ASCO special articles

Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update

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abstract

PURPOSE The aim of this work is to update key recommendations of the ASCO guideline adaptation of the Cancer Care Ontario guideline on the selection of optimal adjuvant chemotherapy regimens for early breast cancer and adjuvant targeted therapy for breast cancer.

METHODS An Expert Panel conducted a targeted systematic literature review guided by a signals approach to identify new, potentially practice-changing data that might translate into revised guideline recommendations.

RESULTS The Expert Panel reviewed abstracts from the literature review and identified one article for inclusion that reported results of the phase III, open-label KATHERINE trial. In the KATHERINE trial, patients with stage I to III human epidermal growth factor receptor 2 (HER2)–positive breast cancer with residual invasive disease in the breast or axilla after completing neoadjuvant chemotherapy and HER2-targeted therapy were allocated to adjuvant trastuzumab emtansine (T-DM1; n = 743) or to trastuzumab (n = 743). Invasive disease–free survival was significantly higher in the T-DM1 group than in the trastuzumab arm (hazard ratio, 0.50; 95% CI, 0.39 to 0.64; $P < .001$), and risk of distant recurrence was lower in patients who received T-DM1 than in patients who received trastuzumab (hazard ratio, 0.60; 95% CI, 0.45 to 0.79). Grade 3 or higher adverse events occurred in 190 patients (25.7%) who received T-DM1 and in 111 patients (15.4%) who received trastuzumab.

RECOMMENDATIONS Patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and HER2-targeted therapy should be offered 14 cycles of adjuvant T-DM1, unless there is disease recurrence or unmanageable toxicity. Clinicians may offer any of the available and approved formulations of trastuzumab, including trastuzumab, trastuzumab and hyaluronidase-oysk, and available biosimilars.

Additional information can be found at www.asco.org/breast-cancer-guidelines

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

In 2016, ASCO published an adaptation of the Cancer Care Ontario (CCO) guideline on the selection of optimal adjuvant chemotherapy regimens for early breast cancer and adjuvant targeted therapy for human epidermal growth factor receptor 2 (HER2)–positive breast cancers.[1] ASCO updates its guidelines at intervals determined by the Expert Panel co-chairs on the basis of targeted literature searching and the expertise of ASCO guideline panel members to identify signals[2] in the literature. ASCO published a focused update of the 2016 guideline adaptation in 2018.[3] The present update was prompted largely by the publication of the KATHERINE phase III trial[4] relevant to the clinical care of patients with breast cancer.

This focused update of the 2018 guideline adaptation provides a new recommendation for the use adjuvant trastuzumab emtansine (T-DM1) after completion of standard preoperative chemotherapy and HER2-targeted therapy in patients with HER2-positive breast cancer with residual invasive cancer in the breast or lymph nodes at surgery. The Expert Panel also decided, in part on the basis of input from members of ASCO's Breast Cancer Guideline Advisory Group, to expand the guideline update scope to address the use of biosimilar forms of trastuzumab. To date, five trastuzumab biosimilars have been approved

THE BOTTOM LINE

Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update

Questions Addressed in Focused Update

Should adjuvant trastuzumab emtansine be offered after completion of standard preoperative chemotherapy and human epidermal growth factor receptor 2 (HER2)–targeted therapy in patients with HER2-positive breast cancer with residual invasive cancer in the breast or lymph nodes at surgery?

Among patients with HER2-positive breast cancer who receive adjuvant trastuzumab therapy, do trastuzumab, trastuzumab and hyaluronidase-oysk, and currently available US Food and Drug Administration–approved biosimilars of trastuzumab differ with respect to safety or efficacy?

Target Population

Patients who have undergone preoperative standard chemotherapy and HER2-targeted therapy being considered for, or who are receiving, systemic therapy after definitive surgery for early-stage invasive breast cancer. (Concomitant endocrine therapy and radiation were allowed according to trial protocol and institutional guidelines).

Target Audience

Medical oncologists, pathologists, surgeons, oncology nurses, patients, and caregivers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations on the basis of a review of signals in the medical literature on the optimal use of adjuvant cytotoxic chemotherapy and HER2-directed therapy.

