



Evidence-based Series 1-15 Version 3- EDUCATION AND INFORMATION 2014

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

**The Role of Trastuzumab (Herceptin®) in the Treatment of
Women with HER2/*neu*-overexpressing Metastatic Breast Cancer**

Members of the Breast Cancer Disease Site Group

An assessment conducted in January 2014 put Evidence-based Series (EBS) 1-15 Version 3 in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

Evidence-based Series (EBS) 1-15 Version 3, the resulting review report, consists of the following 4 parts:

1. Guideline Report Overview
2. Summary
3. Full Report
4. Document Assessment and Review Tool

and is available on the CCO Web site (<http://www.cancercare.on.ca>)

PEBC Breast Cancer DSG page at:

<http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-eb/>

Release Date: September 15, 2011

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Table of Contents

Overview

Guideline Report History	iii
Guideline Review Summary	iv

Summary (November 2005)

Guideline Questions	vi
Question 1	vi
Question 2	viii
Question 3	viii
Question 4	ix
Question 5	ix
Contact Information	x
Preamble, Copyright, & Disclaimer	xi

FULL REPORT (November 2005)

Questions.....	1
Choice of Topic and Rationale	1
Methods	2
Results.....	3
Interpretative Summary	11
Ongoing trials.....	14
Implication for policy	14
External Review.....	15
Practice guideline	19
Conflict of interest	19
Journal Reference	19
Acknowledgements	19
References.....	20
EBS 1-15 Document Assessment Review Tool	24



Evidence-based Series 1-15 Version 3

The Role of Trastuzumab (Herceptin®) in the Treatment of Women with HER2/*neu*-overexpressing Metastatic Breast Cancer

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version October 1999	1995- 1998	Evidence Summary	Peer review publication ¹ Web publication	<ul style="list-style-type: none"> • Original title: “Use of Trastuzumab (Herceptin) in Breast Cancer” • Available evidence was not enough to base a Practice Guideline • Literature search was updated in 2000, 2002, and 2003
Version 2 Nov 2005	1995-2004	Practice guideline replaced the original Evidence Summary	Updated Web publication.	<ul style="list-style-type: none"> • Recommendations added
Version 3 Sep 2011	2004 - 2009	New data found; see Document Assessment & Review Tool	Updated Web publication	<ul style="list-style-type: none"> • New evidence supports and does not contradict existing recommendations • 2004 recommendations ENDORSED with additional qualifying statements / recommendations

1 Crump M, O'Malley F, Pritchard K, Levine M, Johnson M; Breast Cancer Disease Site Group. The use of trastuzumab (Herceptin) for the treatment of metastatic breast cancer and methods of assessing HER2/*neu* status - an evidence summary. *Curr Oncol.* 2000;7(4);242-51.



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Evidence-based Series 1-15 Version 3 ARCHIVED 2014

The Role of Trastuzumab (Herceptin®) in the Treatment of Women with HER2/*neu*-overexpressing Metastatic Breast Cancer

Guideline Review Summary

Review Date: June 11, 2010

The 2005 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care, Cancer Care Ontario, in 1999, as an evidence summary, and the practice guideline version released in 2005. In 2010, the PEBC guideline update strategy was applied and the new updated document released in September 2011. The Summary and the Full Report in this version are the same as in the 2005 version.

Update Strategy

Using the [Document Assessment & Review Tool](#) (located at the end of this report), the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

In women with HER2/*neu*-overexpressing metastatic breast cancer:

1. Does trastuzumab, alone or in combination with other systemic therapy, in first-line chemotherapy and beyond, improve clinically meaningful outcomes (overall response rates, time-to-disease progression, overall survival, toxicity, or quality of life) compared with systemic therapy without trastuzumab?

2. Does continued use of trastuzumab beyond disease progression improve clinically meaningful outcomes compared with discontinuing trastuzumab?
3. What are the adverse events associated with trastuzumab therapy?
4. What are the optimal dose, schedule, and duration for trastuzumab therapy?

Literature Search and New Evidence

The new search (August 2004 - September 2009) yielded 12 references representing eight randomized controlled trials (RCTs) evaluating trastuzumab on one arm. Three of the RCTs were already included in the existing guideline. Five RCTs are potentially new studies, of which four were in abstract form, and one had a full text publication. Brief results of these publications are shown in the [Document Assessment & Review Tool](#) at the end of this report.

Impact on Guidelines and Its Recommendations

The new evidence does not contradict existing recommendations; however, the new evidence includes comparisons of trastuzumab with other agents not addressed in the existing guideline (capecitabine, the hormones anastrozole and letrozole, and lapatinib) that could be used to expand these recommendations. Rather than a full update, the Breast DSG **ENDORSED** the guideline, with the following note to expand the recommendations/qualifying statements:

- The previous version of the guideline recommended the use of trastuzumab only with taxane chemotherapy as first-line therapy for metastatic breast cancer. Several qualifying statements stated that no data addressed second-line therapy and beyond, limited phase II data supported the use of vinorelbine plus trastuzumab after anthracycline/taxane exposure, no data addressed single agent trastuzumab in first or second line therapy and beyond, the addition of another chemotherapy to trastuzumab at progression, or the continuation of trastuzumab beyond disease progression. Since the initial publication, new data has emerged to formulate new Qualifying Statements:
 - Phase III data from a full-text publication shows benefit in TTP and ORR for trastuzumab in combination with capecitabine in second-line chemotherapy and beyond
 - Phase III data from abstracts show benefit in ORR, TTP, PFS, and OS for trastuzumab in combination with letrozole or anastrozole as first-line treatment of hormone-sensitive metastatic breast cancer
 - Phase III data from abstracts show benefit in PFS and OS for trastuzumab added to lapatinib compared with lapatinib alone
 - Further phase III data from abstracts confirm adverse cardiac effects for trastuzumab in combination with anthracycline
 - New data supports continuation of trastuzumab beyond disease progression (SAR)
No new data has emerged regarding the dose or schedule of trastuzumab



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The Role of Trastuzumab (Herceptin®) in the Treatment of Women with HER2/*neu*-overexpressing Metastatic Breast Cancer Practice Guideline Report #1-15 (Version 2.2004)

*M. Crump, M. Trudeau, S. Sinclair, F. O'Malley, and
members of the Breast Cancer Disease Site Group*

Please see the EBS 1-15 Version 2 Guideline Review [Summary](#)
and the [Document Assessment & Review Tool](#)
for the summary of updated evidence published between 2005 and 2009.

Report Date: November 8, 2005

SUMMARY

Guideline Questions

In women with HER2/*neu*-overexpressing metastatic breast cancer:

1. Compared with chemotherapy alone, does trastuzumab in combination with chemotherapy improve clinically meaningful outcomes (overall response rates, time-to-disease progression, overall survival, toxicity, or quality of life)?
2. Compared with placebo or observation, does single-agent trastuzumab therapy improve clinically meaningful outcomes?
3. What is the best way to identify women who will benefit from trastuzumab therapy?
4. What are the adverse events associated with trastuzumab therapy?
5. What are the optimal dose, schedule, and duration for trastuzumab therapy?

Question #1

Compared with chemotherapy alone, does trastuzumab in combination with chemotherapy improve clinically meaningful outcomes?

Recommendations

- Trastuzumab in combination with either six cycles of three-weekly paclitaxel (175mg/m²) or six cycles of three-weekly docetaxel (100mg/m²) is recommended as a first-line therapy for women with HER2/*neu*-overexpressing metastatic breast cancer.
- Due to concerns regarding cardiotoxicity, trastuzumab is not recommended in combination with doxorubicin.
- Due to the lack of randomized trial data, no definitive recommendation regarding the use of trastuzumab with other combinations outside of clinical trials can be made at this time.

Qualifying Statements

- In combination with trastuzumab, there is no data to suggest that one taxane is superior to the other in any metastatic setting.
- No randomized data evaluating the role of trastuzumab in combination with paclitaxel or docetaxel in the second-line or greater setting were identified; however, evidence from non-randomized phase II trials suggests that, for women with HER2/neu-overexpressing metastatic breast cancer who have received non-taxane-containing chemotherapy previously for metastatic breast cancer, trastuzumab in combination with paclitaxel or docetaxel (as above) may be an appropriate treatment.
- No randomized data evaluating the role of trastuzumab in combination with vinorelbine in the treatment of metastatic breast cancer were identified; however, evidence from non-randomized phase II trials suggests that, for women with HER2/neu-overexpressing metastatic breast cancer whose disease has progressed with anthracycline or taxane therapy (either in the adjuvant or metastatic setting), trastuzumab in combination with vinorelbine (25mg/m² or 30mg/m² weekly until disease progression or unacceptable toxicity) may be an appropriate treatment.
- Decisions about the dose, schedule, and duration for second-line or greater paclitaxel and docetaxel treatment in combination with trastuzumab should be individualized based on patient preference, local and institutional standard patterns of practice, and best clinical judgement.

Key Evidence

- Two (one phase III [N=469], one phase II [N=188]) of three randomized trials in the first-line setting detected improved progression-free and overall survival when trastuzumab was administered in combination with chemotherapy versus chemotherapy alone. In the first trial, overall response (41% versus 17%; p<0.001) and median time-to-disease progression (6.9 months versus 3.0 months; p<0.001) were significantly improved when trastuzumab was combined with paclitaxel in anthracycline-exposed patients. Median overall survival (22.1 months vs. 18.4 months, p=0.17) was not improved. In the second trial, overall response (61% versus 36%; p=0.001), time-to-disease progression (10.6 months versus 6.1 months; p=0.0001), and overall survival (27.7 months versus 18.3 months; p=0.0002) were improved when weekly trastuzumab was combined with docetaxel. An interim analysis of the third trial found no difference between the paclitaxel combined with trastuzumab versus paclitaxel but did find significant improvement when the analysis was limited to patients with HER2/neu IHC 3+ disease. Of note, the two positive trials used every-three-week taxane therapy, while the negative trial used every-week taxane therapy.
- Thirteen non-randomized phase II trials, 11 of which included women with previous chemotherapy for metastatic disease, also evaluated trastuzumab in combination with a taxane. Overall response rates ranged from 49% to 69%, and time-to-disease progression ranged from 8.5 months to 12.4 months. The range of ORR in the two trials which included only patients receiving first line therapy was 51% to 69%.
- Seven non-randomized trials, three of which included women with prior chemotherapy for metastatic disease, evaluated the efficacy of trastuzumab in combination with vinorelbine. Overall response rates ranged from 52% to 86%, and time-to-disease progression ranged from four months to 17 months. The range of ORR in the five trials which included only patients receiving first line therapy was 61% to 86%.

Question #2

Compared with placebo or observation, does single-agent trastuzumab therapy improve clinically meaningful outcomes?

Recommendations

- Due to the lack of randomized trial data, no definitive recommendations regarding the use of single-agent trastuzumab therapy can be made at this time.

Qualifying Statements

- No randomized data evaluating the role of single-agent first-line trastuzumab were identified; however, evidence from phase II trials suggests that for women with HER2/neu-overexpressing metastatic breast cancer who wish to postpone the side effects of chemotherapy for as long as possible, trastuzumab may be a reasonable treatment prior to initiating any type of chemotherapy.
- No randomized data evaluating the role of single-agent second-line or greater trastuzumab were identified; however, evidence from phase II trials suggests that, for women with HER2/neu-overexpressing metastatic breast cancer who wish to avoid the side effects of further chemotherapy, trastuzumab is a reasonable second-line or greater single-agent therapy.
- There are no data supporting the addition of chemotherapy to trastuzumab if the use of the trastuzumab alone results in disease progression.

