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CED-CCO Special Advice Report 13 EDUCATION AND INFORMATION 2012

The Continued Use of Trastuzumab Beyond Disease Progression in Patients with Metastatic Breast Cancer

Y. Madarnas, A.E. Haynes, and A. Eisen

Report Date: August 17, 2009

This CED-CCO Special Advice Report was put in the Education and Information in 2012. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol). The report, which consists of consists of a Summary and a Full Report, is available on the CCO web site (http://www.cancercare.on.ca).

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Report Date: August 17, 2009

The 2009 guideline recommendations were put in the

Education and Information section

This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes.

SUMMARY

QUESTION

Does the continued use of trastuzumab (alone or in combination with other systemic therapies) after disease progression improve outcomes in women with metastatic breast cancer (MBC) compared to best supportive care or systemic therapy without trastuzumab? Outcomes of interest include overall survival (OS), progression-free survival (PFS), objective response rate (ORR), quality of life (QOL), and adverse events.

TARGET POPULATION

This evidence-based series applies to adult women with HER2-overexpressing MBC whose disease has progressed following prior treatment with trastuzumab.

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report.

- **For women with MBC whose disease has progressed on trastuzumab, continued use of trastuzumab in combination with capecitabine confers a clinically meaningful gain in progression-free survival and is a valid treatment option.**

- **Until more data becomes available, the continued use of trastuzumab with other agents is not supported.**

QUALIFYING STATEMENTS

- Two RCTS reported non significant trends to improved OS, ranging from 2.9 (1) months for lapatinib in combination with trastuzumab to 5.1 months for capecitabine in combination with trastuzumab (2). However, the O'Shaughnessy study has yet to be published in full, and given the lack of toxicity reporting and one death ascribed to cardiac toxicity, the observation of a 3.6 week difference in PFS is of questionable clinical significance.
- The published data only supports continued use of trastuzumab with either capecitabine or lapatinib and should only be used in this manner until such time as data regarding the continued use of trastuzumab with other agents is published.
- While the published data supports the continued administration of trastuzumab in combination with lapatinib, the current Heath Canada approved indication for lapatinib limits the applicability of this data in the Canadian context.
- Dose and schedule: trastuzumab 6 mg/kg intravenously (IV) every 21 days can be continued in combination with capecitabine 2500 mg/m^2 orally (PO) in divided doses daily x 14 days every 21 days. Trastuzumab 2 mg/kg IV weekly after a 4 mg/kg loading dose can be continued in combination with lapatinib 1000 mg PO daily continuously. However, the 21-day trastuzumab schedule of 6 mg/kg that is considered equivalent to the weekly schedule and is more commonly used in Ontario is an acceptable alternative to the weekly schedule.

KEY EVIDENCE

Two randomized controlled trials were identified that enrolled patients with MBC who had progressed during or after treatment with prior trastuzumab (1,2).

- Von Minckwitz et al (2) randomized patients to either capecitabine plus trastuzumab or to capecitabine alone. The authors reported a significant difference in progression-free survival in favour of capecitabine plus trastuzumab (median 8.2 months versus [vs.] 5.6 months, respectively; hazard ratio [HR]=0.69; 95% confidence interval [CI], 0.48 to 0.97; p=0.0338).
- O'Shaughnessy et al (1) randomized patients to either lapatinib plus trastuzumab to lapatinib alone. The authors reported a significant difference in progression-free survival in favour of lapatinib plus trastuzumab (median 12.0 weeks vs. 8.4 weeks, respectively; HR=0.77; 95% CI 0, 0.6 to 1.0; p=0.029).

FUTURE RESEARCH

One study combining vinorelbine with continued trastuzumab has recently closed and may report preliminary results at the 2009 San Antonio meeting. A number of other studies with various agents added to continued trastuzumab are ongoing.

IMPLICATIONS FOR POLICY

In 2009, an estimated 5400 deaths from breast cancer are expected in Canada, 2100 of which will occur in Ontario. Approximately 25-30% of the advanced breast cancer population is HER2 overexpressing and would be potentially eligible for treatment with trastuzumab at some point in their disease trajectory.

On May 21 2009 Health Canada granted Glaxo Smith Kline a Notice of Compliance (NOC) for lapatinib in combination with capecitabine for the treatment of patients with HER2-overexpressing advanced or metastatic breast cancer following progression on taxanes, anthracyclines, and trastuzumab.

RELATED PROGRAM IN EVIDENCE-BASED CARE GUIDELINES

Evidence-based Series

- #1-12: *The Role of Gemcitabine in the Management of Metastatic Breast Cancer*.
  Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34178.

Practice Guideline Reports

- #1-3 Version 2.2003: *The Role of the Taxanes in the Management of Metastatic Breast Cancer*.
  Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34140.
- #1-6: *Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer*.
  Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34174.
- #1-11 Version 2.2002: *Use of Bisphosphonates in Women with Breast Cancer*.
  Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34182.
- #1-16 Version 2.2003: *Capecitabine in Stage IV Breast Cancer*.
  Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13874.

Evidence Summary Reports

- #1-4: *Vinorelbine in Stage IV Breast Cancer*.
  Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34144.

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For information about the PEBC and the most current version of all reports, please visit the CCO web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES—SUMMARY

1. O'Shaughnessy J, Blackwell KL, Burstein H, Storniolo AM, Sledge G, Baselga J, et al. A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy [abstract]. J Clin Oncol (ASCO Annual Meeting Proceedings). 2008;26(15 Suppl):Abstract 1015.
2. von Minckwitz G, du Bois A, Schmidt M, Maass N, Cufer T, de Jongh FE, et al. 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.[see comment]. J Clin Oncol. 2009;27(12):1999-2006.