Focused Update Recommendations

Recommendation 1.1. Patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and HER2-targeted therapy should be offered 14 cycles of adjuvant trastuzumab emtansine, unless there is disease recurrence or unmanageable toxicity (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 2.1. Clinicians may offer any of the available and approved formulations of trastuzumab, including trastuzumab, trastuzumab and hyaluronidase-oysk, and available biosimilars (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
Refer to Table 1 for the full list of recommendations from the guideline adaptation.

Additional Resources

More information, including a supplement, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

by the US Food and Drug Administration (FDA). This new recommendation is intended to supplement the existing trastuzumab-related recommendations issued by the Expert Panel in the 2018 update (Table 1). The remaining recommendations from the 2018 ASCO guideline adaptation are unchanged because there were no new potentially practice-changing data to support substantive revisions.

FOCUSED GUIDELINE UPDATE QUESTIONS

Clinical Question 1: Should adjuvant T-DM1 be administered after completion of standard preoperative chemotherapy and HER2-targeted therapy in all patients with HER2-positive breast cancer with residual invasive cancer in the breast or lymph nodes at surgery?

Clinical Question 2: Among patients with HER2-positive breast cancer who receive adjuvant trastuzumab therapy, do trastuzumab, trastuzumab and hyaluronidase-oysk, and currently available FDA-approved biosimilars of trastuzumab differ with respect to safety or efficacy?

METHODS

Guideline Update Process

ASCO uses a signals approach to facilitate guideline updating.[2] This approach identifies new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted literature searching and the expertise of ASCO guideline panel members to identify these signals.

For this focused update, one phase III randomized adjuvant trial[4] provided the signal. On the basis of this signal, the ASCO Breast Cancer Advisory Group ranked updating the

TABLE 1. Complete List of Recommendations From 2018 ASCO Guideline Adaptation and From the ASCO 2020 Focused Guideline Update

Recommendation	Evidence Rating
New Recommendations From 2020 Focused Guideline Update	
Patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and HER2-targeted therapy should be offered 14 cycles of adjuvant T-DM1, unless there is disease recurrence or unmanageable toxicity.	Type: evidence based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong
Clinicians may offer any of the available and approved formulations of trastuzumab, including trastuzumab, trastuzumab and hyaluronidase-oysk, and available biosimilars.	Type: evidence based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong
Recommendations Unchanged From 2018 Guideline Adaptation[a]	
In patients who can tolerate it, use of a regimen containing anthracycline-taxane is considered the optimal strategy for adjuvant chemotherapy, particularly for patients deemed to be at high risk.	
For patients with high-risk disease who will not receive a taxane, an optimal-dose anthracycline three-drug regimen (cumulative dose of doxorubicin ≥ 240 mg/m^2 or epirubicin ≥ 600 mg/m^2, but no higher than 720 mg/m^2) that contains cyclophosphamide is recommended. The cumulative dose of doxorubicin in two-drug regimens should not exceed 240 mg/m^2.	
The addition of gemcitabine or capecitabine to an anthracycline-taxane regimen is not recommended for adjuvant chemotherapy.	
In patients age 65 years or older, capecitabine is not recommended as an adjuvant chemotherapy option in lieu of standard regimens, such as doxorubicin-cyclophosphamide or cyclophosphamide-methotrexate-fluorouracil (with oral cyclophosphamide).	
For patients in whom anthracycline-taxane is contraindicated, cyclophosphamide-methotrexate-fluorouracil (with oral cyclophosphamide) is an acceptable chemotherapy alternative to doxorubicin-cyclophosphamide. Of note, the ASCO Panel recommends classic cyclophosphamide-methotrexate-fluorouracil (oral cyclophosphamide days 1 to 14 with IV methotrexate-fluorouracil days 1 and 8, repeated once every 28 days for six cycles) as the default adjuvant cyclophosphamide-methotrexate-fluorouracil regimen. However, the Panel also recognizes that an all-IV cyclophosphamide-methotrexate-fluorouracil regimen once every 21 days is often used in clinical practice and was accepted by some clinical trials (eg, TAILORx; Trial Assigning Individualized Options for Treatment) on the basis of convenience and tolerability, despite the absence of efficacy data from randomized controlled trials.	
These adjuvant chemotherapy regimens can be used for patients with early breast cancer:	
Fluorouracil-epirubicin-cyclophosphamide × 3 → docetaxel × 3 (superior to fluorouracil-epirubicin-cyclophosphamide × 6)	
Doxorubicin-cyclophosphamide × 4 → docetaxel × 4 (superior to doxorubicin-cyclophosphamide × 4)	
Docetaxel-doxorubicin-cyclophosphamide × 6 (superior to fluorouracil-doxorubicin-cyclophosphamide × 6)	
Doxorubicin-cyclophosphamide × 4 → paclitaxel administered once per week	
Dose-dense doxorubicin-cyclophosphamide → paclitaxel administered once every 2 weeks	
Dose-dense epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2 every 2 weeks four cycles → paclitaxel 175 mg/m^2 every 2 weeks for four cycles	
Docetaxel-cyclophosphamide × 4 is recommended as an alternative to doxorubicin-cyclophosphamide × 4 and offers improved disease-free survival and overall survival. Classic cyclophosphamide-methotrexate-fluorouracil with oral cyclophosphamide for six cycles is another option. As mentioned before, the ASCO Panel recommends classic cyclophosphamide-methotrexate-fluorouracil (oral cyclophosphamide days 1 to 14 with IV methotrexate-fluorouracil days 1 and 8, repeated once every 28 days for six cycles) as the default adjuvant cyclophosphamide-methotrexate-fluorouracil regimen. However, the Panel also recognizes that an all-IV cyclophosphamide-methotrexate-fluorouracil regimen once every 21 days is often used in clinical practice and was accepted by some clinical trials (eg, TAILORx) on the basis of its convenience and tolerability, despite the absence of efficacy data from randomized controlled trials.	
Only patients with HER2-positive breast cancer (overexpressed on the basis of immunohistochemistry [3+] or amplified on the basis of in situ hybridization [ratio > 2.0 or average HER2 copy number ≥ 6.0]) should be offered adjuvant trastuzumab.	
Trastuzumab plus chemotherapy is recommended for all patients with HER2-positive, node-positive breast cancer and for patients with HER2-positive, node-negative breast cancer (> 1 cm)	
Trastuzumab therapy can be considered in small, node-negative tumors (≤ 1 cm).	
Trastuzumab can be administered with any acceptable adjuvant chemotherapy regimen.	