Key Evidence

- Among five non-randomized single-agent trastuzumab trials and one single-agent randomized trial of two trastuzumab doses, rates of overall response in the two first-line trials ranged from 19% to 28% and 12% to 26% in the four second- or greater-line trials. Time-to-disease progression was 3.5 months or 3.8 months for standard loading and weekly dose compared to double the loading and weekly dose of trastuzumab dose in one first-line trial. Time-to-disease progression in three second- or greater-line trials ranged from three to four months.

Question #3

What is the best way to identify women who will benefit from trastuzumab therapy?

Recommendations

- Trastuzumab combination therapy is most likely to be effective in women with the highest level of HER2/neu protein overexpression, as indicated by an immunohistochemistry score of 3+ (moderate/strong membrane staining in at least 10% of tumour cells) or by HER2/neu gene amplification (defined as $HER2/CEP17 \geq 2$ by fluorescence in situ hybridization).

Key Evidence

- In the phase III randomized trial, HER2/neu over-expression, documented by fluorescence in situ hybridization, was associated with a survival benefit in women treated with trastuzumab and chemotherapy (odds ratio, 0.71; 95% CI, 0.54 to 0.92; $p=0.009$), while there was no survival benefit seen in women with FISH-negative tumours (odds ratio, 1.11; 95% CI, 0.70 to 1.77; p -value not significant).

- Among several non-randomized combination and single-agent trastuzumab trials, IHC 3+ or FISH-positive assay results tended to be associated with improved overall response and time-to-disease progression compared with IHC 2+ results.

Question #4

What are the adverse events associated with trastuzumab therapy?

Recommendations

- Women should be monitored for signs and symptoms of congestive heart failure during treatment with trastuzumab.

Qualifying Statements

- Although hypersensitivity and infusion reactions were not directly addressed by this systematic review, it is the opinion of the Breast Cancer Disease Site Group that patients receiving trastuzumab should also be monitored for hypersensitivity and infusion reactions, and that, when used in combination with chemotherapy, patients receiving trastuzumab should be monitored for neutropenia.
- Trastuzumab should be administered with extreme caution in women with impaired cardiac function; such patients should be monitored frequently for symptoms and signs of congestive heart failure.

Key Evidence

- In one randomized trial, symptomatic or asymptomatic cardiac dysfunction was observed in 27% of patients receiving anthracycline, cyclophosphamide, and trastuzumab compared with 8% in those receiving anthracycline and cyclophosphamide alone. The incidence of symptomatic congestive heart failure was 2% in women receiving trastuzumab and paclitaxel versus 1% in those receiving paclitaxel alone.
- In a second randomized trial, symptomatic heart failure in two patients receiving trastuzumab and docetaxel occurred compared with none in those receiving docetaxel alone.

Question #5

What are the optimal dose, schedule, and duration for trastuzumab therapy?

Recommendations

- Regardless of combination, trastuzumab should be initiated at 4mg/kg and continued at 2mg/kg weekly until disease progression or unacceptable toxicity.

Qualifying Statements

- Trastuzumab given 6mg/kg every three weeks has been tested alone and combined with chemotherapy in non-randomized trials and appears to provide similar benefit to weekly trastuzumab. Therefore, it is the opinion of the Breast Cancer Disease Site Group that for women who prefer three-weekly treatment, a switch to three-weekly maintenance trastuzumab (6mg/kg) may be appropriate after a reasonable period of weekly therapy.

Key Evidence

- Schedule: Direct comparisons of different trastuzumab schedules have not been reported. The randomized controlled trials that detected a benefit with trastuzumab and

chemotherapy administered the agent weekly; in total only three trials, all non-randomized, reported using a three-weekly regimen.

- Dose: Only one trial directly compared two different doses when trastuzumab was used as a single-agent. No significant differences in response rate, duration of survival, or toxicity were detected between weekly doses of 2mg/kg and 4mg/kg (following loading doses of 4mg/kg and 8mg/kg). The two randomized trials that showed that trastuzumab in combination with chemotherapy was superior to chemotherapy alone used a loading dose of 4mg/kg followed by 2mg/kg weekly.
- Duration: No eligible trials evaluating optimum duration of trastuzumab therapy were identified. In most cases, patients continued to receive trastuzumab until disease progression or unacceptable toxicity.

For further information about this practice guideline report, please contact:

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PREAMBLE: About our Practice Guideline Reports

The Program in Evidence-based Care (PEBC) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PEBC using the methodology of the Practice Guidelines Development Cycle.¹

This practice guideline report, which is based on a systematic review of evidence, is the result of the first three steps of the guideline development cycle. One of the 14 Provincial Disease Site Groups has discussed the best evidence available on the clinical topic in question and has developed clinical recommendations based on this evidence.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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The Role of Trastuzumab (Herceptin®) in the Treatment of Women with HER2/*neu*-overexpressing Metastatic Breast Cancer Practice Guideline Report #1-15 (Version 2.2004)

*M. Crump, M. Trudeau, S. Sinclair, F. O'Malley, and
members of the Breast Cancer Disease Site Group*

Please see the EBS 1-15 Version e Guideline Review [Summary](#)
and the [Document Assessment & Review Tool](#)
for the summary of updated evidence published between 2005 and 2009.

Report Date: November 8, 2005

FULL REPORT

I. QUESTIONS

In women with HER2/*neu*-overexpressing metastatic breast cancer:

1. Compared with chemotherapy alone, does trastuzumab in combination with chemotherapy improve clinically meaningful outcomes (overall response rates, time-to-disease progression [TTP], overall survival, toxicity, or quality of life)?
2. Compared with placebo or observation, does single-agent trastuzumab therapy improve clinically meaningful outcomes?
3. What is the best way to identify women who will benefit from trastuzumab therapy?
4. What are the adverse events associated with trastuzumab therapy?
5. What are the optimal dose, schedule, and duration for trastuzumab therapy?

II. CHOICE OF TOPIC AND RATIONALE

Although a number of hormonal therapy and chemotherapy options have been developed for the palliation of metastatic breast cancer, virtually all patients ultimately develop resistance to those treatments. Furthermore, second-line or greater chemotherapy regimens may be associated with significant adverse effects that diminish patients' quality of life. Thus, the development of effective and safe therapies for use in chemo- or hormone-refractory breast cancer remains a priority.

The HER2/*neu* gene encodes a 185-kd transmembrane glycoprotein (p185HER2/*neu*) that is a member of a family of growth-factor receptors with intrinsic tyrosine kinase activity. HER2/*neu* is overexpressed in 25% to 30% of human breast cancers (1). Overexpression of p185HER2/*neu* in patients with primary breast cancer is associated with a number of adverse prognostic factors, including advanced-stage axillary lymph node involvement, absence of

estrogen and progesterone receptors, increased S-phase fraction, and high nuclear grade (2,3).

The murine monoclonal antibody against HER2/neu, 4D5, has anti-proliferative effects against HER2/neu overexpressing breast cancers in vitro and against breast cancer xenografts (4-6). However, due to their immunogenicity, the therapeutic use of murine antibodies is limited clinically (7). Consequently, one of the more effective antibodies, 4D5, was humanized, resulting in a human immunoglobulin IgG1 agent that retains murine sequences only in the complementarity-determining regions. This antibody became known as trastuzumab (Herceptin®) and was approved for the treatment of metastatic breast cancer in Canada in August 1999.

III. METHODS

Guideline Development

This practice guideline report was developed by the Program in Evidence-based Care (PEBC) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (8). Evidence was selected and reviewed by four members of the Breast Cancer Disease Site Group (DSG), including two medical oncologists, a pathologist, and a research methodologist. Members of the Breast Cancer DSG disclosed potential conflict-of-interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the role of trastuzumab in the treatment of women with metastatic breast cancer, developed through systematic reviews and evidence synthesis. Because the body of evidence in this report includes randomized controlled trial data, the DSG is able to offer treatment recommendations. The report is intended to promote evidence-based practice. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey consisting of items that address the quality of the practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the practice guideline report is obtained from the Report Approval Panel.

The PEBC has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

An evidence summary on this topic was originally completed in October 1999 and published in *Current Oncology* 2000;7(4):242-51. At that time, only two randomized trials (both published in abstract form) and four uncontrolled trials (one published as an abstract) evaluating the efficacy of trastuzumab in metastatic breast cancer were identified. Sixteen case series examining methods of assessment of HER2/neu status were also included. As abstract reports were published in full form and as new data emerged, regular updates were made to the evidence summary. In November 2003, after examining the body of evidence, the Breast Cancer DSG decided that the evidence had evolved such that a practice guideline with recommendations was required. This document replaces the 1999 report.

Literature Search Strategy

MEDLINE was searched to August 2004 using disease-specific medical subject heading terms ("breast neoplasms" and "neoplasm metastasis") and an agent-specific MeSH term ("antibodies, monoclonal") or an oncogene-specific MeSH term ("receptor, erbB-2"). The Excerpta Medica database (EMBASE) was also searched up to August 2004 using a disease-specific Excerpta Medica Tree (EMTREE) subject-heading term ("breast cancer") and keywords

(“advanced” or “metastatic” or “metastases”) as well as an agent-specific Emtree subject heading term (“trastuzumab”) or an oncogene-specific Emtree subject heading term (“oncogene c erb”).

The Cochrane Library, conference proceedings from the American Society of Clinical Oncology, the European Society for Medical Oncology, and the San Antonio Breast Cancer Symposium, article bibliographies, and personal files were also searched up to August 2004 for relevant evidence.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Trastuzumab, in combination or alone, was evaluated using a randomized controlled trial, meta-analysis, evidence-based clinical practice guideline, or non-randomized trial (for the non-randomized trials, only those with 25 or more patients evaluable for efficacy outcomes were included).
- Reported outcomes included overall response rates, TTP, overall survival, toxicity, or quality of life.
- Clinical trial results were reported in either full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and add to the evidence available from fully published studies. Those data often appear first in meeting abstracts and may not be published for several years (9).

Exclusion Criteria

Papers published in languages other than English were not considered.

Synthesizing the Evidence

The data included in this review was not pooled because most of the evidence was immature and clinically heterogeneous.

IV. RESULTS

Assessment of HER2/neu Status

In the trials eligible for inclusion, HER2/neu status was assessed by immunohistochemical (IHC) or fluorescence in situ hybridization (FISH) analyses. A positive FISH result indicated HER2/neu gene amplification, defined as HER2/CEP17 ratio > 2. IHC-analysed specimens were scored as 0, 1+, 2+, or 3+ for cell-surface-membrane expression. HER2/neu protein overexpression was defined as an IHC score of at least 2+ (10-29) or 3+ only (30-44). Two trials defined HER2/neu positivity as 25% or more tumour cells exhibiting characteristic membrane staining for p185HER2 (45,46), and two trials failed to identify their method of determining HER2/neu overexpression (47,48). All but four (13,21,31,43) trials excluded HER2/neu-negative women; in those trials, HER2/neu-negative women were analysed separately (either as a comparison group or in a subgroup analysis).

Literature Search Results

Question #1: Compared with chemotherapy alone, does trastuzumab in combination with chemotherapy improve clinically meaningful outcomes?

Three randomized trials compared chemotherapy plus trastuzumab to the same chemotherapy without trastuzumab (10,11,30) (Table 1). Thirty-one non-randomized trials (n≥25) assessed the efficacy of trastuzumab in combination with other agents (12-17,21-29,31-34,37-44,46-48)

(Table 2). Two (11,30) of the three (10) randomized and 16 (16,17,24,26,32,33,37,38,40-44,47-49) of the 31 (12-15,21-23,25,27-29,31,34,39,46) non-randomized combination trials were reported in meeting abstract form.