FULL REPORT

QUESTION

Does the continued use of trastuzumab (alone or in combination with other systemic therapies) after disease progression improve outcomes in women with metastatic breast cancer (MBC) compared to best supportive care or systemic therapy without trastuzumab? Outcomes of interest include overall survival (OS), progression-free survival (PFS), objective response rate (ORR), quality of life (QOL), and adverse events.

INTRODUCTION

Despite significant advances in the adjuvant systemic therapy of breast cancer and the improvements in survival seen over the past decade, a significant proportion of women with breast cancer will experience recurrence and develop metastatic disease. In 2009, an estimated 5400 deaths from breast cancer are expected in Canada, 2100 of which will occur in Ontario (1). Although incurable, recurrent breast cancer is highly treatable, with the intent of symptom palliation through disease control, improved QOL, and prolonged survival. Improvements in palliative systemic therapy over the last decade have led to a prolongation in median survival with MBC from 18-24 months to the current 24-36 months (2). Some of the most significant recent advances in the systemic therapy of breast cancer have come from the development of less toxic targeted therapies such as trastuzumab.

Palliative systemic therapy for MBC is characterized by the sequential administration of multiple agents before the patient's eventual death. For individuals with good performance status, each line of therapy contributes a small incremental gain in disease control on the patient's trajectory of breast cancer. Commonly used endpoints for clinical trials in MBC are PFS, time to progression (TTP), ORR, OS, and QOL. The control arm of such studies is always an active agent selected from a limited number of standard therapies, rather than best supportive care. The optimal sequence of therapy in MBC remains undefined, but the majority of women with metastatic breast cancer will at some point receive an anthracycline, a taxane, capecitabine, and for those who have HER2-overexpressing disease, trastuzumab.

METHODS

This advice report, produced by the Program in Evidence-based Care (PEBC) of CCO, is a convenient and up-to-date source of the best available evidence on the continued use of trastuzumab beyond disease progression in the treatment of adult women with MBC, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

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

Literature Search Strategy

MEDLINE (Ovid) (1990 through June Week 3 [June 26] 2009), EMBASE (Ovid) (1990 through Week 25 [June 26] 2009), and the Cochrane Library (2009, Issue 2) databases were searched. The search strategies for MEDLINE and EMBASE are shown in Appendix 1. Search strategies in other databases were similar.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) 2004 to 2009, the San Antonio Breast Cancer Symposium (SABCS) 2003 to 2008, the European Breast Cancer Conference (EBCC) 2004 to 2008, and the Congresses of the European Society for Medical Oncology (ESMO) and the European Cancer Organization (ECCO) 2003 to

2008 were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp), and the National Institute for Clinical Excellence (http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published full-report articles or published meeting abstracts of:

1. Randomized trials that compared systemic therapy with trastuzumab to either best supportive care or systemic therapy without trastuzumab in adult women with MBC who had progressive disease following previous treatment with trastuzumab.
2. Single-arm phase II trials of trastuzumab, alone or in combination with other systemic therapies, in adult women with MBC who had progressive disease following previous treatment with trastuzumab.
3. Systematic reviews, meta-analyses, or clinical practice guidelines of trastuzumab in adult women with MBC who had progressive disease following previous treatment with trastuzumab.
4. Publications of single-arm trials, randomized trials, systematic reviews, or meta-analyses that have reported data on one or more of the following outcomes: OS, PFS, ORR, QOL, or adverse events.

Exclusion Criteria

Studies were excluded if they were:

1. Single-arm trials reported in abstract form only.
2. Letters, comments, books, notes, or editorial publications.
3. Articles published in a language other than English, due to financial considerations for translation.

