhea†, hypersensitivity, and infusion-related reactions, nausea/vomiting, increased risk of adverse reactions in patients with reduced UGT1A1 activity, embryo-fetal toxicity	-	-	-	Surgical site infection, electrolyte derangement

HR, hormone receptor; LFT, liver function tests; mBC, metastatic breast cancer; Rx, treatment; TTE, transthoracic echocardiogram; UGT1A1, uridine diphosphate glucuronosyltransferase 1 family polypeptide A1.
*Omits indications for nonbreast cancers.
†Warnings and precautions with FDA black box warnings.
‡The American Heart Association recommends echocardiography before, during, and every 2–5 years following immunotherapy with an anti-HER2 agent.
§The European Society of Medical Oncologists recommends checking serum transaminases, alkaline phosphatase, and bilirubin before every treatment cycle.
¶The American Society of Clinical Oncology, National Comprehensive Cancer Network, and Society for Immunotherapy of Cancer recommend checking TSH and free T4 at least every 4–6 weeks while receiving ICI therapy.

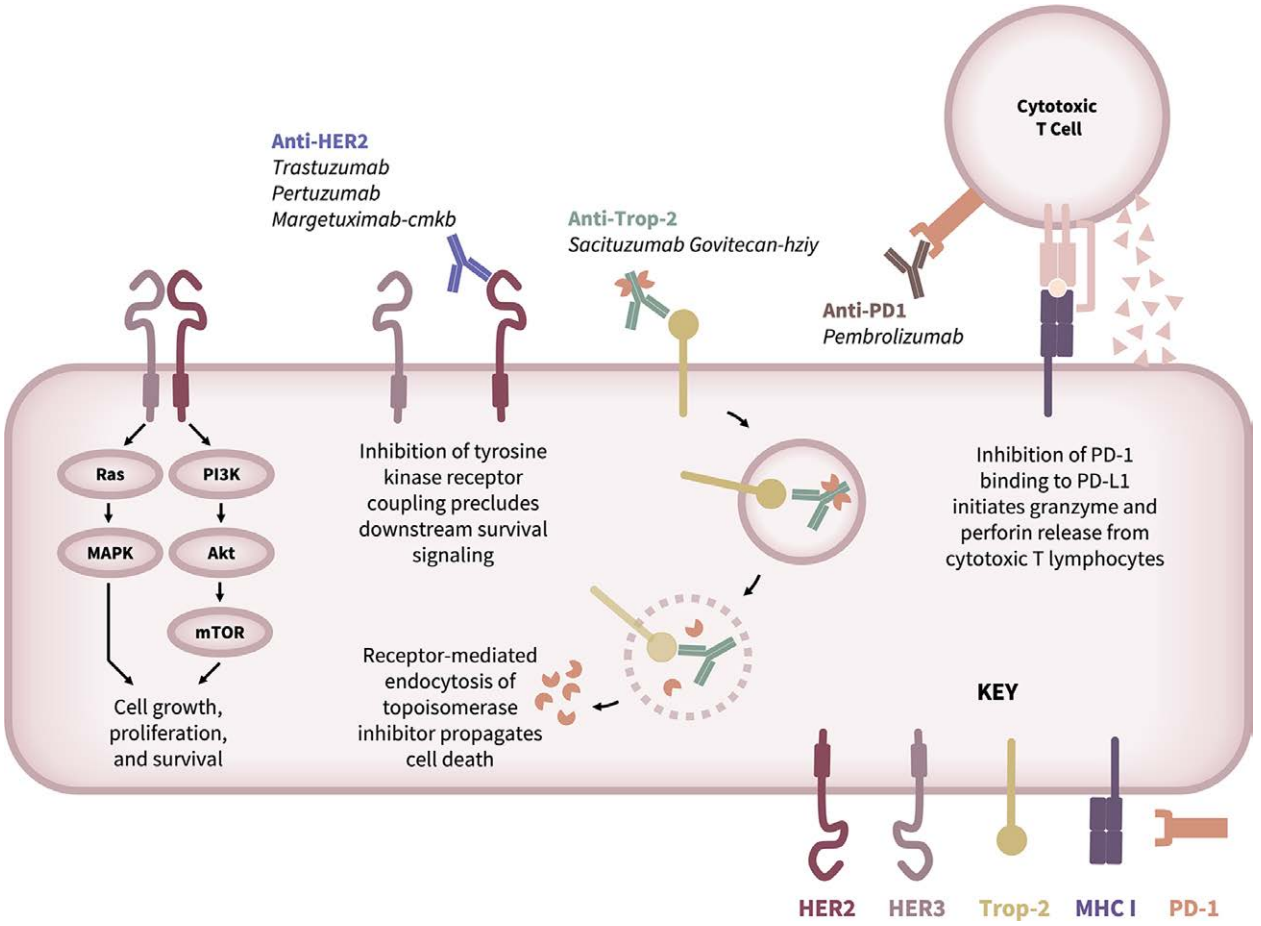

Fig. 1. FDA-approved immunotherapies for the treatment of breast cancer.

medical management with pertuzumab, trastuzumab, or both agents. Like trastuzumab, pertuzumab has FDA black box warnings for heart failure.[10] Patients receiving pertuzumab had almost a 97% increased risk of heart failure and a 67% increased risk of febrile neutropenia.[11,12] Like trastuzumab, trastuzumab warrants a preoperative evaluation including transthoracic echocardiography for assessment of left ventricular ejection fraction in addition to routine laboratories. Given the risk for neutropenia, a low threshold for suspicion of postoperative infection is advised.

Ado-trastuzumab Emtansine

In 2013, trastuzumab was conjugated with the microtubule inhibiting agent DM1, to produce ado-trastuzumab emtansine (Kadcyla). This anti-HER2 microtubule inhibitor conjugate is indicated for refractory metastatic breast cancer and the adjuvant treatment of residual HER2-positive early breast cancer following neoadjuvant therapy. Like trastuzumab and pertuzumab, ado-trastuzumab emtansine has an FDA black box warning for heart failure, with cardiotoxicity reported in 3.37% of patients.