(continued on following page)

TABLE 1. Complete List of Recommendations From 2018 ASCO Guideline Adaptation and From the ASCO 2020 Focused Guideline Update (continued)

New Recommendations From 2020 Focused Guideline Update

Recommendation	Evidence Rating
The administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is not recommended because of the potential for increased cardiotoxicity.	
Trastuzumab should be preferentially administered concurrently (not sequentially) with a nonanthracycline chemotherapy regimen.	
Less cardiotoxicity is seen with docetaxel-carboplatin-trastuzumab than with doxorubicin-cyclophosphamide → docetaxel-trastuzumab, and docetaxel-carboplatin-trastuzumab is recommended for patients at higher risk for cardiotoxicity.	
No phase III evidence exists for the addition of trastuzumab to some chemotherapy regimens, such as docetaxel-cyclophosphamide. However, those regimens might be in use and are reasonable options, particularly for mitigating cardiotoxicity in certain patients.	
Patients should be offered 1 year total of adjuvant trastuzumab, with regular assessments of cardiac function during that period.	
Patients with early-stage, HER2-negative breast cancer with pathologic invasive residual disease at surgery after standard anthracycline and taxane-based preoperative therapy may be offered up to six to eight cycles of adjuvant capecitabine.	
Qualifying Statements. If clinicians decide to use capecitabine, then the Expert Panel preferentially supports the use of adjuvant capecitabine in the hormone receptor–negative, HER2-negative patient subgroup. The capecitabine dose used in the CREATE-X study (1,250 mg/m^2 twice daily) is associated with higher toxicity in patients age ≥ 65 years.	
Clinicians may add 1 year of adjuvant pertuzumab to trastuzumab-based combination chemotherapy in patients with early-stage, HER2-positive breast cancer.	
Qualifying Statements. The Expert Panel preferentially supports pertuzumab in the node-positive, HER2-positive population, in view of the clinically insignificant absolute benefit observed among node-negative patients. After a median follow up of 3.8 years, pertuzumab was found to offer a modest disease-free survival benefit; the first planned interim analysis did not show an overall survival benefit. There are no data to guide the duration of pertuzumab in patients who received neoadjuvant pertuzumab and achieved a pathologic complete response.	
Clinicians may use extended adjuvant therapy with neratinib in patients with early-stage, HER2-positive breast cancer.	
Neratinib causes substantial diarrhea, and diarrhea prophylaxis must be used.	
Qualifying Statements. The Expert Panel preferentially favors the use of neratinib in hormone receptor–positive and node-positive patients. At 5.2-year follow up, no overall survival benefit has been observed. Patients who began neratinib within 1 year of trastuzumab completion seemed to derive the greatest benefit. There are no data on the added benefit of neratinib in patients who also received pertuzumab in the neoadjuvant or adjuvant setting.	