Randomized trials

Three randomized trials compared combination therapy with trastuzumab to therapy without (10,11,30). Slamon et al conducted a multinational phase III trial in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease (10). Those patients were randomized to receive chemotherapy alone or in combination with trastuzumab given intravenously as a 4mg/kg loading dose, followed by weekly doses at 2mg/kg. Women who had received prior anthracycline chemotherapy in the adjuvant setting were treated with paclitaxel (175mg/m²) every 21 days for at least six cycles; for all other patients, chemotherapy consisted of anthracycline (doxorubicin 60mg/m² or epirubicin 75mg/m²) plus cyclophosphamide (600mg/m²) every 21 days for six cycles. In the case of disease progression, patients were offered trastuzumab at the same doses or in combination with other therapies. The method of randomization and patient blinding to treatment were not reported; however, response evaluation was conducted by a blinded independent committee. The rationale for the sample size was provided, and intent-to-treat analyses were employed. Primary and secondary outcomes were defined a priori.

The addition of trastuzumab to standard anthracycline-based or paclitaxel chemotherapy (N=235) resulted in a significant improvement in response rate (50% versus (vs.) 32%; p<0.001), time-to-treatment failure (6.9 months vs. 4.5 months; p<0.001), response duration (9.1 vs. 6.1 months; p<0.001), and better overall survival (25.1 vs. 20.3 months; p=0.046) compared with chemotherapy alone (N=234). Statistically significant improvements in response rate and time-to-progression were found in both the subgroup treated with anthracycline-based chemotherapy plus trastuzumab and the subgroup treated with paclitaxel plus trastuzumab, compared to chemotherapy alone (Table 1). No differences in median overall survival were detected within subgroups.

Two randomized trials administered first-line trastuzumab in combination with a taxane compared with the taxane alone (11,30). As those trials were reported in meeting abstracts, little information on study quality was available. In the phase II multicentre trial reported by Extra et al, women were randomized to receive docetaxel (100mg/m²) every 21 days for six cycles and trastuzumab at 4mg/kg loading dose followed by 2mg/kg weekly until disease progression, or the same docetaxel regimen alone (30). Patients progressing on docetaxel alone were allowed to cross over to receive the combination therapy. Ninety-five percent of patients had IHC 3+ and/or FISH-positive disease. Primary and secondary outcomes were defined a priori.

The overall response rate, time-to-progression, and overall survival were significantly improved in the combination arm, despite at least 44% of the docetaxel arm crossing over to the combination arm (Table 1). It was not clear whether the analyses were based on the intent-to-treat principle.

In an interim analysis of their ongoing randomized phase II trial, Gasparini et al administered weekly paclitaxel at 80mg/m² and trastuzumab at 2mg/kg (4mg/kg loading dose) (11). Of note, both IHC 2+ and 3+ patients were included in the study. The overall response was significantly higher with trastuzumab in the sub-group of patients with IHC 3+ disease (83.4% vs. 62.6%; p-value not reported); however, when both 2+ and 3+ patients were included, there were no differences in overall response rate and median TTP (Table 1). Intent-to-treat principles were not employed in the analysis.

Table 1. Efficacy data from randomized trials of combination trastuzumab therapy.

Trial	Treatment arms	Line	n	Med. f/u	ORR (%)	Median TTP (months)	Median OS (months)
Slamon, 2001 (10)	T (q1w) + AC (q3w)	1 st	469	30 mo.	56*	7.8*	26.8
	AC (q3w)				42	6.1	21.4
	T (q1w) + paclitaxel (q3w)				41*	6.9*	22.1
Extra ^a , 2003 (30)	T (q1w) + docetaxel (q3w)	1 st	188	NR	61*	10.6*	27.7*
	Docetaxel (q3w)				36	6.1	18.3
Gasparini ^a , 2003 (11)	T + paclitaxel (q1w)	1 st	62	NR	74	6.5	NR
	Paclitaxel (q1w)				71	5.6	

*Difference was statistically significant at the 5% level.

^aPublished in abstract form.

Abbreviations: A, doxorubicin; C, cyclophosphamide; Med. f/u, median follow-up in months; n, number of patients evaluable for response; NR, not reported; ORR, overall response rate (complete plus partial response); OS, median overall survival; T, trastuzumab; TTP, median time-to-disease progression; w, week(s).

Non-randomized trials

Thirteen non-randomized phase II trials evaluated trastuzumab in combination with a taxane (paclitaxel or docetaxel) (13,16,21,22,27,28,31-33,38,39,46,48), seven in combination with vinorelbine (14,25,26,34,37,43,44), two in combination with pegylated liposomal doxorubicin (17,41), two in combination with gemcitabine (12,47), one in combination with cisplatin (15), and six in combination with more than one agent (23,24,29,40,42,49) (Table 2).

Taxanes

Of 13 phase II trastuzumab and taxane combination trials (13,16,21,22,27,28,31-33,38,39,46,48), all administered trastuzumab weekly, eight administered the taxane weekly, three administered the taxane every three weeks, and two did not report the taxane schedule. Weekly doses for paclitaxel ranged from 60 to 90mg/m² in the only weekly paclitaxel trial that reported dose (27). Weekly docetaxel doses ranged from 33mg/m² to 40mg/m² in the three trials for which that information was reported (21,31,39). Two of the weekly trials administered the taxane until disease progression (21,31). Two of the three three-weekly taxane trials reported dose; the first administered paclitaxel at 175mg/m² every three weeks for seven cycles (27), and the second administered docetaxel at 75mg/m² every three weeks for six cycles (28). Only two trials excluded women with prior therapy for metastatic disease (32,38). Many of the women in the 11 trials that permitted previous therapy for metastatic disease had received anthracycline or taxane regimens. Overall response rates in women receiving either taxane ranged from 49% to 69%. TTP ranged from 8.5 months to 12.4 months. That large difference likely reflects differences in patient populations.

Vinorelbine

Trastuzumab and vinorelbine were administered weekly in all seven phase II trials (14,25,26,34,37,43,44). Two trials administered 30mg/m² (14,37); the remaining five trials administered 25mg/m² (25,26,34,43,44). Chemotherapy was continued until documented disease progression or unacceptable toxicity. Four trials excluded women with any prior chemotherapy for metastatic disease (14,34,37,44). Of the three second-line or greater trials, Bayo et al failed to describe the previous therapies administered for metastatic disease (26).

In the report by Papaldo et al, 35% (20/57) of women had received prior anthracycline therapy and 74% (42/57) had received prior taxane therapy for metastatic disease (43). In the 2001 Burstein et al trial, 53% (21/40) of patients had received prior chemotherapy, including anthracyclines and/or taxane regimens, for metastatic disease (25). Overall response (complete and partial response) rates for vinorelbine plus trastuzumab ranged from 52% to 86%. TTP ranged from four months to 17 months.

Anthracyclines

Two phase II trials administered weekly trastuzumab in combination with four- (41) or three-weekly (17) pegylated liposomal doxorubicin. The four-weekly trial did not exclude women with prior chemotherapy for metastatic disease, whereas the three-weekly trial did. Overall response rates were 65% and 58%, respectively.

Gemcitabine

Two phase II trials administered weekly trastuzumab in combination with three- or four-weekly gemcitabine (12,47). Women with previous chemotherapy for metastatic breast cancer were not excluded. Overall response rates were 38% and 36%, and median TTP was 5.8 months and 7.8 months, respectively.

Other combinations

One phase II trial administered trastuzumab in combination with cisplatin (15), and six trials administered trastuzumab in combination with two other agents (15,23,24,29,40,42,49). Those trials were heterogeneous in nature and will not be further summarized here.

Table 2. Efficacy data from non-randomized trials of combination trastuzumab therapy.

Trial	Treatment(s)	Line	n	ORR	Median TTP	Median OS
Trastuzumab + Vinorelbine						
Burstein, 2003 (34)	T + vinorelbine (q1w)	1 st	54	68%	NR	NR
Burstein, 2001 (25)	T + vinorelbine (q1w)	1 st 2 nd -3 rd	19 21	84% 61%	8.5m ^b 14m ^b	19.4m ^b NR
Jahanzeb, 2002 (14)	T + vinorelbine (q1w)	1 st	37	78%	17m	NR
^a Papaldo, 2003 (43)	HER2+: T + vinorelbine (q1w) HER2-: Vinorelbine (q1w)	≥1 st	25 27	52% 26%	9m 6m	68.8% ^c 26.8% ^c
^a Bernardo, 2004 (44)	T + vinorelbine (q1w)	1 st	48	86%	9m	NR
^a Guillem Porta, 2004 (37)	T + vinorelbine (q1w)	1 st	66	61%	10m	NR
^a Bayo, 2004 (26)	T + vinorelbine (q1w)	≥1 st	49	61%	7.2m	NR
Trastuzumab + Taxanes						
Raff, 2004 (21)	HER2+: T + docetaxel (q1w) HER2- : Docetaxel (q1w)	≥1 st	17 35	59% 21%	8.5m 4.5m	17.8m 14.8m
Montemurro, 2004 (28)	T (q1w) + docetaxel (q3w)	≥1 st	53	67%	9m	NR
Tedesco, 2004 (39)	T + docetaxel(q1w)	1 st -2 nd	26	50%	12.4m	NR
Esteva, 2002 (31)	T + docetaxel (q1w)	≥1 st	30	63%	9m	NR
Leyland-Jones, 2003 (27)	T + paclitaxel (q3w)	≥1 st	32	59%	12.2m	NR
Gori, 2004 (22)	T + paclitaxel (q1w)	≥1 st	25	56%	8.6m	NR
Christodoulou, 2003 (46)	T + paclitaxel (q1w)	≥1 st	26	62%	11m	34m
Seidman, 2001 (13)	T + paclitaxel (q1w)	≥2 nd	88	61.4%	NR	NR
^a John, 2003 (33)	T + paclitaxel (q1w)	≥1 st	77	69%	NR	NR
^a Toi, 2002 (16)	T + paclitaxel (q1w) T + docetaxel (q1w)	1 st -2 nd	26	67% 57%	NR	NR
^a Schwartz, 2002 (32)	T (q1w) + taxane	1 st	57	51%	NR	NR
^a Stewart, 2004 (38)	T + taxane (q3w)	1 st	32	69%	NR	NR
^a Reddy, 2004 (48)	T (q1w) + taxane	≥1 st	352	49%	NR	NR
Trastuzumab + Anthracycline						
^a Chia, 2004 (41)	T (q1w) + PLD (q4w)	1 st	29	65%	NR	NR
^a Theodoulou, 2002 (17)	T (q1w) + PLD (q3w)	≥1 st	33	58%	NR	NR
Trastuzumab + Gemcitabine						
O'Shaughnessy, 2004 (12)	T (q1w) + gemcitabine (q3w)	≥1 st	61	38%	5.8m	14.7m
^a Christodoulou, 2003 (47)	T (q1w) + gemcitabine (q4w)	≥1 st	25	35.7%	7.8m	18.7m
Trastuzumab + Platinum salts						
Pegram, 1998 (15)	T (q1w) + cisplatin	≥2 nd	37	24.3%	NR	NR
Trastuzumab Triplets						
Pegram, 2004 (23)	T + docetaxel + cisplatin (q3w) T + docetaxel + carboplatin (q3w)	≥1 st	62 59	79% 58%	9.9m 12.7m	NR
Burris, 2004 (29)	T + paclitaxel + carboplatin (q1w)	1 st	31	84%	14.2m	32.2m
^a Polyzos, 2004 (24)	T (q1w) + gemcitabine +docetaxel (q2w)	1 st	30	56%	14.6m	86.7% ^d
^a Yardley, 2004 (42)	T (q1w) + vinorelbine +docetaxel (q2w)	1 st	29	75%	11.3m	NR
^a Trigo, 2004 (40)	T + paclitaxel (q1w) + PLD (q3w)	1 st	32	87.5%	NR	NR
^a Venturini, 2003 (49)	T + docetaxel + epirubicin (q1w)	1 st	45	68.8%	11m	NR

^aReported in abstract form; ^bReported in weeks and converted to months using 1 month = 4 weeks; ^cAt two years; ^dStill alive at median 15 months follow-up.