[13,14] It also has a black box warning for hepatotoxicity, with hepatitis 3.76 times more likely to occur in patients receiving ado-trastuzumab emtansine than other chemotherapy regimens.[13,15] Pulmonary hypertension was also 3.34 times more likely to occur in patients receiving ado-trastuzumab emtansine than other chemotherapy regimens, which may affect the ability of patients to tolerate general anesthesia.[16] Finally, patients receiving ado-trastuzumab emtansine are 10.66-fold more likely to experience severe thrombocytopenia and experience neutropenia with an incidence rate of 6.7%.[13,16] In addition to routine laboratories, thorough preoperative evaluation of patients receiving trastuzumab includes transthoracic echocardiography for assessment of heart failure and severe pulmonary hypertension and a liver function panel for assessment of hepatitis. Given the risk for thrombocytopenia and neutropenia, low thresholds for suspicion of postoperative infection or hematomas are also advised.

Trastuzumab and Hyaluronidase-oysk

In 2019, subcutaneous co-administration of trastuzumab with hyaluronidase was approved by the FDA as trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) for HER2-overexpressing breast cancer. Like other trastuzumab-based regimens, subcutaneous trastuzumab has black box warnings for heart failure and pulmonary toxicities, such as anaphylaxis, angioedema, interstitial pneumonitis, and ARDS.[17] The incidence of heart failure in patients receiving trastuzumab and hyaluronidase-oysk

is approximately 3.8%; however, 17% of patients experience other cardiac events, including reduced ejection fraction.[17] Neutropenia was reported in 44% of patients, with associated leukopenia, and granulocytopenia in 4% and 1% of patients, respectively.[17] Like other trastuzumab-based regimens, transthoracic echocardiography should be considered for preoperative evaluation. Given the risk for leukopenia and neutropenia, a low threshold for suspicion of postoperative infection is also advised.