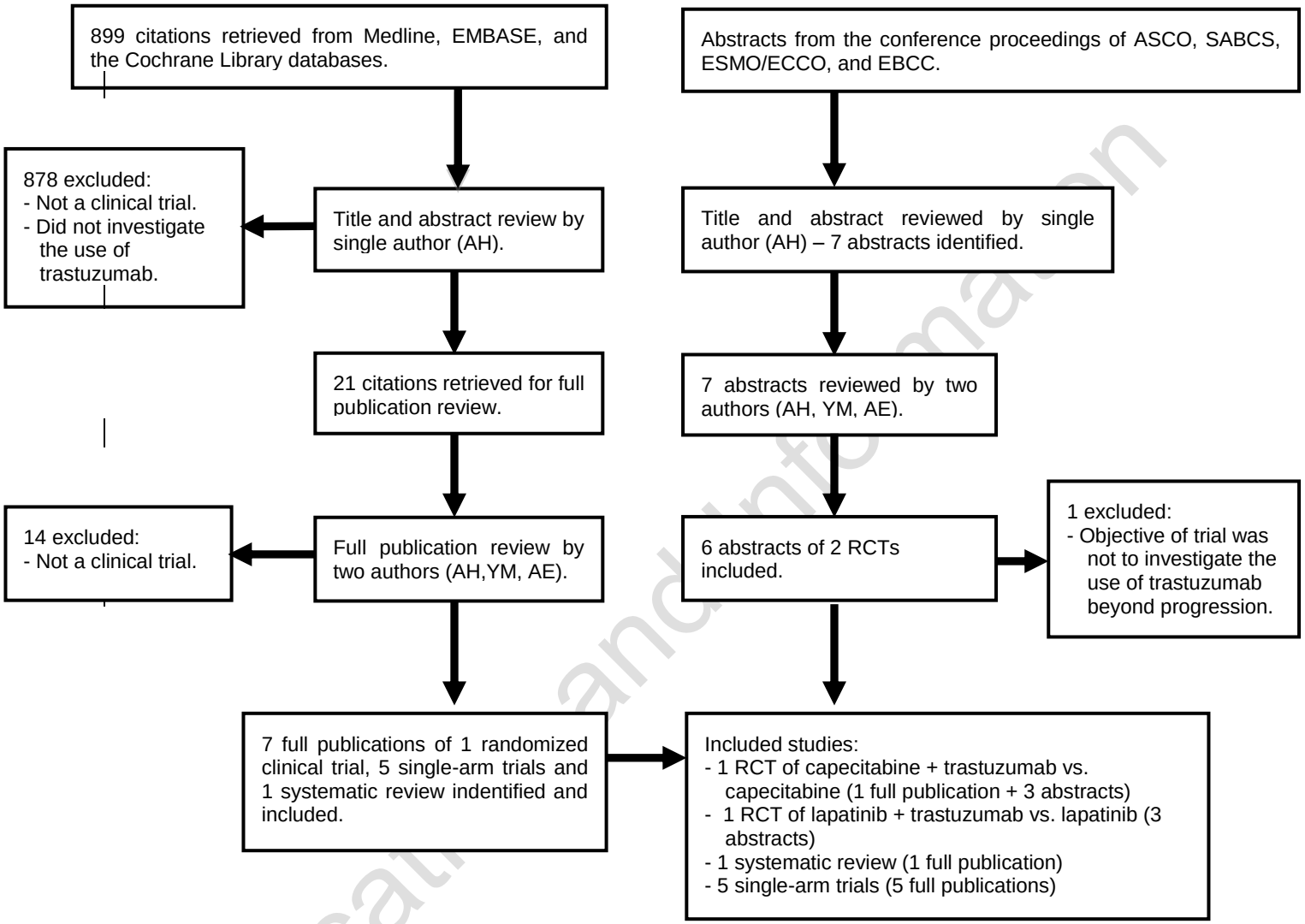
Synthesizing the Evidence

Data appropriate for pooling or meta-analysis are not expected but will be investigated if the possibility exists. For planned analyses, the primary outcome of interest is PFS, secondary outcomes of interest are response rate and OS, and subset analyses will be conducted by histology.

Literature Search Results

A total of 899 citations of studies that investigated the continued use of trastuzumab in women with locally advanced or metastatic breast cancer who had progressed after prior trastuzumab were identified from the MEDLINE, EMBASE, and Cochrane Library databases. From those citations, a total of seven full publications (3-9) met eligibility criteria and were included (Figure 1). In addition, six abstracts of two randomized trials met the eligibility criteria and were included (10-15). Thus, in total, two randomized trials, five single-arm trials, and one systematic review were identified.

Figure 1. Selection of studies investigating trastuzumab beyond progression in metastatic breast cancer from the search results of MEDLINE, EMBASE, and the Cochrane Library databases, and the conference proceedings of ASCO, SABCS, ESMO/ECCO, and EBCC.



One additional trial, reported in abstract form by Najagami et al (16), was identified that randomized patients with MBC who had not received previous chemotherapy for MBC nor did they received any previous trastuzumab or docetaxel to sequential trastuzumab monotherapy until progression followed by combination trastuzumab and docetaxel versus combination trastuzumab and docetaxel until progression. The objective of the trial was to determine whether treating MBC with trastuzumab monotherapy followed by combination trastuzumab and docetaxel after progression was superior to first-line combination therapy in previously untreated MBC patients. The trial did not meet our eligibility criteria and was excluded.

Systematic Reviews

One systematic review was identified (3). Fabi et al reported the results of a systematic review and a retrospective study of MBC patients who progressed following treatment with trastuzumab. Only the systematic review was included in this report as the retrospective study did not meet the inclusion criteria. Of the eight studies included in the systematic review, only two met our eligibility criteria (4,5) and are reviewed separately in the corresponding section of this document.

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool (17) was used to assess the methodological quality of the systematic review, because the tool has been demonstrated to be both reliable and valid (18,19). The AMSTAR tool consists of 11 items assessing the quality of systematic reviews. The ratings for each item on the tool for the systematic review reported by Fabi et al can be found in Table 1. The systematic review scored a 'yes' on three items: publication type as an eligibility criterion, the appropriateness of the methods used to combine the study findings, and the declaration of conflict of interest. The remaining eight items were either not reported or were not performed. Overall, the quality of the systematic review was low. Importantly, the authors only searched MEDLINE, and they did not provide the dates of the search. In addition, the authors did not report the methods used to select studies (e.g., number of reviewers, inclusion or exclusion criteria) nor the methods used to extract data. Objective response rates for each study were combined using a weighted mean to provide a combined objective response rate.

Table 1. AMSTAR ratings of included systematic reviews.

Item	Fabi, 2008 (3)
A priori design provided?	N
Duplicate study selection and data extraction?	N
Comprehensive literature search performed?	N
Status of publication used as an inclusion criteria?	Y
List of included/excluded studies provided?	N
Characteristics of included studies provided?	N
Scientific quality of included studies assessed and reported?	N
Scientific quality of included studies used appropriately to form conclusions?	N
Study findings combined appropriately?	Y
Assessment of publication bias?	N
Declaration of conflict of interest?	Y

Fabi et al (3) identified nine studies, including their own retrospective series reported within the systematic review. A total of 937 patients were included in the nine studies. The authors reported data on objective response rates for this group of patients; however, it was impossible to determine whether the data were reporting the response rate after continuing trastuzumab following an initial progression or if the data were reporting the response rate for the initial progression prior to continuing trastuzumab. Given the lack of clarity and lack of further data, this systematic review is not referred to further in this report.