Abbreviations: m, months; n, number of patients evaluable for response; NR, not reported; OS, overall survival; PLD, pegylated liposomal doxorubicin; ORR, overall response rate; T, trastuzumab; TTP, time-to-disease progression; w, weeks;

Question #2: Compared with placebo or observation, does single-agent trastuzumab therapy improve clinically meaningful outcomes?

No randomized trials comparing single-agent trastuzumab therapy to placebo or observation were identified. One randomized trial of two different doses (18) and five non-randomized phase II trials (19,20,35,36,45) assessing the efficacy of single-agent trastuzumab were identified (Table 3); three of those were reported in abstract form (19,35,36).

Vogel et al randomized patients with no prior chemotherapy for metastatic breast cancer to two different doses of trastuzumab: either the standard loading dose of 4mg/kg followed by 2mg/kg/wk or a high-dose regimen of 8mg/kg followed by 4mg/kg/wk (18). Seventy-six percent of patients scored 3+ for HER2/neu overexpression, 44% of patients had lung metastases, and 39% had liver metastases. Fifty-one percent had received prior adjuvant chemotherapy, and 13% had received a prior adjuvant bone marrow transplant. The overall response rate was 26% (95% confidence interval (CI), 18.0% to 34.3%) among 111 evaluable patients. Median TTP and median duration of survival in the high- versus the standard-dose group was 3.8 months (95% CI, 2.4 to 5.5) versus 3.5 months (95%CI, 3.3 to 5.1) and 25.8 months (95% CI, 13.3 to 34.7) versus 22.9 months (95% CI, 16.0 to 31.1), respectively.

Cobleigh et al administered trastuzumab at a loading dose of 4mg/kg, followed by a weekly dose of 2mg/kg in 222 women (20). Sixty-eight percent of those women had received prior adjuvant chemotherapy: 32% had received one regimen for metastatic disease, and 68% had received two or more regimens; 26% had previously received high-dose chemotherapy with bone marrow or stem cell transplantation. The rate of overall response in trastuzumab-treated patients was 15% (95% CI, 11% to 21%), and the median duration of response was 9.1 months. The median TTP was 3.1 months, and the median overall survival time was 13 months.

Baselga et al administered trastuzumab (250mg loading dose followed by 100mg weekly) to 46 women (45). Eighty-three percent had received previous chemotherapy for metastatic breast cancer, with 63% of those having received two or more regimens. The overall response rate was 11.6% (95% CI, 4.5% to 26%), and the median TTP was 5.1 months.

Table 3. Efficacy data from trials of single-agent trastuzumab therapy.

1 st Author, year (reference)	Line	n	Dose		ORR (%)	Median TTP (mo.)	Median OS (mo.)
			Loading	Maintenance			
Vogel, 2002 (18)	1 st	53	8mg/kg/w	→ 4mg/kg/w	28.3	3.8	25.8
		58	4mg/kg/w	→ 2mg/kg/w	24.1	3.5	22.9
Cobleigh, 1999 (20)	≥1 st	213	4mg/kg/w	→ 2mg/kg/w	14.6	3.1	13.0
Baselga, 1999 (45)	≥1 st	43	250mg/w	→ 100mg/w	11.6	5.1	NR
^a Castellon, 2002 (35)	1 st	64	8mg/kg/3w	→ 6mg/kg/3w	18.8	4.0	NR
^a Clemens, 2002 (36)	≥2 nd	62	4mg/kg/w	→ 2mg/kg/w	19.4	2.8	NR
^a Sun, 2002 (19)	≥1 st	31	4mg/kg/w	→ 2mg/kg/w	25.8	NR	NR

^aTrial was reported in abstract form only

Abbreviations: mo., months; n, number of patients evaluable for efficacy outcomes; NR, not reported; ORR, overall response rate; OS, overall survival; TTP, time-to-progression; w, week(s).

Question #3: What is the best way to identify women who will benefit from trastuzumab therapy?

Eight of the combination trials (10,13,14,23,25,29,31,39) and two of the single-agent trials (18,20) reported subgroup analysis of HER2/neu overexpression and response to trastuzumab.

Combination trials

Using fluorescence in situ hybridization, Mass et al (50) re-analysed histological material from 451 of 469 patients enrolled in the Slamon trial (10). FISH-positivity (N=343) was associated with a significant survival benefit in the patients treated with trastuzumab and chemotherapy (odds ratio, 0.71; 95% CI, 0.54 to 0.92; p=0.009), while the patients with FISH-negative tumours did not show a survival benefit (odds ratio, 1.11; 95% CI, 0.70 to 1.77; p-value not significant).

Of the 30 non-randomized trials, seven reported interpretable subgroup analysis according to IHC or FISH results (Table 4). While sample sizes were small and most differences were not significant, women with tumours with IHC 3+ or FISH-positive assay results tended to have improved overall response and TTP compared to those with tumours that were IHC 2+ or FISH negative.

Table 4: Overall response and TTP according to HER2/neu status.

Trial	Test	Score	n	ORR (% [95% CI/p-value])	Median TTP (months [95% CI])
Burststein, (25)	IHC	3+	30	80 (61 to 92)	NR
		2+	10	60 (26 to 88)	
Jhanzeb, (14)	IHC	3+	22	82 (NR)	NR
		2+	12	58 (NR)	
	FISH	+	12	83 (NR)	NR
		-	13	54 (NR)	
Tedesco, (39)	IHC	3+	19	63 (38 to 84)	12.3 (NR)
		2+	7	14 (1 to 58)	9.5 (NR)
	(Ventana) FISH	+	17	65 (38-86)	12.4 (NR)
		-	4	0 (NR)	9.5 (NR)
	(Abbott) FISH	+	16	63 (35-85)	12.4 (NR)
		-	4	25 (NR)	9.5 (NR)
Esteva, (31)	IHC	3+	19	63 (38-84)	NR
		0-2+	5	60 (15-95)	
	FISH	+	24	67 (45 to 84)	NR
		-	4	50 (6 to 93)	
Seidman, (13)	IHC	3+	51	69 (p=0.032)	NR
		2+	39	46	
	FISH	+	40	75 (p=0.004)	NR
		-	39	44	
Pegram, 2004 (23)	(cisplatin) FISH	+	35	77 (59 to 90)	12.7 (8.9 to 14.2)
		-	19	84 (60 to 96)	7.9 (5.8 to 13.2)
	(carboplatin) FISH	+	40	63 (46 to 77)	15.6 (9.1 to 17.3)
		-	17	41 (19 to 67)	7.4 (6.7 to 12.0)
Burriss, (29)	IHC	3+	34	79 (NR)	10.9 [†] (0.5 to 55.7+)
		2+	18	50 (NR)	6.2 ^{††} (0.3 to 48.7+)

[†]N=41; ^{††}N=20

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NR, not reported; ORR, overall response rate; TTP, time-to-disease progression.

Single-agent trials

In univariate analysis of the Cobleigh et al trial, median TTP was longer among patients with HER2/neu overexpression scored as 3+ compared with those scored 2+ (3.3 months vs. 1.9 months; $p=0.0034$) (20). The level of overexpression was still a significant predictor of response to trastuzumab therapy in multivariate analysis ($p<0.05$).

Similarly, Vogel et al reported improved response rates and TTP in patients with 3+ HER2/neu overexpression and in patients whose tumours showed HER2/neu amplification by FISH (Table 5).

Table 5: Retrospective analysis trastuzumab therapy response in the Vogel et al trial (18).

Method of Assessment	Score	n	Response (% [95% CI])	Median TTP (months)
IHC	3+	84	35 (NR)	NR
	2+	27	0 (NR)	
FISH	+	79	34 (23.9, 45.7)	4.9 (3.4, 8.0)
	-	29	7 (0.8, 22.8)	1.7 (1.5, 3.3)

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NR, not reported; TTP, time-to-disease progression.

Question #4: What are the adverse events associated with trastuzumab therapy?

Sixteen trials included relevant data on the harms associated with trastuzumab (10,12-15,17,25,31-34,37,44,46,47,51).

Toxicity

In the phase III report by Slamon et al, symptomatic or asymptomatic cardiac dysfunction was observed in 39 of 143 patients (27%) receiving doxorubicin-cyclophosphamide (AC) with trastuzumab, compared to 11 of 135 (8%) receiving AC alone; the incidence of grade 3 or 4 New York Heart Association heart failure was 16% versus 3% (10). The incidence of symptomatic congestive heart failure was 2% in women receiving trastuzumab plus paclitaxel versus 1% in those receiving paclitaxel alone. Extra et al reported symptomatic heart failure in two patients in the arm that received trastuzumab and docetaxel in their phase II randomized trial; however, in one case progressive disease, and in the other subsequent anthracycline use, may have been the cause (30).

Of the 15 phase II non-randomized combination trials that reported on adverse cardiac events, symptomatic cardiotoxicity was generally infrequent (12-15,17,25,31-34,37,46,47,52). Of note, Venturini et al detected similar cardiotoxicity with trastuzumab, epirubicin ($75\text{mg}/\text{m}^2$ q3w), and paclitaxel ($75\text{mg}/\text{m}^2$ q3w) (49). Eleven percent (5/45) of patients experienced an asymptomatic decline in left ventricular ejection fraction. An additional 11% (5/45) experienced congestive heart failure, for a total of 10 cardiac events (22%).

The most common reported adverse reactions associated with trastuzumab use are mild and include fever, diarrhea, chills, increased cough, headache, rash, and insomnia. Trastuzumab can result in the development of ventricular dysfunction and congestive heart failure, especially when administered with doxorubicin or epirubicin (10,49).

Quality of life

Only three trials reported quality-of-life data. Quality-of-life data for the Slamon et al trial (10) were reported separately in a meeting abstract (53). Assessments were made at baseline and at several points during treatment, using the items from established instruments plus six newly developed items. The authors did not provide data in the abstract report but did state

that there were no statistically significant differences between chemotherapy alone and chemotherapy (anthracycline plus cyclophosphamide or paclitaxel) plus trastuzumab.

Vogel et al assessed quality of life at baseline, every 12 weeks, and at study termination using the European Organization for Research and Treatment of Cancer's (EORTC) Quality of Life C30 questionnaire with the module for breast cancer (BR-23) (18). Quality-of-life scores did not change substantially over time. Responders tended to show improvements in all scales at week 12, which gradually declined over the following weeks, whereas non-responders showed slight deterioration at week 12 and additional deterioration over time. Subgroup (standard vs. high-dose) analysis was not reported.

Cobleigh et al also assessed quality of life at baseline and every 12 weeks until study completion, using the EORTC C-30 Quality of Life Questionnaire (20). After 12 weeks of treatment, an improvement from baseline was observed in scores on the global quality of life scale (from 62.6 to 66.9 out of 100) and social functioning scale (from 70.4 to 76.9 out of 100). There was no change observed in physical or role functioning or in fatigue.

Question #5: What are the optimal dose, schedule, and duration for trastuzumab therapy?

One of the single-agent trials randomized women to two different doses of trastuzumab (18). No trials directly compared different trastuzumab schedules (e.g., weekly versus three-weekly) or durations of therapy.

Schedule

Direct comparisons of different schedules have not been reported. The randomized controlled trials that showed a benefit with trastuzumab and chemotherapy administered the agent weekly (10,30). Only three trials, all non-randomized, reported using a three-weekly regimen (23,35,38).