Fam-trastuzumab Deruxtecan-nxki

Like ado-trastuzumab emtansine, trastuzumab was again conjugated with a chemotherapeutic agent in 2019 to produce fam-trastuzumab deruxtecan-nxki (Enhertu). This anti-HER2 and topoisomerase inhibitor conjugate is indicated for HER2-positive metastatic breast cancer but also carries indications for advanced gastric cancer and HER2-mutant nonsmall cell lung cancer. Notably, this is the only anti-HER2 agent without a black box warning for heart failure; however, reductions in left ventricular ejection fraction have been observed in 2.7% of patients.[18] Fam-trastuzumab has a black box warning for interstitial lung disease and pneumonitis, with 22% of recipients experiencing respiratory infections.[18] It is also associated with hepatitis in 67% of patients.[18] In addition to routine laboratories, thorough preoperative evaluation of patients receiving trastuzumab includes a liver function panel for assessment of hepatitis. A low threshold for suspicion of postoperative pneumonia is also advised.

Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf

In 2020, the primary anti-HER2 agents pertuzumab and trastuzumab were combined with hyaluronidase to produce subcutaneous *pertuzumab, trastuzumab, and hyaluronidase-zzxf* (Phesgo). This combination was approved for the management of HER2-positive breast cancer and for the neoadjuvant management of locally advanced, inflammatory, or early breast cancer. Notably, there was no significant difference in pathological complete response between patients receiving pertuzumab and trastuzumab with or without hyaluronidase. This regimen has black box warnings for heart failure and pulmonary toxicity, and hepatitis and leukopenia were observed in more than 30% of recipients.[19] Cardiomyopathy, exacerbation of chemotherapy-induced neutropenia, hepatitis. In addition to routine laboratories, thorough preoperative evaluation of patients receiving pertuzumab, trastuzumab, and hyaluronidase-zzxf includes a transthoracic echocardiogram for assessment of heart failure and a liver function panel for assessment of hepatitis. A low threshold for suspicion of postoperative infection is also advised.

Margetuximab-cmkb

Margetuximab-cmkb (Margenza) is the newest anti-HER2 immunotherapy indicated for breast cancer. Specifically, it is indicated in combination with chemotherapy for HER2-positive metastatic breast cancer in patients who have received two or more previous anti-HER2 regimens. Like the humanized anti-HER2 agents trastuzumab and pertuzumab, the chimeric agent margetuximab-cmkb also has an FDA black box warning for heart failure.[20] Left ventricular dysfunction has been reported in 1.9% of patients, and hepatitis, in 32% of patients.[20] Notably, 69% of recipients experience elevated creatinine.[20] In addition to routine laboratories, thorough preoperative evaluation of patients receiving margetuximab-cmkb includes transthoracic echocardiography for assessment of heart failure and a liver function panel for assessment of hepatitis. Given the risk for nephrotoxicity, patient creatinine levels and fluid balance should be closely monitored to avoid concomitant prerenal and intrarenal acute kidney injury.

ANTI-PROGRAMMED CELL DEATH PROTEIN 1

Programmed cell death protein 1 (PD-1, CD279) is a checkpoint receptor on the surface of lymphocytes that mediates the immunologic response to antigens. When host cells present antigens to lymphocytes, they co-express various checkpoint proteins that can tip the immunologic scale toward cell death or survival. One of these checkpoint proteins, programmed death ligand-1 (PD-L1), is expressed by antigen-presenting cells. It binds PD-1 on the surface of lymphocytes and suppresses death signaling. Cells expressing PD-L1 are favored to survive, whereas those without PD-L1 are more likely to undergo apoptosis. Cancer cells overexpressing PD-L1 have a survival advantage because they readily bind PD-1 and repress the innate immune response. Anti-PD-1 antibodies block this survival signaling and promote lymphocyte-mediated cytotoxicity against tumor cells. Although several immune checkpoint inhibitors (ICIs) exist, only one is currently FDA-approved for the treatment of breast cancer.