Randomized Trials

Trial and Patient Characteristics

Two randomized trials evaluating the use of trastuzumab beyond disease progression were identified (9-15). One trial, reported by von Minckwitz et al (9), was fully published, and the other trial was reported in abstract form only (13-15). Trial and patient characteristics can be found in Table 2.

Both von Minckwitz and O'Shaughnessy enrolled patients with HER2-positive MBC who had progressed during prior treatment with a trastuzumab-containing therapy. O'Shaughnessy et al (14) randomized 296 patients to lapatinib plus trastuzumab versus lapatinib alone. Patients had to have received prior taxane and anthracycline therapy. O'Shaughnessey et al (14) did not report whether differences existed between the treatment groups at baseline.

Von Minckwitz et al (9) randomized 156 patients to capecitabine plus trastuzumab versus capecitabine alone. Patients could have received no more than one prior chemotherapeutic agent for metastatic disease. Baseline characteristics were similar between treatment groups. Sixty-eight percent of 78 patients who received capecitabine alone and 71% of 78 patients who received capecitabine plus trastuzumab had previously received an anthracycline. Eight-two percent and 87% of patients, respectively, had previously received a taxane.

Table 2. Patient and intervention details for RCTs of trastuzumab beyond disease progression in metastatic breast cancer.

Author, year (ref)	Patient characteristics	Treatment	Differences between treatment groups at baseline
von Minckwitz, 2009 (9)	HER2 positive MBC (or locally advanced) that progressed during treatment with trastuzumab with or without adjuvant or first-line metastatic chemo.	CAP 2,500 mg/m^2 d1-14 + trastuzumab 6 mg/kg q3w CAP 2,500 mg/m^2 d1-14 q3w	Similar
O'Shaughnessy, 2008 (14) abs Burstein, 2008 (13) abs Blackwell, 2008 (15) abs	HER2 positive MBC who progressed on prior trastuzumab-containing therapy and who had received prior taxane and anthracycline therapy.	Lapatinib 1000 mg/d + trastuzumab 2 mg/kg q1w (LD 4 mg/kg) Lapatinib 1500 mg/d	NR

Notes: abs=abstract; CAP=capecitabine; chemo=chemotherapy; d=day(s); DCT=Docetaxel; LD=loading dose; MBC=metastatic breast cancer; NR=not reported; PD=progressive disease; RCTs=randomized controlled trials; q=every; ref=reference; w=week(s).

Trial Quality

Quality characteristics of the two trials are shown in Table 3. Von Minckwitz et al (9) reported the final analysis of an unblinded, randomized trial that was terminated early due to poor accrual. The primary outcome was TTP, with secondary outcomes of OS and the clinical benefit rate. The final analysis was intent-to-treat.

Many of the quality aspects of the trial reported by O'Shaughnessy et al (14) were simply not reported as the trial has not been fully published. The primary endpoint was PFS and the secondary outcomes were the clinical benefit rate, defined as complete response plus objective response plus stable disease, OS, and the ORR. The authors did not report a sample-size calculation.

Table 3. Quality characteristics of identified RCTs.

Author, year (ref)	Primary outcome	Required sample size	Secondary outcomes	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Losses to follow-up	Ethical Approval
Fully published											
von Minckwitz, 2009 (9)	TTP	482 pts req'd to give 80% power at α=0.05 to detect a 27.5% improvement in TTP (4 mos to 5.1 mos).[A]	CBR, OS	Block permutation – stratified[B]	Yes	No	Yes	Yes	Yes[A]	NR	Yes
Abstracts											
O'Shaughnessy, 2008 (14)	PFS	NR	24w CBR, ORR, OS	NR – stratified[C]	NR	NR	Yes	NR	NR	NR	NR

Notes: abs=abstract; CBR=clinical benefit rate (complete response + objective response + stable disease); ITT=intention-to-treat; mos=months; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; pts=patients; ref=reference; req'd=required; w=week(s).

[A]Trial was terminated early because of poor accrual due to the registration of lapatinib.

[B]Stratified by pre-treatment: taxane/trastuzumab as first-line therapy, n=111; taxane/trastuzumab as adjuvant, n=3; trastuzumab alone or without taxanes as first line therapy, n=42.

[C]Stratified by hormone receptor status and visceral disease status.

Efficacy Outcomes

Data on efficacy outcomes for trials of continued trastuzumab beyond disease progression in MBC can be found in Table 4.

Table 4. Efficacy outcomes for RCTs of trastuzumab beyond disease progression in metastatic breast cancer.