Dose

Only one trial directly comparing two doses has been reported: in the small trial reported by Vogel et al, there was no significant difference in response rate, duration of survival (median duration of follow-up was 19 months), or toxicity between weekly doses of 2mg/kg weekly and 4mg/kg (following loading doses of 4mg/kg and 8mg/kg, respectively) when trastuzumab was administered as first-line therapy (18). In the two randomized trials where trastuzumab in combination with chemotherapy was shown to be superior to chemotherapy alone, it was administered as a 4mg/kg loading dose followed by 2mg/kg weekly (10,30). Of note, four non-randomized trials administered a loading dose of 8mg/kg followed by a three-weekly 6mg/kg maintenance dose (23,27,35,38).

Duration

The optimum duration of trastuzumab therapy (i.e., whether to stop chemotherapy and trastuzumab or continue with trastuzumab alone) in women responding to the combination of chemotherapy plus trastuzumab is not known. In most of the trials summarized above, patients continued to receive trastuzumab until disease progression or unacceptable toxicity.

V. INTERPRETIVE SUMMARY AND DISEASE SITE GROUP CONSENSUS

Question #1: Compared with chemotherapy alone, does trastuzumab in combination with chemotherapy improve clinically meaningful outcomes?

Two randomized trials (one phase III, one phase II) detected improved outcomes when trastuzumab was administered in combination with chemotherapy compared to chemotherapy alone. Specifically, Slamon et al detected improved overall response and TTP with first-line

weekly trastuzumab and six cycles of three-weekly anthracycline-cyclophosphamide (doxorubicin at 60mg/m² or epirubicin at 75mg/m², cyclophosphamide at 600mg/m²) in anthracycline-naïve patients or paclitaxel (175mg/m²) in anthracycline-exposed patients (10). Although survival was statistically significantly better in the experimental arm as a whole, the difference in the subgroups (paclitaxel and anthracycline-cyclophosphamide) was not statistically significant. Extra et al detected improved overall response, TTP, and overall survival with the addition of weekly trastuzumab to docetaxel 100mg/m² given every three weeks (30). Based on that randomized evidence, the Breast Cancer DSG members felt it reasonable to recommend first-line trastuzumab in combination with either six cycles of three-weekly paclitaxel (175mg/m²) or six cycles of three-weekly docetaxel (100mg/m²). In combination with trastuzumab, there was no data to suggest that one taxane is superior to the other in the first-line setting.

Among the 13 non-randomized trastuzumab and taxane combination trials (13,16,21,22,27,28,31-33,38,39,46,48), trastuzumab was always administered weekly in all but two (27,38). Schedule, dose, and duration of paclitaxel or docetaxel treatment varied greatly. Only two trials excluded women with prior therapy for metastatic disease (32,38). Many of the women in the 11 trials that permitted previous therapy for metastatic disease had received anthracycline or taxane regimens. Overall response rates in women receiving either taxane ranged from 49% to 69% where that outcome was reported. TTP ranged from 8.5 months to 12.4 months. Based on non-randomized evidence, the members agreed that weekly trastuzumab in combination with a taxane could be offered in the second-line or greater setting for women who have received chemotherapy previously for metastatic breast cancer. In combination with trastuzumab, there was no data to suggest that one taxane is superior to the other in the second-line or greater setting. Due to the lack of consistent evidence for one regimen, the members agreed that the dose, schedule, and duration of taxane should be individualized according to patient preference, local and institutional standard patterns of practice, and best clinical judgement.

Several trials have evaluated the efficacy of trastuzumab in combination with weekly vinorelbine at doses of 25mg/m² or 30mg/m² until disease progression or unacceptable toxicity. Overall response rates for vinorelbine plus trastuzumab ranged from 52% to 86%, and TTP ranged from four months to 17 months. Based on this non-randomized evidence, the Breast Cancer DSG members felt it reasonable to offer trastuzumab in combination with vinorelbine, particularly for those women whose disease has progressed after previous therapy with anthracyclines and/or taxanes, either in the adjuvant or metastatic setting.

The Breast Cancer DSG members agreed that the evidence for trastuzumab in combination with gemcitabine, platinum salts, or liposomal pegylated doxorubicin is insufficient to recommend their use outside clinical trials at this time.

Question #2: Compared with placebo or observation, does single-agent trastuzumab therapy improve clinically meaningful outcomes?

Among five non-randomized single-agent trastuzumab trials (19,20,35,36,45) and one single-agent randomized trial of two trastuzumab doses (18), rates of overall response in the two first-line trials ranged from 19% to 28% (18,35) and 12% to 26% in the four second- or greater-line trials (19,20,36,45). TTP was 3.5 months or 3.8 months depending on trastuzumab dose in one first-line trial (18). TTP in three second- or greater-line trials ranged from three to four months (20,36,45). Based on this evidence, the Breast Cancer DSG agreed that trastuzumab is effective as a single-agent for women with untreated metastatic breast cancer. Therefore, the use of single-agent trastuzumab, which is relatively non-toxic, could be an appropriate choice prior to initiating any type of chemotherapy, for those women who would like to avoid the side effects of chemotherapy (nausea and vomiting, alopecia and myelosuppression) for as

long as possible. As there were no randomized trials identified comparing single-agent trastuzumab to chemotherapy, there is no way to judge the effect on overall survival.

The Breast Cancer DSG also agreed that the evidence suggests that trastuzumab has a unique mechanism of action, producing responses in women whose cancer has progressed following treatment with anthracyclines or taxanes, the most active chemotherapy agents in metastatic breast cancer. Therefore, the members offered the opinion that trastuzumab could be an appropriate second- or greater-line single-agent therapy for women who wish to avoid the side effects of further chemotherapy.

Question #3: What is the best way to identify women who will benefit from trastuzumab therapy?

In general, among trials where subgroup analysis of the level of HER2/neu overexpression was available, the most benefit was seen with an IHC score of 3+ or FISH positivity. In the experience of the Breast Cancer DSG members, tumour samples scoring 2+ (weak membrane staining) by IHC testing should undergo FISH analysis and receive trastuzumab therapy if the FISH test is positive. Therefore, the Breast Cancer DSG members felt it reasonable to include a qualifying statement that trastuzumab combination therapy is appropriate for women whose tumours show IHC 3+ staining (i.e., moderate to strong membrane staining in at least 10% of tumour cells) or show HER2/neu gene amplification by FISH analysis (defined as HER2/CEP ratio ≥ 2).

Question #4: Adverse events associated with trastuzumab

The risk of cardiotoxicity from trastuzumab in combination with anthracyclines (10,49) led the Breast Cancer DSG members to conclude that this combination could not be recommended. Furthermore, women with significant pre-existing cardiac dysfunction should not receive trastuzumab therapy. Women receiving trastuzumab should undergo a thorough baseline cardiac assessment and continued monitoring for monitored for signs and symptoms of congestive heart failure during treatment.

In addition to cardiac events, hypersensitivity reactions, infusion reactions, exacerbation of chemotherapy-induced neutropenia, and pulmonary events leading to death have been infrequently or rarely reported with trastuzumab (1). While these events were not addressed in this systematic review, the Breast Cancer DSG believed that women should be monitored for hypersensitivity, infusion reactions, and neutropenia and treated accordingly.

Question #5: Trastuzumab dose, duration, and schedule

While the two randomized trials that showed a benefit with combination therapy administered trastuzumab weekly (10,30), four non-randomized trials administered a loading dose of 8mg/kg followed by a three-weekly 6mg/kg maintenance dose (23,27,35,38). Pharmacokinetic and safety data suggest that the increased dose and reduced frequency of trastuzumab administration are feasible (54). The members of the Breast Cancer DSG members agreed that until randomized controlled data are available to confirm the efficacy of three-weekly trastuzumab, weekly therapy should be considered standard. The members felt that it might be reasonable to switch to three-weekly maintenance trastuzumab (6mg/kg) at a later time in women who are finding weekly treatments difficult. In the members' experience, the decision to switch from weekly to three-weekly therapy should be based on concurrent chemotherapy scheduling and patient preference.

The two randomized trials that showed a benefit with combination therapy administered a loading dose of 4mg/kg followed by 2mg/kg weekly doses. There is little evidence to suggest that higher doses offer any added benefit. Therefore the DSG members

agreed that a loading dose of 4mg/kg followed by weekly doses of 2mg/kg should be recommended.

There is little data available regarding trastuzumab therapy duration. There are no prospective data to suggest that continuing trastuzumab therapy beyond progression offers any benefit; thus, the Breast Cancer DSG members recommend trastuzumab therapy only until disease progression.

VI. ONGOING TRIALS

The majority of relevant phase III trials are ongoing with unreported results. The National Cancer Institute's clinical trials online database (<http://www.cancer.gov/clinicaltrials>), review articles, and eligible trials were searched for reports of new or ongoing trials. Trials that had not published efficacy data at the time this report was written are summarized in Table 6. In addition to those phase III trials, the Breast Cancer DSG is aware of a key phase II trial designed to evaluate a single-agent three-weekly trastuzumab regimen in women with HER2/neu-positive metastatic breast cancer (Roche protocol number, M016982).

The results from the Seidman et al trial were reported at the 2004 ASCO meeting (55). Due to methodological irregularities and little detail with respect to trastuzumab outcomes, the Breast Cancer DSG agreed that the data should be excluded from the evidence summary at this time; however, the members felt it important to note that the addition of trastuzumab to paclitaxel did not improve the response rate (35% vs. 29%, $p=0.34$), TTP (seven months vs. six months; $p=0.09$), or overall survival (22 months vs. 20 months; $p=0.67$).

Table 6: Ongoing phase III trials evaluating trastuzumab therapy.

Principle investigator (ref.)	Main Protocol ID	Target accrual	Accrual Status	Treatments
Langer	ROCHE-B016216	202	Open	T + anastrozole vs. Anastrozole
Goldhirsch	SWS-SAKK-22/99	170-250	Open	T + paclitaxel vs. T → T+ paclitaxel (upon progression)
Seidman	CALGB-9840	580	Closed	<i>HER2/neu-positive</i> Weekly paclitaxel + T vs. <i>HER2/neu-positive</i> Weekly paclitaxel 3-weekly paclitaxel + T vs. 3-weekly paclitaxel
Burstein	DFCI-01087	250	Closed	T + vinorelbine vs. T + paclitaxel/docetaxel
Shak	GENENTECH-HO648G	450	Closed	T+ Chemotherapy Chemotherapy
Slamon	UCLA-HSPC-9510492	100	Closed	Patients are randomly assigned to receive 1 of 2 different doses of trastuzumab.

Abbreviations: T, trastuzumab; vs., versus.

VII. IMPLICATIONS FOR POLICY

First- or second-line trastuzumab in combination with a taxane was approved by the Policy Advisory Committee (PAC) in 1999. Single-agent trastuzumab as a second- or third-line therapy was approved in 2002.

In October 2004, the Breast Cancer DSG will submit a funding request to the PAC for trastuzumab in combination with vinorelbine as a first-, second-, or third-line therapy for women with metastatic, HER2/neu-overexpressing breast cancer. Based on current evidence,

trastuzumab in combination with vinorelbine will generate reasonable tumour response and potentially prolong disease progression and overall survival.

VIII. EXTERNAL REVIEW OF PRACTICE GUIDELINE REPORT

Based on the evidence reviewed, the Breast Cancer DSG drafted the following recommendations:

Question #1

Compared with chemotherapy alone, does trastuzumab in combination with chemotherapy improve clinically meaningful outcomes?