Pembrolizumab

Pembrolizumab (Keytruda) is an anti-PD-1 ICI indicated for triple-negative breast cancer (TNBC). It also carries indications for several lung, skin, genitourinary, and gastrointestinal cancers, as well as leukemias and lymphomas. Pembrolizumab has been associated with numerous adverse reactions and has black box warnings for infusion-mediated adverse reactions, pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies. It also has FDA warnings for dermatologic adverse reactions and solid organ transplant rejection.[21] Hypothyroidism has been reported in 2.2% of pembrolizumab recipients, and hepatitis has been reported in 20%–30% of recipients.[21] Pembrolizumab has also been associated with an increased risk of pulmonary embolism (incidence 2.4%), pneumonia (incidence 7%), and febrile neutropenia (incidence 14.6%).[21] In addition to routine laboratories, thorough preoperative evaluation of patients receiving pembrolizumab includes thyroid stimulating hormone (TSH), free thyroxine (T4) levels, and a liver function panel to assess for hypothyroidism and hepatitis. Additionally, given the risk for neutropenia, a low threshold for suspicion of postoperative infection is advised.

ANTI-TROPHOBLAST CELL-SURFACE ANTIGEN 2

Trophoblast cell-surface antigen 2 (TROP-2) is a transmembrane glycoprotein that propagates intracellular

survival and proliferation signaling. It is overexpressed in a variety of cancers, making it a promising therapeutic target. Although it interacts with several ligands, its chemotherapeutic potential relies on its ability to facilitate receptor-mediated endocytosis. Monoclonal antibodies against TROP-2 draw several receptors into proximity. This clustering of receptors induces endocytosis of the receptor-antibody complex. Like a Trojan horse, the antibody is conjugated to a chemotherapy agent that is only released once the antibody has traversed into the cancer cell. This mechanism allows the delivery of toxic chemotherapy agents specifically to cancer cells overexpressing TROP-2. Several drugs using this mechanism are in development; however, only one is approved for the treatment of breast cancer.

Sacituzumab Govitecan-hziy

Sacituzumab govitecan-hziy (Trodelvy) is an anti-TROP2 monoclonal antibody conjugated to the topoisomerase inhibitor, SN38.[22] It is indicated for unresectable, locally advanced, or metastatic TNBC but also carries indications for urothelial cancer. Unlike other immunotherapy agents, this immunotherapy has not demonstrated severe cardiotoxic effects; however, it does have black box warnings for severe neutropenia and diarrhea.[22] Given this risk for neutropenia, a low threshold for suspicion of postoperative infection is advised. Additionally, given the risk of diarrhea, electrolytes should be closely monitored and repleted to prevent the sequelae of electrolyte imbalances such as arrhythmias in the setting of hypokalemia.

DISCUSSION

Immunotherapies have become an important tool in the oncologic fight against breast cancer. Therefore, plastic and reconstructive surgeons must be familiar with these drugs and their impacts on perioperative complications. Clinical trials of immunotherapies have offered promising outcomes in terms of overall and event-free survival, but they offer little data to plastic surgeons regarding the optimal timing and extent of reconstructive surgery. Outside these trials, we found very few studies reporting on reconstructive outcomes after immunotherapy. One retrospective analysis by Talwar et al reported a decreased risk of postoperative vascular compromise in patients undergoing autologous breast reconstruction after neoadjuvant immunotherapy with trastuzumab.[23] These results were challenged by Wilson et al, who reported that autologous reconstruction in the setting of neoadjuvant ICI therapy may predispose patients to mastectomy skin necrosis.[24] This group also published evidence that ICIs do not contribute to worse outcomes after nipple-sparing mastectomy.[25] Although interesting, the data are mixed and extremely limited. We need prospective data from reconstructive surgeons to elucidate which unique complication profiles, if any, are attributable to immunotherapies.

The use of immunotherapy for breast cancer management will likely increase in the coming years. Unfortunately, there is no consensus data on the safe washout period between the last cycle of immunotherapy and the first stage of reconstruction, leaving plastic surgeons without evidence-based recommendations for surgical planning. Furthermore, studies assessing the efficacy and safety of dozens of new immunotherapies are ongoing, as are studies assessing these novel agents in combination with RT. On the one hand, RT induces both tumor antigen presentation and systemic immune activation, thus working synergistically with immunotherapy against tumor cells.[26–28] On the other hand, neoadjuvant RT complicates breast reconstruction owing to radio-induced damage of the chest wall and adjacent soft tissues.[29–34] Therefore, this combination therapy may offer a powerful approach to cancer treatment while making the process of postoncologic reconstruction more complex for plastic surgeons.