Author, year (ref)	Treatment	N	OR (%)	Comp	OS			PFS/TTP[A]			Follow-up, mdn (mos)
					Mdn (mos)	Comp	HR (95% CI)	Mdn (mos)	Comp	HR (95% CI)	
von Minckwitz, 2009 (9)	CAP + T	78	48.1	p=0.0115	25.5	p=0.257	0.77 (NR)	8.2	p=0.0338	0.69 (0.48-0.97)	15.6
	CAP	78	27.0		20.4			5.6			
O'Shaughnessy, 2008 (14) abs	L + T	296	10.3	p=0.46	11.9	p=0.106	0.75 (0.5-1.1)	12.0 w	p=0.029	0.77 (0.6-1.0)	NR
	L		6.9		9.0			8.4 w			

Notes: abs=abstract; CAP=capecitabine; CI=confidence interval; comp=comparison; HR=hazard ratio; L=lapatinib; mdn=median; mos=months; N=number of patients; NR=not reported; NS=not significant; NYR=not yet reached; OR=objective response rate; OS=overall survival; PFS=progression-free survival; ref=reference; TTP=time-to-progression; T=trastuzumab; w=weeks.
[A]Von Minckwitz et al (ref) reported TTP and O'Shaughnessy et al (ref) reported PFS.
[B]Objective response rate for patients with measurable disease: BVZ 15 mg/kg, N=206; BVZ 7.5 mg/kg, N=201; placebo, N=207.

Survival

Both trials reported better median overall survival for patients that received trastuzumab in combination with other systemic therapies compared to the same therapy without trastuzumab; however, both trials reported that the observed differences were not statistically significant (Table 4).

Progression

Both randomized trials reported significant differences in progression endpoints. Von Minckwitz et al (9) reported that median TTP was longer for patients who received capecitabine plus trastuzumab compared to capecitabine alone (8.2 months vs. 5.6 months; HR=0.69; p=0.0338). O'Shaughnessy et al (14) reported that median PFS was longer for patients who received lapatinib plus trastuzumab compared to trastuzumab alone (12.0 weeks vs. 8.4 weeks; HR=0.77; p=0.029).

Response

Von Minckwitz et al (9) also reported a statistically higher objective response rate for patients who received trastuzumab combination therapy compared to without trastuzumab (48.1% vs. 27.0%; p=0.0115). In addition, the authors reported a significantly greater clinical benefit rate for the capecitabine plus trastuzumab arm compared to the capecitabine alone arm (75.3% vs. 54.1%; p=0.0068).

O'Shaughnessy et al (14) reported a higher objective response rate for patients who received lapatinib plus trastuzumab compared to lapatinib alone; however, that difference was not statistically significant (10.3% vs. 6.9%; p=0.46). Of note, the authors reported that the clinical benefit rate was significantly higher for lapatinib plus trastuzumab compared to lapatinib alone (25.2% vs. 13.2%; p=0.020).

Quality of life

An abstract by Burstein et al (13) reported a QOL analysis for the trial of lapatinib plus trastuzumab compared to lapatinib alone. QOL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B), Functional Assessment of Cancer Therapy-General (FACT-

G) questionnaires, and the trial outcome index. Patients were assessed at baseline, week 4, and every eight weeks thereafter. The authors reported that QOL was comparable for patients receiving lapatinib plus trastuzumab compared to lapatinib alone following progression on previous trastuzumab therapy.

Adverse Events

O'Shaughnessy et al (14) reported that the rate of grade 1 or 2 diarrhea was 53% vs. 41% for patients receiving lapatinib plus trastuzumab compared to lapatinib alone, respectively. The authors did not report whether that difference was statistically significant. One patient in the lapatinib plus trastuzumab arm died due to cardiac toxicity. No further data on adverse events were reported.

Von Minckwitz et al (9) reported the rates of several grade 3 or 4 adverse events, which can be found in Table 5. The authors reported no statistically significant differences in grade 3 or 4 adverse events. Grade 1 to 4 anemia was significantly more common in the capecitabine plus trastuzumab arm compared to the capecitabine-alone arm (64.0% vs. 44.4%; p=0.0208). No other significant differences in any grade of adverse events were reported.

Table 5. Grade 3 or 4 adverse events in RCTs of trastuzumab beyond disease progression in metastatic breast cancer.

Author, year (ref)	Treatment	N	Neutropenia (%)	Febrile neutropenia (%)	Thrombocytopenia (%)	Anemia (%)	Vomiting (%)	Diarrhea (%)	Mucositis (%)	Edema (%)	Fatigue (%)	Skin Changes (%)	Nail changes (%)	Sensory neuropathy (%)	Infection (%)	Fever (%)	Dyspnea (%)	Cardiovascular disorder (%)
von Minckwitz, 2008 (9) abs	CAP + T	78	5.33	2.60	0	0	1.3	15.58	1.30	0	3.90	32.47	3.90	2.60	2.60	1.30	2.60	5.19
	CAP	78	4.35	0	1.39	2.78	4.05	18.92	2.70	1.35	5.41	24.32	0	5.41	8.11	0	6.76	2.70
O'Shaughnessy, 2008 (14) abs	L + T	296	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	L		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Notes: abs=abstract; CAP=capecitabine; L=lapatinib; N=number of treated patients; RCTs=randomized controlled trials; ref=reference; T=trastuzumab.

Single-arm Phase II Trials

Trial and Patient Characteristics

Five prospective single-arm trials were identified that investigated the use of trastuzumab beyond disease progression in patients with MBC (Table 6). All the trials combined trastuzumab with another systemic therapy (Table 6). One trial enrolled 26 patients who did not receive prior trastuzumab (4); however, the authors reported that patients continued to receive trastuzumab after progression. The remaining four trials enrolled patients with MBC who had progressed on prior trastuzumab-containing therapy. Dang et al (6) enrolled only 12 patients, and Bartsch et al enrolled 29 patients (8) and 40 patients (7) in two separate trials. Tripathy et al (5) had the largest sample size, enrolling 93 patients in an extension study of a previous study that investigated trastuzumab plus chemotherapy compared to chemotherapy alone in MBC. The extension study enrolled 154 patients who progressed following chemotherapy alone and 93 patients who progressed following trastuzumab plus chemotherapy. Only the data for the 93 patients who progressed on prior trastuzumab are reported in this systematic review. Both Christodoulou et al (4) and Tripathy et al (5) allowed trastuzumab after disease progression in combination with other systemic therapies, which were at the discretion of the treating physician. Patients in the trials reported by Christodoulou et al (4) and Bartsch et al, 2007 (7) had a median of two prior lines of therapy. Dang et al (6) reported that patients had a median of two or more lines of prior therapy, and Bartsch et al, 2008 (8) reported that patients had a median of three lines of prior therapy.