Abbreviations: HER2, human epidermal growth factor receptor 1; IV, intravenous; T-DM1, trastuzumab emtansine.

[a]Evidence and analysis for recommendations unchanged from 2018 are described in Eisen et al,[5] and later by Denduluri et al,[1,3] in ASCO's adaptation of the Cancer Care Ontario guideline in 2016 and in the 2018 focused update of that adaptation.

adjuvant therapy guideline adaptation among its highest priorities. To that end, ASCO convened an Expert Panel to review the evidence and formulate updated recommendations for practice. In addition, the Expert Panel decided to expand the scope of the present update to amend the trastuzumab-related recommendations from the 2018 guideline update.[3] The new recommendation addresses the use of biosimilar forms of this HER2-targeted therapy.

This systematic review–based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel searched the PubMed database to identify any additional randomized controlled trials that addressed the focused update's one clinical question. The Methodology Manual available at www.asco.org/guideline-methodology provides additional information about the guideline update approach. Additional information about the results of the updated literature search and search strategy strings and results is reported in the supplement.

The entire Expert Panel (Appendix Table A1, online only) contributed to the development of the guideline, provided critical review, and finalized the guideline recommendations. The ASCO Clinical Practice Guidelines Committee reviews and approves all ASCO guidelines. All funding for the administration of the project was provided by ASCO.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

The broad PubMed search—from January 1, 2018 to February 19, 2020—that was conducted to identify publications reporting on studies that addressed the clinical question yielded a total of 10 records; the search string included the terms Ado-Trastuzumab Emtansine AND Breast Neoplasms (Data Supplement, online only). Articles were selected for inclusion in the systematic review of the evidence if they were phase III randomized controlled trials of adjuvant trastuzumab emtansine (T-DM1) that enrolled patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and HER2-targeted therapy. Articles were excluded from the systematic review if they were meeting abstracts not subsequently published in peer-reviewed journals; editorials, commentaries, letters, news articles, case reports, or narrative reviews; or published in a non-English language. After review of the identified abstracts, one full-text article reporting on a phase III clinical trial, the KATHERINE trial,[4] was selected for review by the Expert Panel.

No additional formal literature search was conducted to inform the recommendation concerning the use of the various formulations of trastuzumab, including trastuzumab biosimilars. Evidence related to the use of trastuzumab reviewed for the original CCO guideline on selection of

optimal adjuvant chemotherapy regimens for early breast cancer and adjuvant targeted therapy for HER2-positive breast cancers was described by Eisen et al,[5] and later by Denduluri et al,[1,3] in ASCO's adaptation of the CCO guideline in 2016 and the 2018 focused update of that adaptation. Data informing the FDA's approval of the trastuzumab biosimilar are reported in the FDA-approved labels for the five products. The labels include data from pharmacodynamic and pharmacokinetic studies, studies of immunogenicity and other toxicities, and any additional studies evaluating efficacy, comparative clinical dose ranging, and safety[6] for each of the approved trastuzumab biosimilars. The reader is referred to the relevant FDA-approved labels that are accessible at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

FOCUSED UPDATE RECOMMENDATIONS

CLINICAL QUESTION 1

Should adjuvant T-DM1 be offered after the completion of standard preoperative chemotherapy and HER2-targeted therapy in patients with HER2-positive breast cancer with residual invasive cancer in the breast or lymph nodes at surgery?