Evidence from nonbreast cancers may offer some guidance to plastic surgeons looking to plan reconstruction around immunotherapy. In a study comparing neoadjuvant immunochemotherapy to neoadjuvant chemoradiotherapy in patients with locally advanced esophageal squamous cell carcinoma, there was no significant difference in postoperative complications, including cardiac and pulmonary complications, or 30-day mortality between groups.[35] In another study of patients with resectable stage IIIB to IVC melanoma, Patel et al found that patients receiving neoadjuvant-adjuvant pembrolizumab experienced more postoperative complications (7% versus 4%, respectively), fewer immune-related adverse events (12% versus 14%, respectively), and greater event-free survival at 2 years (72% versus 49%, respectively) compared with patients receiving adjuvant-only pembrolizumab.[36] Lung cancer trials also offer robust neoadjuvant data. One randomized controlled trial comparing neoadjuvant platinum chemotherapy with and without the anti-PD-1 agent nivolumab found greater rates of serious adverse events in the immunotherapy arm.[37] Nevertheless, patients receiving nivolumab experienced fewer surgery-related adverse events and fewer adverse events of any severity compared with those receiving chemotherapy alone. An expert consensus on the topic affirmed the perioperative safety of neoadjuvant immunotherapy for nonsmall cell lung cancer, describing the risk profile as akin those of neoadjuvant radiation or chemotherapy.[38] Taken together, these studies suggest oncologic surgery may be safe to perform in the setting of immunotherapy; however, additional evidence regarding reconstructive breast surgery is needed, especially as these novel agents are combined with other treatment modalities.

Reconstructive surgeons should remain cautious when caring for patients receiving immunotherapy. We recommend assessing key immunotherapy adverse reactions and laboratory abnormalities as part of a comprehensive preoperative evaluation. Given the prevalence of thyroid dysfunction induced by ICIs like pembrolizumab, the American Society of Clinical Oncology,[39] the National Comprehensive Cancer Network,[40] and the Society for Immunotherapy of Cancer[41] recommend that patients undergo routine screening TSH and free T4 at least every 4–6 weeks while receiving ICIs. Similarly, the European Society of Medical Oncologists recommends that all patients undergoing ICI therapy should be routinely assessed with serum transaminases, alkaline phosphatase, and bilirubin before every treatment cycle.[42] For

patients on anti-HER2 regimens, the American Heart Association published a scientific statement recommending echocardiography before, during, and every 2–5 years following immunotherapy with an anti-HER2 agent.[43] This Statement also recommends repeat echocardiography for patients experiencing cardiac symptoms after other immunotherapy regimens, including ICI therapy. Although this testing and follow-up is typically managed by medical oncologists and other subspecialists, surgeons should at least ensure that all recommended testing is up to date and within normal limits before proceeding with surgery.

Diligence is also critical in the postoperative period, as immunotherapy-related adverse events (irAEs) may mimic both surgical complications and local oncologic symptoms. For example, immunotherapy-mediated pneumonitis may present with fever, cough, and dyspnea, falsely suggesting postoperative atelectasis or pneumonia. Such irAEs are expected in most patients and facilitate admission in approximately 10%, with as many as 25.9% requiring repeat hospitalizations.[44] Therefore, it is critical for reconstructive surgeons to parse operative complications from irAEs to ensure appropriate treatment. Using Table 1, providers may review drug warnings and precautions and review which factors may aid in preoperative evaluation and postoperative monitoring.

CONCLUSIONS

Immunotherapies are a valuable treatment option for patients with breast cancer, but they present several challenges for plastic and reconstructive surgeons. Using data from clinical trials, we recommend a preoperative evaluation tailored to the immunotherapeutic regimen of individual patients. We also highlight immunotherapy regimens that may predispose to postoperative complications, such as venous thromboembolism, hematoma, and infection. We encourage plastic and reconstructive surgeons to report their experiences operating on patients receiving immunotherapy, as there is a paucity of research available in the setting of reconstructive breast surgery.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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