Table 6. Patient and intervention details of single-arm trials of trastuzumab beyond disease progression in metastatic breast cancer.

Author, year (ref)	Patient characteristics	Treatment	N
Christodoulou, 2003 (4)	HER2 positive MBC. Age ≥ 18 years, ECOG PS ≤ 2. No prior trastuzumab.	Trastuzumab 2 mg/kg iv 30 min (LD 4 mg/kg iv over 90 min) + PAC 70-90 mg/m^2, q1w until progression then trastuzumab + chemo[A] until death or toxicity	26
Tripathy, 2004 (5)	HER2 positive MBC who progressed on prior trastuzumab-containing therapy.	Trastuzumab 2 mg/kg q1w + chemo[A]	93
Dang, 2004 (6)	HER2 positive MBC who progressed on prior trastuzumab-containing therapy for at least 12w, either as a single agent or in combination. Age ≥ 18 years.	Trastuzumab: 2 mg/kg iv 30 min q1w; or, 6 mg/kg iv 90 min q3w combined with celecoxib 400 mg orally, twice daily	12
Bartsch, 2007 (7)	HER2 positive MBC who progressed on prior trastuzumab-containing therapy and prior adjuvant or palliative anthracylcline and taxane or vinorelbine.	CAP 2,500 mg/m^2/d d1-14 + trastuzumab 6 mg/kg (LD 8 mg/kg), q3w	40
Bartsch, 2008 (8)	HER2 positive MBC. Karnofsky PS ≥ 70. All patients had progressed on prior trastuzumab-containing therapy.	GEM 1250 mg/m^2 d1,8 + trastuzumab 6 mg/kg (LD 8 mg/kg), q3w	29

Notes: abs=abstract; CAP=capecitabine; chemo=chemotherapy; d=day(s); ECOG=Eastern Cooperative Oncology Group; GEM=gemcitabine; iv=intravenous; LD=loading dose; MBC=metastatic breast cancer; N=number of patients; NR=not reported; PAC=paclitaxel; PS=performance status; q=every; ref=reference; w=week(s).

[A]Patients could receive chemotherapy at the discretion of their treating physician.

Efficacy Outcomes

Efficacy outcomes for the single-arm trials of trastuzumab beyond disease progression can be found in Table 7. Christodoulou et al (4) did not provide sufficient details regarding the reported response rates and progression outcomes to determine if they were for the initial treatment period or after disease progression. As the objective of this systematic review is focused on the efficacy of trastuzumab beyond disease progression, the data from that trial on objective response and progression outcomes was not useful, given the lack of information. Only the OS data were used in this systematic review.

Table 7. Efficacy outcomes for single-arm trials of trastuzumab beyond disease progression in metastatic breast cancer.

Author, year (ref)	Treatment	N	OS mdn (mos)	PFS mdn (mos)	TTP mdn (mos)	OR (%)	Follow-up mdn (mos)
Christodoulou, 2003 (4)	T + chemo	26	34+	NR	NR	NR	32
Tripathy, 2004 (5)	T + chemo	93	NR	NR	NR	11	NR
Dang, 2004 (6)	T + celecoxib	12	NR	NA	NA	0	NR
Bartsch, 2007 (7)	T + CAP	40	24	NR	8	20	19
Bartsch, 2008 (8)	T + GEM	29	17	NR	3	17.2	NR

Notes: CAP=capecitabine; chemo=chemotherapy; GEM=gemcitabine; mdn=median; mos=months; N=number of patients; NA=not applicable; NR=not reported; OR=objective response; OS=overall survival; PFS=progression-free surival; ref=reference; T=trastuzumab; TTP=time-to-progression.

Survival

Christodoulou et al (4) reported median overall survival of more than 34 months for 26 patients who received trastuzumab in combination with other systemic therapy after disease progression, after a median follow-up of 32 months. Bartsch et al reported median overall survival of 17 months for 29 patients who received trastuzumab in combination with gemcitabine (8) and 24 months for 40 patients who received trastuzumab in combination with capecitabine (7).

Response and progression

Bartsch et al reported that median TTP was three months for patients who received trastuzumab plus gemcitabine (8) and eight months for patients who received trastuzumab plus capecitabine (7). The ORRs were 17.2% of 29 patients (8) and 20% of 40 patients (7). Dang et al (6) reported that none of 12 patients had an objective response for trastuzumab in combination with celecoxib. Tripathy et al (5) reported an ORR of 11% of 93 patients who received trastuzumab in combination with systemic therapy.

Quality of life

None of the single-arm trials reported data on QOL.

Adverse Events

Each of the trials reported different grade 3 or 4 adverse events (Table 8). The only adverse event that was reported in more than one trial was grade 3 or 4 neutropenia: 11.5% of 26 patients in the trial reported by Christodoulou et al (4) and 20.7% of 29 patients in Bartsch et al (8). Of note, Bartsch et al, 2007 (7) reported that no patient experienced grade 3 or 4 neutropenia. Grade 1 or 2 adverse events were reported in all four trials and included, but were not limited to, rash, fatigue, mucositis, diarrhea, neutropenia, thrombocytopenia, anemia, nausea, and vomiting (4-6,8).