Recommendation 1.1. Patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and HER2-targeted therapy should be offered 14 cycles of adjuvant T-DM1, unless there is disease recurrence or unmanageable toxicity (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Literature review and analysis. The KATHERINE open-label, phase III clinical trial (Table 2) compared adjuvant T-DM1 with trastuzumab in patients with stage I to III HER2-positive breast cancer who had residual invasive disease in the breast or axilla after completing neoadjuvant chemotherapy plus HER2-targeted therapy.[4] Patients were randomly assigned to receive either postoperative T-DM1 (n = 743) at a dose of 3.6 mg per kilogram of body weight or trastuzumab (n = 743) at a dose of 6 mg per kilogram intravenously every 3 weeks for 14 cycles (42 weeks). Random assignment occurred irrespective of postoperative HER2 status. Concomitant endocrine therapy and radiation were allowed according to trial protocol and institutional guidelines. Invasive disease–free survival—defined as freedom from ipsilateral invasive breast tumor recurrence, ipsilateral locoregional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, or death from any cause—was the primary end point of the trial.

Approximately 18% of patients received dual HER2 targeted therapy with trastuzumab and pertuzumab. Invasive disease or death occurred in 91 patients (12.2%) who had received T-DM1 and in 165 patients (22.2%) who had received trastuzumab. In the T-DM1 group, the estimated percentage of patients free of invasive disease at 3 years was 88.3, and the estimated percentage in the trastuzumab group was 77.0. Invasive disease–free survival was significantly higher in the T-DM1 group than in the trastuzumab arm (hazard ratio, 0.50; 95% CI, 0.39 to 0.64; $P < .001$), and the risk of distant recurrence was lower in patients who received T-DM1 than in patients who received trastuzumab (hazard ratio, 0.60; 95% CI, 0.45 to 0.79). T-DM1 benefit was noted irrespective of baseline characteristics, postoperative tumor size, nodal status, hormone receptor status, chemotherapy, and HER2 targeted therapy backbone.

Safety analyses revealed that a higher percentage of patients in the T-DM1 group experienced adverse events than did patients in the trastuzumab group. Grade 3 or higher adverse events occurred in 190 patients (25.7%) who received T-DM1 and in 111 patients (15.4%) who received trastuzumab. Serious adverse events occurred in 94 patients (12.7%) in the T-DM1 group and 58 patients (8.1%) in the trastuzumab group. Peripheral sensory neuropathy (any grade) was reported in 18.6% of patients who received T-DM1 and in 6.9% of patients who received trastuzumab. There was a higher incidence of radiation pneumonitis in the T-DM1 group (11 patients [1.5%]) than in the control group (5 patients [0.7%]), although all cases were resolved at the data cutoff point. An adverse event that led to discontinuation of the trial drug occurred in 133 patients (18.0%) in the T-DM1 group and 15 patients (2.1%) in the trastuzumab group. Of the 133 patients who discontinued T-DM1 early, 71 switched to trastuzumab and 63 completed 14 total cycles of HER2 targeted therapy postoperatively.

These data underscore the need for multidisciplinary management and consideration of preoperative systemic therapy in select patients with HER2-positive breast cancer to further tailor adjuvant therapy. Future trials should focus on optimizing outcomes on the basis of risk for recurrence and response to HER2 targeted therapy.

CLINICAL QUESTION 2

Among patients with HER2-positive breast cancer who receive adjuvant trastuzumab therapy, do trastuzumab, trastuzumab and hyaluronidase-oysk, and currently available FDA-approved biosimilars of trastuzumab differ with respect to safety or efficacy?

Recommendation 2.1. Clinicians may offer any of the available and approved formulations of trastuzumab, including trastuzumab, trastuzumab and hyaluronidase-oysk, and available biosimilars (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Literature review and analysis. To date, the FDA has approved five biosimilar formulations of trastuzumab. Relevant data for the five trastuzumab biosimilars are reported