Draft Recommendations

- Trastuzumab in combination with either six cycles of three-weekly paclitaxel (175mg/m²) or six cycles of three-weekly docetaxel (100mg/m²) is recommended as a first-line therapy for women with HER2/neu-overexpressing metastatic breast cancer.
- No randomized data evaluating the role of trastuzumab in combination with paclitaxel or docetaxel in the second-line or greater setting were identified; however, evidence from phase II trials suggests that for women with HER2/neu-overexpressing metastatic breast cancer who have received non-taxane containing chemotherapy previously for metastatic breast cancer, trastuzumab in combination with paclitaxel or docetaxel (as above) may be an appropriate treatment.
- No randomized data evaluating the role of trastuzumab in combination with vinorelbine in the treatment of metastatic breast cancer were identified; however, evidence from phase II trials suggests that for women with HER2/neu-overexpressing metastatic breast cancer whose disease has progressed with anthracycline or taxane therapy (either in the adjuvant or metastatic setting), trastuzumab in combination with vinorelbine (25mg/m² or 30mg/m² weekly until disease progression or unacceptable toxicity) may be an appropriate treatment.
- The use of trastuzumab with other combinations is not recommended outside of clinical trials.

Qualifying Statements

- In combination with trastuzumab, there is no data to suggest that one taxane is superior to the other in any metastatic setting.
- Decisions about the dose, schedule, and duration for second-line or greater paclitaxel and docetaxel treatment in combination with trastuzumab should be individualized based on patient preference, standard patterns of practice, and best clinical judgement.

Question #2

Compared with placebo or observation, does single-agent trastuzumab therapy improve clinically meaningful outcomes?

Draft Recommendations

- No randomized data evaluating the role of single-agent first-line trastuzumab were identified; however, evidence from phase II trials suggests that for women with HER2/neu-overexpressing metastatic breast cancer who wish to postpone the side effects of chemotherapy for as long as possible, trastuzumab may be a reasonable treatment prior to initiating any type of chemotherapy.
- No randomized data evaluating the role of single-agent second-line or greater trastuzumab were identified; however, evidence from phase II trials suggests that for

women with HER2/neu-overexpressing metastatic breast cancer who wish to avoid the side effects of further chemotherapy, trastuzumab is a reasonable second-line or greater single-agent therapy.

Qualifying Statements

- There are no data supporting the addition of chemotherapy to trastuzumab if the use of the trastuzumab alone results in disease progression.

Question #3

What is the best way to identify women who will benefit from trastuzumab therapy?

Draft Recommendations

- Trastuzumab combination therapy is most likely to be effective in women with the highest level of HER2/neu protein overexpression, as indicated by an IHC score of 3+, (moderate/strong membrane staining in at least 10% of tumour cells), or by HER2/neu gene amplification (defined as HER2/CEP17 ≥ 2 by FISH).

Question #4

What are the adverse events associated with trastuzumab therapy?

Draft Recommendations

- Women should be monitored for signs and symptoms of congestive heart failure during treatment with trastuzumab.

Qualifying Statements

- Patients receiving trastuzumab should also be monitored for hypersensitivity and infusion reactions. When used in combination with chemotherapy, patients receiving trastuzumab should be monitored for neutropenia.
- Trastuzumab should be administered with extreme caution in women with impaired cardiac function; such patients should be monitored frequently for symptoms and signs of congestive heart failure.

Question #5

What are the optimal dose, schedule, and duration for trastuzumab therapy?

Draft Recommendations

- Trastuzumab should be initiated at 4mg/kg and continued at 2mg/kg weekly until disease progression or unacceptable toxicity.

Qualifying Statements

- Trastuzumab given 6mg/kg every three weeks has been tested alone and combined with chemotherapy, and appears to provide similar benefit to weekly. For women who prefer three-weekly treatment, a switch to three-weekly maintenance trastuzumab (6mg/kg) may be appropriate after a reasonable period of weekly therapy.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 102 practitioners in Ontario (76 medical oncologists and 26 hematologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on October 14, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer DSG reviewed the results of the survey.

Results

Fifty-six responses were received out of the 102 surveys sent (54.9% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 39 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 7.

Table 7. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number ^a (%) ^b		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	37 (94.9%)	0	2 (5.1%)
There is a need for a clinical practice guideline on this topic.	39 (100%)	0	0
The literature search is relevant and complete.	36 (92.3%)	3 (7.7%)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	38 (97.4%)	1 (2.6%)	0
The draft recommendations in this report are clear.	37 (94.9%)	1 (2.6%)	1 (2.6%)
I agree with the draft recommendations as stated.	34 (87.2%)	2 (5.1%)	3 (7.7%)
This report should be approved as a practice guideline.	32 (86.4%)	3 (8.1%)	2 (5.4%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	33 (84.6%)	6 (15.4%)	0

^a For some items, numbers may not total 39 due to missing responses.

^b For some items, percentages may not total 100 due to rounding error.

Summary of Written Comments

12 respondents (30.8%) provided written comments. The main points contained in the written comments were:

1. There were concerns raised about the funding of trastuzumab, and whether funding would still be available for certain treatment regimens if the guideline were approved. Specific concerns were funding for 2nd line or greater therapy, funding for trastuzumab after six cycles, expense of trastuzumab making funding for other drugs more difficult, funding for trastuzumab as a single 1st line agent, and patient's concerns about inability to obtain trastuzumab if funding not available.
2. The guideline makes no mention of combining trastuzumab with hormonal therapies, even though there have been studies addressing the issue.

3. The guideline contains no discussion of the evidence for or against continuing trastuzumab with a new chemotherapy agent in response to progression after treatment with trastuzumab and another chemotherapy agent.
4. The guideline states that providing trastuzumab as the sole 1st line therapy “...does not compromise survival compared to initiating treatment with chemotherapy first...” with no evidence to support the statement.
5. The guideline implies that trastuzumab plus taxane therapy is preferable to anthracycline combination therapy for 1st line therapy when there is no evidence to support this implication.
6. The guideline contains no discussion of the evidence for or against using trastuzumab with a taxane in a dose dense regimen.
7. The guideline does not address the common practice of using more than 6 cycles of trastuzumab.
8. The guideline uses phase II study data in an inconsistent fashion. For example, the guideline recommends the use of trastuzumab with vinorelbine or taxanes as 2nd line therapy, but does not recommend the use of trastuzumab every three weeks even though the evidence for each regimen is similar.
9. The guideline does not give consistent and clinically relevant recommendations related to cardiac complications and monitoring in patients given trastuzumab.

Modifications/Actions

In response to the practitioner feedback process, the following modifications and actions were taken:

1. The statement referred to in comment 4 was altered to reflect the state of the currently available evidence.
2. In response to comment 6, a statement was added to the key evidence regarding every three week taxane therapy versus every week taxane therapy.
3. In response to comment 8, several key statements based on phase II data were changed from recommendations to qualifying statements.

Also, some of the comments above generated no modifications but are addressed below:

1. Comment 1 above deals with fiscal and policy issues that the Program in Evidence-Based Care and the Breast Cancer DSG cannot address. The committee does make the recommendation, in response to Question #5, that trastuzumab be continued until disease progression or unacceptable toxicity, but this recommendation does not necessarily reflect a prioritization of trastuzumab compared to other therapies. The charge of the PEBC and the Breast Cancer DSG is to develop practice guidelines based on the best scientific evidence available.
2. In response to comment 2, the use of hormonal therapies with trastuzumab was not the subject of this practice guideline, and therefore this topic was not included in the literature search strategy.
3. In response to comment 3, the issue of continuing trastuzumab with a new chemotherapy agent in response to progression was not one of the questions addressed by this practice guideline. However, no trials were identified during the literature search that would have relevant data for this question.
4. In response to comment 5, the first recommendation states that trastuzumab plus a taxane is recommended as a first-line treatment but does not make any recommendation in comparison to other available first-line treatments.
5. In response to comment 7, the evidence at this time does not support any statement regarding more than six cycles of taxane chemotherapy.
6. In response to comment 9, the recommendation provided in response to Question #4 is all that is currently supported by the evidence.

Review by the Report Approval Panel (RAP)

The final Evidence-based Series report was reviewed and approved by one member of the PEBC RAP with expertise in clinical and methodology issues. This reviewer, as well as providing significant feedback regarding the clarity, consistency, and quality of the document, had one key issue of concern. Given that trastuzumab plus anthracycline-based chemotherapy showed similar benefits to trastuzumab plus paclitaxel chemotherapy in the Slamon trial (10), the reviewer felt that the draft recommendations did not clearly state why only trastuzumab plus paclitaxel was recommended. In response to this valid concern, the authors included an additional recommendation stating that due to cardiac toxicity, trastuzumab should not be combined with doxorubicin.

IX. PRACTICE GUIDELINE

This practice guideline report, whose recommendations, key evidence, and qualifying statements can be found in the summary at the beginning of the document, reflects the integration of the draft recommendations with feedback obtained from the external review process. The report has been approved by the Breast Cancer DSG.

X. CONFLICTS OF INTEREST

The members of the Breast Cancer DSG disclosed potential conflicts of interest relating to the topic of this practice guideline. Two of the four lead authors reported related research involvement and research funding. One author (MC) reported receiving grant or research funding from Roche Canada, and one (MT) reported the receipt of honoraria from that same company.

XI. JOURNAL REFERENCE

The previous version of this document was published as:

- Crump M, O'Malley F, Pritchard K, Levine M, Johnson M; Breast Cancer Disease Site Group. The use of trastuzumab (Herceptin) for the treatment of metastatic breast cancer and methods of assessing HER2/neu status - an evidence summary. *Curr Oncol.* 2000;7(4);242-51.

XII. ACKNOWLEDGEMENTS

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For a complete list of the Breast Cancer Disease Site Group members, please visit the CCO Web site at <http://www.cancercare.on.ca/>.

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52. Bernardo G, Palumbo R, Bernardo A, Villani G, Melazzini M, Frascaroli M. Weekly trastuzumab (Herceptin) and vinorelbine (navelbine) in chemo-naïve patients with HER2-overexpressing metastatic breast cancer: a phase II trial [abstract]. *Ann Oncol*. 2002;13 Suppl 5:51.
53. Baselga J, Kerrigan M, Burchmore M, Ash M. Health-related quality of life (HRQL) in women with HER2-overexpressing metastatic breast cancer (MBC) in a phase III study of Herceptin (R) plus chemotherapy versus chemotherapy alone [abstract]. *Breast Cancer Res Treat*. 1999;58 Suppl 1:S318.
54. Leyland-Jones B. Dose scheduling—Herceptin. *Oncology*. 2001;61 Suppl 2:31-6.
55. Seidman A, Berry D, Cirrincione C, Harris L, Dressler L, Muss H, et al. CALBG 9840: Phase III study of weekly (W) paclitaxel (P) via 1-hour (h) infusion versus standard (S) 3h infusion every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomized for T in HER2 normal MBC [abstract]. *J Clin Oncol (Meeting Abstracts)*. 2004;22(14 Suppl):A512.

EBS 1-15 Document Assessment and Review Tool.



Document Assessment and Review Tool

Number and title of document under review	UPG 1-15 The Role of Trastuzumab (Herceptin®) in the Treatment of Women with HER2/neu-overexpressing Metastatic Breast Cancer
Date of current version	November 8, 2005
Clinical reviewer	Dr. Yolanda Madarnas
Research coordinator	Rovena Tey
Date initiated	June 26, 2009
Date and final results / outcomes	June 11, 2010 (ENDORSED)
Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.	
1. Is there still a need for a guideline covering one or more of the topics in this document? Answer Yes or No, and explain if necessary:	1. YES
	If No, then the document should be ARCHIVED ¹ with no further action; go to 11 . If Yes, then go to 2 .
2. Are all the current recommendations based on the current questions definitive [*] or sufficient ⁵ , and have less than 5 years elapsed since the latest search? Answer Yes or No, and explain if necessary:	2. NO (not definitive, not sufficient, 5 y elapsed) • Guideline can be updated to incorporate a recent special advice report about trastuzumab beyond progression (CED/CCO 13)
	If Yes, the document can be ENDORSED ² with no further action; go to 11 . If No, go to 3 .
3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:	3. NO
	If Yes, the document should be taken off the Web site as soon as possible. A WARNING ¹ should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, go to 4 .
4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:	4. YES • Updated search to be completed by January 2010
	If No, a DEFERRAL ³ should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go to 5 .
5a. List below any new, relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Changes in BOLD .	
<ul style="list-style-type: none"> • Rephrase Q1 to include mono and combination therapies and multiple lines of treatment • Eliminate Q2 because it can be incorporated into Q1 • Add a new Q to address trastuzumab beyond progression • Eliminate Q3 because candidacy for trastuzumab is implicit in the HER2+ population selected for the studies • Q4-5 to remain the same, renumber to Q3-4. 	