Table 8. Grade 3 or 4 adverse events in single-arm trials of trastuzumab beyond disease progression in metastatic breast cancer.

Author, year (ref)	Treatment	N	Neutropenia (%)	Thrombocytopenia (%)	Leukopenia (%)	Nausea/ Vomiting (%)	Alopecia (%)	Neuropathy (%)	Pain (%)	Asthenia (%)	Back pain (%)	Headache (%)	Dyspnea (%)	Addominal pain (%)	Diarrhea (%)	Hand-foot syndrome (%)
Christodoulou, 2003 (4)	T + chemo	26	11.5	0	11.5	0	46.1	15.4	0	0	0	0	0	0	0	0
Tripathy, 2004 (5)	T + chemo	93	NR	NR	11	NR	NR	NR	10	10	6	6	2	NR	NR	NR
Dang, 2004 (6)	T + celecoxib	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	8	0	NR
Bartsch, 2007 (7)	T + CAP	40	0	0	NR	0	0	0	0	0	0	0	0	0	5.0	15.0
Bartsch, 2008 (8)	T + GEM	29	20.7	13.8	0	3.4	0	0	0	0	0	0	0	0	0	0

Notes: abs=abstract; CAP=capecitabine; GEM=gemcitabine; N=number of treated patients; ref=reference; T=trastuzumab.

DISCUSSION

The current evidence for the continued use of trastuzumab in MBC beyond disease progression is very limited and consists of two RCTs reported in abstract form only, one systematic review, and five single-arm trials. The systematic review included only single-arm trials and retrospective series (3). The systematic review was of poor quality, and only three of the single arm studies it summarized met the inclusion criteria for review in this document.

One RCT investigated the use of trastuzumab combined with capecitabine compared to capecitabine alone after disease progression on trastuzumab (9). Unfortunately that trial was terminated early due to poor accrual. The final analysis demonstrated a statistically significant 2.6 month gain in TTP in favour of the trastuzumab combination (HR=0.69; 95% CI, 0.48 to 0.97). No significant difference in overall survival was seen but the trial was underpowered to detect statistically significant differences in OS as the primary endpoint of the trial was time-to-progression and the trial was closed early. The remaining RCT investigated the use of a new non-cytotoxic agent, lapatinib in combination with trastuzumab compared to lapatinib alone (14). The authors reported a statistically significant gain of 3.6 weeks in PFS (HR=0.77; 95% CI 0.6 to 1.0; p=0.029). The authors reported no significant difference in OS. Both RCTS reported non significant trends to improved OS, ranging from 2.9 months (14) to 5.1 (9) months. The O'Shaughnessy study has yet to be published in full, and given the lack of toxicity reporting and one death ascribed to cardiac toxicity, the observation of a 3.6 week difference in PFS is of questionable clinical significance. Furthermore, lapatinib has Health Canada approval limited to the treatment of MBC in combination with capecitabine, and therefore, the applicability of this trial in the Canadian context is limited.

The single-arm trials of trastuzumab beyond progression demonstrated ORRs of 0% of 12 patients when a non-cytotoxic agent (celecoxib) was added to trastuzumab (6) to 60% of 40 patients with the addition of capecitabine to trastuzumab (7). Following progression on trastuzumab, median survival rates ranged from 17 months for patients who received trastuzumab and gemcitabine (8) to 20 months for patients who received trastuzumab and capecitabine (8). Christodoulou et al (4) reported a median OS exceeding 34 months after a median 32 months of follow-up for patients who received trastuzumab in combination with other systemic therapy.

Although limited toxicity data was reported across all the studies, no unexpected or worrisome toxicity signals were reported. Grade 3 or 4 neutropenia was reported in two single-arm trials (4,8) and one RCT (9) of trastuzumab beyond disease progression. Other commonly reported adverse events of any grade included nausea and vomiting, leukopenia, and diarrhea. It should be noted that the two single-arm trials reported by Christodoulou et al (4) and Tripathy et al (5) allowed trastuzumab to be combined with different systemic therapies, at the discretion of the treating physician. For both trials, it is difficult to determine what adverse events could be specifically ascribed to the continued use of trastuzumab.

In terms of dose and schedule, trastuzumab 6 mg/kg intravenously (IV) every 21 days can be continued in combination with capecitabine 2500 mg/m^2 orally (PO) in divided doses daily for 14 days every 21 days. Trastuzumab 2mg/kg IV weekly after a 4mg/kg loading dose can be continued in combination with lapatinib 1000 mg PO daily continuously. However, the 21-day trastuzumab schedule of 6mg/kg that is considered equivalent to the weekly schedule and is more commonly used in Ontario is an acceptable alternative to the weekly schedule.

Although trastuzumab can be safely used in combination with a number of agents, the published data for continued use beyond progression supports its use only in combination with capecitabine or lapatinib. One study combining vinorelbine with continued trastuzumab has recently closed and may report preliminary results at the 2009 San Antonio meeting. A

number of other studies with various agents added to continued trastuzumab are ongoing. Until such time these are reported, continued use of trastuzumab beyond progression can only be supported with capecitabine or lapatinib.