TABLE 2. Results of the KATHERINE Open-Label, Phase III Clinical Trial

Source	Intervention/Comparison	Primary End Point	No. of Patients Evaluated	Survival		Safety Outcome
				3-Year Invasive DFS, (estimated %)	Distant Recurrence as First Invasive Disease Event, No. of Patients (%)	
von Minckwitz et al[4]	Adjuvant T-DM1 for 14 cycles after receiving neoadjuvant therapy containing a taxane (with or without anthracycline) and trastuzumab	Primary: Invasive DFS (defined as freedom from ipsilateral invasive breast tumor recurrence, ipsilateral locoregional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, or death from any cause). Secondary: DFS, including noninvasive breast cancers, OS, distant recurrence–free survival, and safety	743	88.3	78 (10.5)	71.4% of patients in the T-DM1 group completed all 14 cycles of therapy *v* 81.0% of patients in the trastuzumab group. Grade 3 or higher AEs occurred in 190 patients (25.7%) who received T-DM1. Most common Grade 3 or higher AEs were decreased platelet count (5.7%) and hypertension (2.0%). Grade 3 or higher adverse events occurred in and in 111 patients (15.4%) who received trastuzumab. Most common Grade 3 or higher AEs were hypertension (1.2%) and radiation-related skin injury (1.0%). Serious AEs occurred in 94 patients (12.7%) in the T-DM1 group and in 15 patients (8.1%) in the trastuzumab group. AEs leading to discontinuation of study drug occurred in 133 patients (18.0%) in the T-DM1 group and in 15 (2.1%) in the trastuzumab group.
	Adjuvant trastuzumab for 14 cycles after receiving neoadjuvant therapy containing a taxane (with or without anthracycline) and trastuzumab		743	77.0 Invasive DFS significantly higher among patients who received T-DM1 *v* trastuzumab (HR, 0.50; 95% CI, 0.39 to 0.64; $P < .001$)	118 (15.9) Risk of distant recurrence lower in the T-DM1 group *v* trastuzumab group (HR, 0.60; 95% CI, 0.45 to 0.79)	

Abbreviations: AE, adverse event; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; T-DM1, trastuzumab emtansine.

in the FDA-approved labels for each the approved products: trastuzumab-dkst,[7] trastuzumab-pkrb,[8] trastuzumab-anns,[9] trastuzumab-dttb,[10] and trastuzumab-qyyp.[11] The Expert Panel acknowledges and reinforces ASCO's call for ongoing patient and professional education on biosimilars to establish and maintain confidence in their safety and efficacy as their accessibility grows.[12] Furthermore, post-approval surveillance will be crucial to track the safety, effectiveness, and clinical usefulness of biosimilars as they are integrated into clinical practice.[6]

COST CONSIDERATIONS IN THE SELECTION OF OPTIMAL ADJUVANT CHEMOTHERAPY AND ADJUVANT TARGETED THERAPY FOR BREAST CANCER

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance. Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[13,14]

Of note, medication prices of these agents vary markedly, depending on negotiated discounts and rebates. Discussion of cost can be an important part of shared decision making. Clinicians should exercise judgment and, whenever it is practical and feasible, discuss with patients the use of less expensive alternatives when considering two or more treatment options that are comparable in terms of benefits and harms.[15]

Depending on a patient's particular insurance coverage, reimbursement for the various agents may originate in their medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between pharmacies. Patients should be asked about their financial concerns by their caregivers and be offered financial counseling to address this complex and heterogeneous landscape.[15]

Cost-effectiveness analyses can help highlight which costly treatments offer the greatest value, especially when multiple costly treatments are available. Conducting a formal cost-effectiveness analysis to guide the selection of an optimal targeted adjuvant therapy was beyond the scope of this guideline; however, several manuscripts have analyzed the cost effectiveness of targeted therapies for breast cancer.[16-22]

OPEN COMMENT

The draft recommendation was released to the public for open comment from June 8, 2020, through June 22, 2020. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree, see comments" were captured for every proposed recommendation, with five written comments received across draft recommendations. All 12 respondents agreed (92%) or agreed with slight modifications (8%; one written comment) with the draft T-DM1 recommendation as drafted. All 12 respondents agreed with the recommendation concerning the use of any of the available and approved formulations of trastuzumab as drafted. The Expert Panel co-chairs reviewed comments from all sources and determined whether to maintain the original draft recommendations, revise with minor language changes, or consider major recommendation revisions. A single minor wording change was made to the T-DM1 clinical question on the basis the feedback. All changes were incorporated before ASCO Clinical Practice Guidelines Committee final review and approval.

ADDITIONAL RESOURCES

Additional Information including a supplement, and clinical tools and resources can be found at www.asco.org/breast-cancer-guidelines. Patient information is available there and at www.cancer.net.