Questions:

In women with HER2/neu-overexpressing metastatic breast cancer:

1. ~~Compared with chemotherapy alone, d~~Does trastuzumab, alone or in combination with other systemic therapy, in first-line chemotherapy and beyond, improve clinically meaningful outcomes (overall response rates, time-to-disease progression, overall survival, toxicity, or quality of life) compared with systemic therapy without trastuzumab?

2. ~~Compared with placebo or observation, does single-agent trastuzumab therapy improve clinically meaningful outcomes?~~

2. Does continued use of trastuzumab beyond disease progression improve clinically meaningful outcomes compared with discontinuing trastuzumab?

3. ~~What is the best way to identify women who will benefit from trastuzumab therapy?~~

3 4. What are the adverse events associated with trastuzumab therapy?

4 5. What are the optimal dose, schedule, and duration for trastuzumab therapy?

5b. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence). Changes in **BOLD**.

Include only RCTs; studies of 1st, 2nd, 3rd, 4th line chemotherapies, and beyond, progression; studies evaluating trastuzumab as a single agent or in various combinations

Inclusion Criteria:

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Trastuzumab, alone or in combination with other systematic therapy ~~or alone, was compared with systemic therapy without trastuzumab, evaluated using a randomized controlled trial, meta-analysis, or evidence-based clinical practice guideline or non-randomized trial (for the non-randomized trials, only those with 25 or more patients evaluable for efficacy outcomes were included).~~
- Reported outcomes included overall response rates, TTP, overall survival, toxicity, or quality of life.
- Clinical trial results were reported in either full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and add to the evidence available from fully published studies. Those data often appear first in meeting abstracts and may not be published for several years.

Exclusion Criteria:

Papers published in languages other than English were not considered.

Other documents to consider:

Madarnas Y, Haynes AE, Eisen A. The continued use of trastuzumab beyond disease progression in patients with metastatic breast cancer. CED/CCO Special Advice Report #13. 2009 Jun 28.

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.

Full Selection Criteria, Including Types of Evidence (e.g., randomized, non-randomized, etc.):

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Trastuzumab, alone or in combination with other systematic therapy, compared with systemic therapy without trastuzumab, evaluated using a randomized controlled trial, meta-analysis, or evidence-based clinical practice guideline.

- Reported outcomes included overall response rates, TTP, overall survival, toxicity, or quality of life.
- Clinical trial results were reported in either full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and add to the evidence available from fully published studies. Those data often appear first in meeting abstracts and might not be published for several years.

Exclusion Criteria:

- non-English language studies

Search Period:

- Aug 2004 to 4 Sep 2009 (Embase + Medline)
- 2006-2009 (ASCO)
- 2006-2009 (San Antonio BCS)

Brief Summary/Discussion of New Evidence:

Of 607 total hits from Medline + Embase and 874 total hits from ASCO + San Antonio conference abstract searches, 12 references representing 8 RCTs evaluated trastuzumab on 1 arm. 3 of the RCTs were already included in the existing guideline (rows highlighted in grey). 5 RCTs are potentially new studies of which, 4 were in abstract form, and 1 had a full text publication.

Interventions	Name of RCT	Phase of RCT	Population	Outcomes	Brief results	References
trastuzumab + capecitabine vs. capecitabine (2 nd line, beyond disease progression)	GBG26/ BIG 03-05 TBP	3	HER2+ metastatic, pretreated with taxane or trastuzumab	1 = TTP 2 = OS, DoR, PFS, response rate, toxicity	Trastuzumab improved ORR and TTP. Grps had similar toxicity.	Von Minckwitz G et al. 2009. J Clin Oncol. 27:1999-2006. Von Minckwitz G, 2008. ASCO 1025 Von Minckwitz G, 2007. San Antonio 4056
trastuzumab + anastrozole vs. anastrozole	TANDEM	3	HER2+ HR+ metastatic	1 = PFS 2 = TTP, ORR, OS, clinical benefit rate	Trastuzumab improved all outcomes.	Mackey J, et al. 2006. San Antonio 3
trastuzumab + letrozole vs. letrozole	ELECTRA		HER2+ HR+ metastatic	1 = TTP 2 = ORR, clinical benefit rate, safety	Trastuzumab led to longer TTP and higher clinical benefit rate.	Huober J, et al. 2009. San Antonio 4094
trastuzumab + epirubicin + cyclophosphamide vs. epirubicin + cyclophosphamide	HERCULES	2	HER2+ metastatic	1 = cardiac safety (e.g., LVEF) 2 = ORR and TTP	Trastuzumab reduced LVEF and improved ORR and TTP	Untch M, et al. 2007. San Antonio 4058
trastuzumab + lapatinib vs. lapatinib	EGF104900	3	HER2+ metastatic, pretreated with anthracycline and taxanes	1 = PFS 2 = clinical benefit rate, response rate, OS	Trastuzumab improved OS, PFS and clinical benefit rate.	Blackwell K, et al. 2009. San Antonio 61. O'Shaughnessy J, et al. 2008. ASCO 1015
vs. paclitaxel		2	HER2+ advanced	1 = ORR 2 = TTP, DoR, safety	ORR = trastuzumab + paclitaxel was superior to paclitaxel alone	Gasparini G et al. 2007. Breast Cancer Res Treat. 101:355-65.
trastuzumab + docetaxel vs. docetaxel (1 st line)	M77001		HER2+, metastatic	tumour response, ORR, OS, PFS, TTP, TTF, DoR, adverse events	Trastuzumab provided long-term survival benefit.	Marty M et al. 2005. J Clin Oncol. 23:4265-74. Marty M, 2006. San Antonio 2067.
trastuzumab + chemotherapy vs. chemotherapy (beyond disease progression)	H0659g	3	HER2+ metastatic	ORR, DoR, adverse events	Extension of trial H0648g. Prolonged use of trastuzumab is safe and well tolerated.	Tripathy D et al. 2004. J Clin Oncol. 22:1063-70.

DoR = duration of response; Grps = Groups HR = hormone receptor; LVEF = left ventricular ejection fraction; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TTF = time to treatment failure; TTP = time to disease progression; vs. = versus; 1 = primary endpoint; 2 = secondary endpoint

New References Identified of Studies with Trastuzumab on 1 Arm (alphabetical order):

Blackwell K, Burstein H, Sledge G, et al. 2009. Updated survival analysis of a randomized study of lapatinib alone or in combination with trastuzumab in women with HER2-positive metastatic breast cancer progressing on trastuzumab therapy. San Antonio 61. [abstract]

Gasparini G, Massimo G, Mariani L, et al. 2007. Randomized Phase II Trial of weekly paclitaxel alone versus trastuzumab plus weekly paclitaxel as first-line therapy of patients with Her-2 positive advanced breast cancer. Breast Cancer Research and Treatment. 101:355-65.

Huober J, Fasching P, Paepke S, et al. 2009. Letrozole in combination with trastuzumab is superior to letrozole monotherapy as first-line treatment in patients with hormone-receptor-positive, HER2-positive metastatic breast cancer - results of the eLEcTRA trial. San Antonio 4094. [abstract]

Mackey J, Kaufman B, Clemens M, et al. 2006. Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer. San Antonio BCS 3 [abstract]

Marty M, Cognetti F, Maraninchi D, et al. 2005. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: The M77001 study group. J Clin Oncol. 23:4265-74.

Marty M, Cognetti F, Maraninchi D, et al. 2006. Superior long-term survival benefits of trastuzumab plus docetaxel compared to docetaxel alone in patients with HER2-positive metastatic breast cancer: patients surviving more than 4 years in the M77001 study. San Antonio BCS 2067 [abstract]

O'Shaughnessy J, Blackwell K, Burstein H, et al. 2008. A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy. ASCO 1015 [abstract]

Tripathy D, Slamon D, Cobleigh M, et al. 2004. Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. J Clin Oncol. 22:1063-70. [extension of RCT]

Untch M, Tjulandin S, Jonat W, et al. 2007. Evaluation of first-line trastuzumab in combination with epirubicin/cyclophosphamide for patients with HER2-positive metastatic breast cancer. San Antonio BCS 4058 [abstract]

Von Minckwitz G, du Bois A, Schmidt M, et al. 2009. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: A German Breast Group 26/Breast International Group 03-05 study. J Clin Oncol. 27:1999-2006.

Von Minckwitz G, Vogel P, Schmidt M, et al. 2007. Trastuzumab treatment beyond progression in patients with HER-2 positive metastatic breast cancer the TBP study (GBG 26/BIG 3-05). San Antonio BCS 4056 [abstract]

Von Minckwitz G, Zielinski C, Maarteense E, et al. 2008. Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05). ASCO 1025 [abstract]

Literature Search Strategies:

Medline

1. meta-Analysis as topic/
2. meta analysis.pt.
3. (meta analy\$ or metaanaly\$).tw.
4. (systematic review\$ or pooled analy\$ or statistical pooling or mathematical pooling or statistical summar\$ or mathematical summar\$ or quantitative synthes?s or quantitative overview).tw.
5. (systematic adj (review\$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list\$ or bibliograph\$ or hand-search\$ or relevant journals or manual search\$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi\$ control\$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random\$.tw.
23. (clinic\$ adj trial\$1).tw.
24. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.