RELATED ASCO GUIDELINES

Patient-Clinician Communication[23] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer[24] (http://ascopubs.org/doi/10.1200/JCO.2017.74.0472)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/breast-cancer-guidelines

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Denduluri N, Somerfield MR, Eisen A, et al: Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2) -negative and adjuvant targeted therapy for HER2-positive breast cancers: An American Society of Clinical Oncology guideline adaptation of the Cancer Care Ontario clinical practice guideline. J Clin Oncol 34:2416-2427, 2016
2. Shojania KG, Sampson M, Ansari MT, et al: How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 147:224-233, 2007
3. Denduluri N, Chavez-MacGregor M, Telli ML, et al: Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO Clinical Practice Guideline Focused Update. J Clin Oncol 36:2433-2443, 2018
4. von Minckwitz G, Huang CS, Mano MS, et al:KATHERINE Investigators: Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 380:617-628, 2019
5. Eisen A, Fletcher GG, Gandhi S, et al: Optimal systemic therapy for early breast cancer in women: A clinical practice guideline. Curr Oncol 22:S67-S81, 2015 (suppl 1)
6. Lyman GH, Zon R, Harvey RD, et al: Rationale, opportunities, and reality of biosimilar medications. N Engl J Med 378:2036-2044, 2018
7. Mylan: Ogivri (trastuzumab-dkst) [package insert]. Canonsville, PA, Mylan, 2017
8. Celltrion: Herzuma (trastuzumab-pkrb) [package insert]. Incheon, Republic of Korea, Celltrion, 2018
9. Amgen: Kanjinti (trastuzumab-anns) [package insert]. Thousand Oaks, CA, Amgen, 2019
10. Samsung Bioepis: Ontruzant (trastuzumab-dttb) [package insert]. Incheon, Republic of Korea, Samsung Bioepis, 2019
11. Pfizer: Trazimera (trastuzumab-qyyp) [package insert]. New York, NY, Pfizer, 2019
12. Lyman GH, Balaban E, Diaz M, et al: American Society of Clinical Oncology statement: Biosimilars in oncology. J Clin Oncol 36:1260-1265, 2018
13. Dusetzina SB, Winn AN, Abel GA, et al: Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol 32: 306-311, 2014
14. Streeter SB, Schwartzberg L, Husain N, et al: Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. J Oncol Pract 7:46s-51s, 2011 (suppl)
15. Meropol NJ, Schrag D, Smith TJ, et al: American Society of Clinical Oncology guidance statement: The cost of cancer care. J Clin Oncol 27:3868-3874, 2009
16. Diaby V, Tawk R, Sanogo V, et al: A review of systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer. Breast Cancer Res Treat 151:27-40, 2015
17. Garrison LP Jr, Babigumira J, Tournier C, et al: Cost-effectiveness analysis of pertuzumab with trastuzumab and chemotherapy compared to trastuzumab and chemotherapy in the adjuvant treatment of HER2-positive breast cancer in the United States. Value Health 22:408-415, 2019 [Erratum: Value Health 22:843, 2019]
18. Schwartz NRM, Flanagan MR, Babigumira JB, et al: Cost-effectiveness analysis of adjuvant neratinib following trastuzumab in early-stage HER2-positive breast cancer. J Manag Care Spec Pharm 25:1133-1139, 2019
19. Clarke CS, Hunter RM, Shemilt I, et al: Multi-arm cost-effectiveness analysis (CEA) comparing different durations of adjuvant trastuzumab in early breast cancer, from the English NHS payer perspective. PLoS One 12:e0172731, 2017
20. Hajjar A, Ergun MA, Alagoz O, et al: Cost-effectiveness of adjuvant paclitaxel and trastuzumab for early-stage node-negative, HER2-positive breast cancer. PLoS One 14:e0217778, 2019
21. Genuino AJ, Chaikledkaew U, Guerrero AM, et al: Cost-utility analysis of adjuvant trastuzumab therapy for HER2-positive early-stage breast cancer in the Philippines. BMC Health Serv Res 19:874, 2019
22. Hassett MJ, Li H, Burstein HJ, et al: Neoadjuvant treatment strategies for HER2-positive breast cancer: Cost-effectiveness and quality of life outcomes. Breast Cancer Res Treat 181:43-51, 2020
23. Gilligan T, Coyle N, Frankel RM, et al: Patient-clinician communication: American Society of Clinical Oncology consensus guideline. J Clin Oncol 35:3618-3632, 2017
24. Krop I, Ismaila N, Andre F, et al: Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. J Clin Oncol 35:2838-2847, 2017

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update

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APPENDIX

TABLE A1. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Guideline Update Expert Panel Membership

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Abbreviation: PGIN, Practice Guidelines Implementation Network.