32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. limit 36 to human
38. exp breast neoplasms/
39. (cancer? or carcinoma? or neoplasm? or tumor?)r).tw.
40. (breast? or mammary).tw.
41. 39 and 40
42. 38 or 41
43. (metasta\$ or advanc\$).tw.
44. 42 and 43
45. (trastuzumab or herceptin).mp.
46. 44 and 45
47. 37 and 46
48. (200408: or 2005: or 2006: or 2007: or 2008: or 2009:).ed.
49. 47 and 48

Embase

1. exp meta analysis/ or exp systematic review/
2. (meta analy\$ or metaanaly\$).tw.
3. (systematic review\$ or pooled analy\$ or statistical pooling or mathematical pooling or statistical summar\$ or mathematical summar\$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review\$ or overview?)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list\$ or bibliograph\$ or hand-search\$ or relevant journals or manual search\$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi\$ control\$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random\$.tw.
18. (clinic\$ adj trial\$1).tw.
19. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. limit 31 to human
33. exp breast neoplasms/
34. (cancer? or carcinoma? or neoplasm? or tumor?)r).tw.
35. (breast? or mammary).tw.
36. 34 and 35
37. 33 or 36
38. (metasta\$ or advanc\$).tw.
39. 37 and 38
40. (trastuzumab or herceptin).mp.
41. 39 and 40
42. 32 and 41
43. (200432\$ or 2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$).ew.
44. 42 and 43

ASCO Annual Meeting - manually checked www.asco.org for all abstracts in the section: Breast cancer (2006) and Breast cancer - metastatic (2007-2009)

San Antonio Breast Cancer Symposium - searched www.sabcs.org with keywords: trastuzumab or herceptin and metast*

Go to 6.	
6. Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?	6. NO If Yes, then the document should be ARCHIVED with no further action; go to 11 . If No, go to 7 .
7. On initial review, does the newly identified evidence support the existing recommendations ? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:	7. YES <ul style="list-style-type: none"> • New evidence supports and does not contradict existing recommendations • However, new evidence includes comparisons of trastuzumab with other agents not addressed in the existing guideline (capecitabine, hormones - anastrozole and letrozole, lapatinib) that could be used to expand the recommendations • Rather than a full update, guideline #1-15 should be ENDORSED with the following note to expand the recommendations/qualifying statements: <p>The previous version of the guideline recommended the use of trastuzumab only with taxane chemotherapy as first-line therapy for metastatic breast cancer. Several qualifying statements stated that no data addressed second-line therapy and beyond, limited phase II data supported the use of vinorelbine plus trastuzumab after anthracycline/taxane exposure, no data addressed single-agent trastuzumab in first- or second-line therapy and beyond, the addition of another chemotherapy to trastuzumab at progression, or the continuation of trastuzumab beyond disease progression.</p> <p>Since the initial publication, new data has emerged to formulate new Qualifying Statements:</p> <ul style="list-style-type: none"> • Phase III data from a full-text publication shows benefit in TTP and ORR for trastuzumab in combination with capecitabine in second-line chemotherapy and beyond • Phase III data from abstracts show benefit in ORR, TTP, PFS, and OS for trastuzumab in combination with letrozole or anastrozole as first-line treatment of hormone-sensitive metastatic breast cancer • Phase III data from abstracts show benefit in PFS and OS for trastuzumab added to lapatinib compared with lapatinib alone • Further phase III data from abstracts confirm adverse cardiac effects for trastuzumab in combination with anthracycline • New data supports continuation of trastuzumab beyond disease progression (SAR) • No new data has emerged regarding the dose or schedule of trastuzumab

	If Yes, the document can be ENDORSED . If No, go to 8 .
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	8. Not applicable.
	If Yes, a WARNING note will be placed on the web site. If No, go to 9 .
9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	9. Not applicable.
	If Yes, the document update will be DEFERRED , indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 10 .
10. An update should be initiated as soon as possible. List the expected date of completion of the update:	10. Not applicable.
	An UPDATE ⁴ will be posted on the Web site, indicating an update is in progress.
11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.	
DSG Approval Date:	11 June 2010
Comments by DSG members:	<p>The phase 3 TANDEM trial (cited above as Mackey J et al 2006, San Antonio abstract 3) comparing trastuzumab + anastrozole versus anastrozole now has a full-text publication since the literature search for this form.</p> <ul style="list-style-type: none"> • Full text reference: J Clin Oncol. 2009 Nov 20;27(33):5529-37. • Overall survival in the overall and centrally confirmed hormone receptor-positive populations showed no statistically significant treatment difference; however, 70% of patients in the anastrozole-alone arm crossed over to receive trastuzumab after progression on anastrozole alone.

DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART

STEPS	Outcomes	Action
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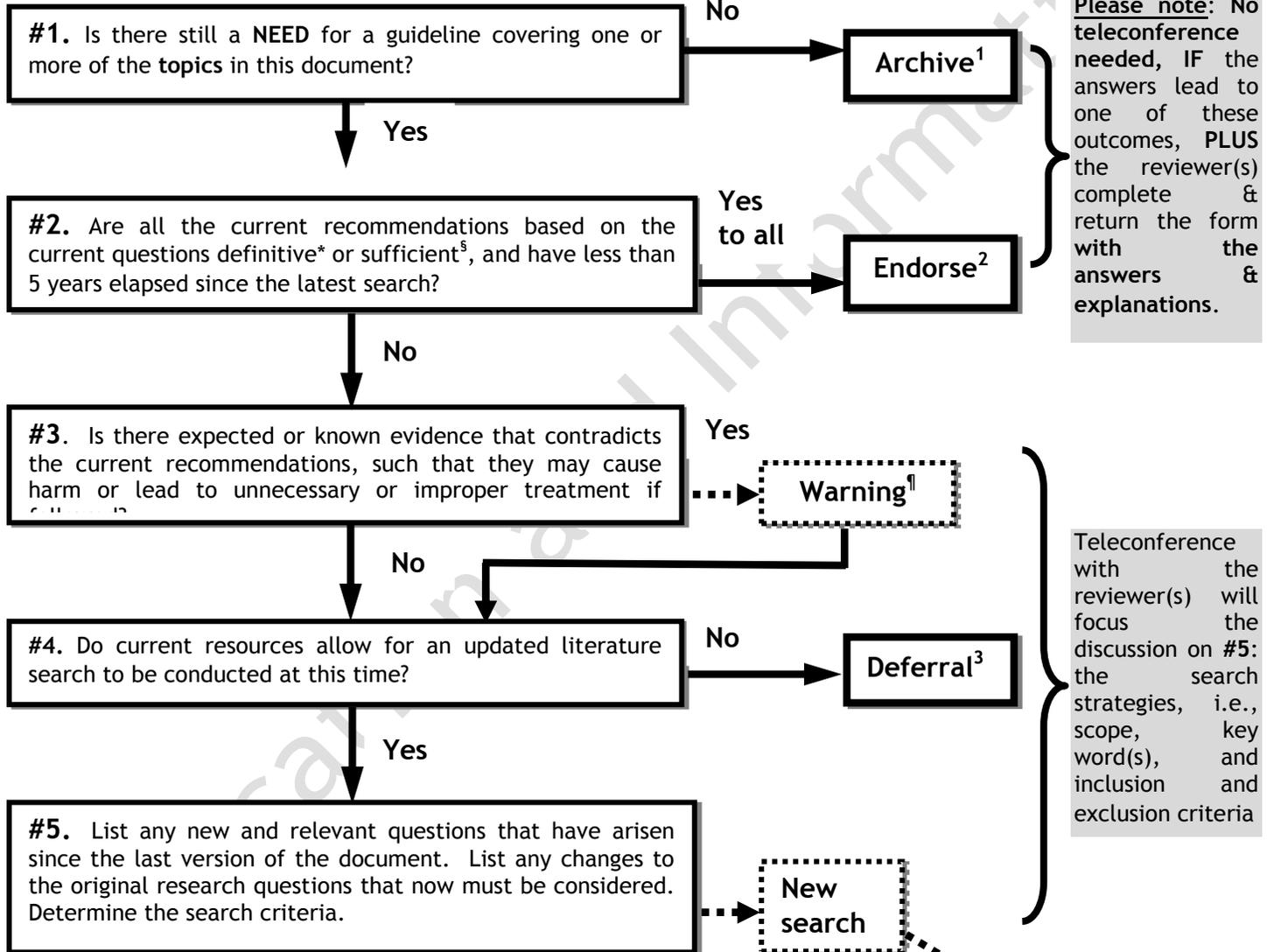
STEP 1: Initiation of the Document Assessment & Review process

RC emails DSG reviewer(s) the protocol

STEP 2: First teleconference to determine:

- the clinical relevance of the guideline,
- if a new literature search is needed, and
- if Yes, the search criteria.

Discuss questions #1-5



STEP 3: A new literature search based on input from #5 will be conducted, and the result will be sent to the reviewers with a follow-up date

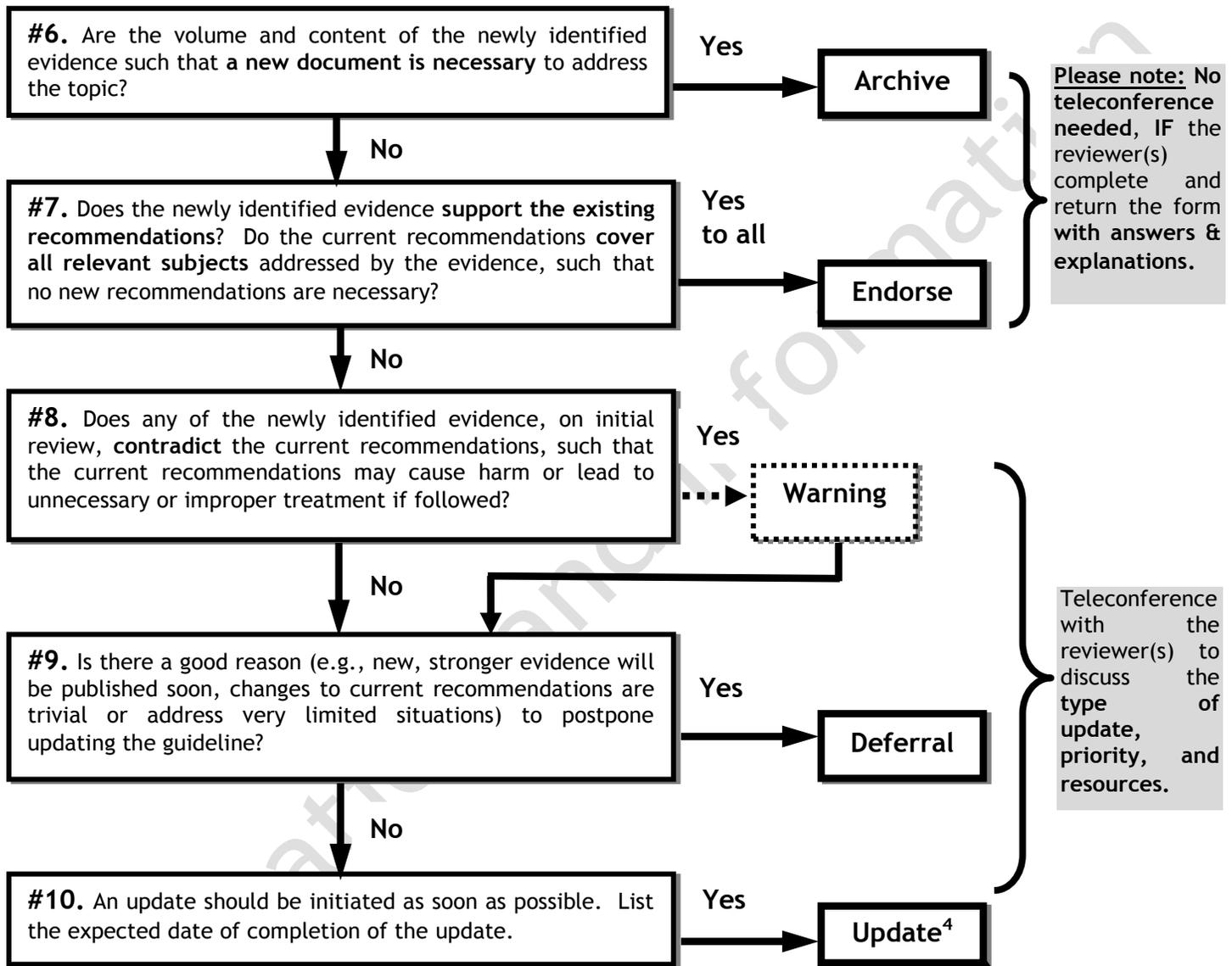
RC conducts new search

FLOW CHART (cont.)

STEPS	Outcomes	Action
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STEP 4: Second teleconference to determine the ultimate status of the document

Review questions #6-9



STEP 5: Final outcome approval; Document Assessment & Review questions #11

#11. Circulate this form, the new evidence, and a draft document for approval by the appropriate DSG. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.

RC emails draft for DSG approval

DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

***DEFINITIVE RECOMMENDATIONS** - Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§SUFFICIENT RECOMMENDATIONS - Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶WARNING - A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the Web site, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. **ARCHIVED** - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase "ARCHIVED".
2. **ENDORSED** - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.
3. **DEFERRAL** - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool (Appendix 2).
4. **UPDATE** - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.