CONCLUSIONS

Women with heavily pretreated HER2-overexpressing MBC have limited treatment options. It is the opinion of the authors that the continued use of trastuzumab in combination with capecitabine offer clinically meaningful gains in PFS for this difficult-to-treat poor-prognosis subset of women with MBC and that both treatment strategies are options for women with HER2-overexpressing MBC progressing on trastuzumab.

ONGOING TRIALS

The National Cancer Institute clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical Trials database (http://clinicaltrials.gov/) were searched for reports of new or ongoing randomized trials investigating the continued use of trastuzumab in patients with locally advanced or metastatic breast cancer who have progressed following prior treatment with trastuzumab. Appendix 2 provides details of the identified ongoing trials.

CONFLICT OF INTEREST

The authors of this special advice report were asked to disclose potential conflicts of interest related to the topic of this special advice report and reported no conflicts of interest.

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Appendix 1. Literature search strategies.

Ovid MEDLINE

1. exp breast neoplasms/
2. ((breast or mammary or mammarian) and (cancer$ or carcinoma$ or neoplasm$ or tumo?r$ or malignan$)).tw.
3. 1 or 2
4. HER2$.tw.
5. receptor, erbB-2/
6. 4 or 5
7. 3 and 6
8. metasta$.tw.
9. exp Neoplasm Metastasis/
10. advanc$.tw.
11. (stage adj3 iv).tw.
12. or/8-11
13. 7 and 12
14. trastuzumab$.tw.
15. herceptin$.tw.
16. 14 or 15
17. 13 and 16
18. meta-analysis as topic/
19. meta analysis.pt.
20. meta analy$.tw.
21. metaanaly$.tw.
22. (systematic adj (review$1 or overview$1)).tw.
23. or/18-22
24. cochrane.ab.
25. embase.ab.
26. (cinahl or cinhal).ab.
27. science citation index.ab.
28. bids.ab.
29. cancerlit.ab.
30. or/24-29
31. reference list$.ab.
32. bibliograph$.ab.
33. hand-search$.ab.
34. relevant journals.ab.
35. manual search$.ab.
36. or/31-35
37. selection criteria.ab.
38. data extraction.ab.
39. 37 or 38
40. review.pt.
41. review literature as topic/
42. 40 or 41
43. 39 and 42
44. comment.pt.
45. letter.pt.
46. editorial.pt.
47. or/44-46

48. 23 or 30 or 36 or 43
49. 48 not 47
50. randomized controlled trials as topic/
51. randomized controlled trial.pt.
52. random allocation/
53. double blind method/
54. single blind method/
55. exp Clinical Trials as Topic/
56. exp clinical trial/
57. (clinic$ adj trial$1).tw.
58. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
59. placebos/
60. placebo$.tw.
61. (allocated adj2 random$).tw.
62. random allocation.tw.
63. randomly allocated.tw.
64. or/50-63
65. case report.tw.
66. letter.pt.
67. historical article.pt.
68. or/65-67
69. 64 not 68
70. 49 or 69
71. practice guideline/
72. practice guideline$.mp.
73. 71 or 72
74. 70 or 73
75. 17 and 74
76. limit 75 to (English language and humans)

EMBASE

1. exp Breast Cancer/
2. ((breast or mammary or mammarian) and (cancer$ or carcinoma$ or neoplasm$ or tumo?r$ or malignan$)).tw.
3. 1 or 2
4. her2$.tw.
5. oncogene neu/
6. epidermal growth factor receptor 2/

7 or/4-6

8. 3 and 7
9. metasta$.tw.
10. Breast Metastasis/
11. advance$.tw.
12. (stage adj3 iv).tw.
13. or/9-12
14. 8 and 13
15. trastuzumab$.tw.
16. herceptin$.tw.
17. trastuzumab/

18. or/15-17
19. 14 and 18
20. exp meta-analysis/
21. ((meta adj analy$) or metaanaly$).tw.
22. (systematic adj (review$1 or overview$1)).tw.
23. or/20-22
24. cancerlit.ab.
25. cochrane.ab.
26. embase.ab.
27. (cinahl or cinhal).ab.
28. science citation index.ab.
29. bids.ab.
30. or/24-29
31. reference list$.ab.
32. bibliograph$.ab.
33. hand-search$.ab.
34. manual search$.ab.
35. relevant journals.ab.
36. or/31-35
37. data extraction.ab.
38. selection criteria.ab.
39. 37 or 38
40. review.pt.
41. 39 and 40
42. letter.pt.
43. editorial.pt.
44. 42 or 43
45. 23 or 30 or 36 or 41
46. 45 not 44
47. clinical trial/
48. randomized controlled trial/
49. randomization/
50. single blind procedure/
51. double blind procedure/
52. crossover procedure/
53. placebo/
54. randomi?ed control$ trial$.tw.
55. rct.tw.
56. random allocation.tw.
57. randomly allocated.tw.
58. allocated randomly.tw.
59. (allocated adj2 random$).tw.
60. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
61. placebo$.tw.
62. prospective study/
63. or/47-62
64. case study/
65. case report.tw.
66. abstract report/
67. letter/

68. or/64-67
69. 63 not 68
70. 46 or 69
71. exp practice guideline/
72. practice guideline$.tw.
73. 71 or 72
74. 70 or 73
75. 19 and 74
76. limit 75 to (human and English language)

Appendix 2. Ongoing trials.

A randomized, open-label study to compare progression-free survival in patients with HER2 positive metastatic breast cancer who continue or discontinue Herceptin in combination with 2nd line chemotherapy, having progressed on 1st line chemotherapy in combination with Herceptin.

Protocol ID:	NCT00448279
Last date modified:	June 16, 2009
Trial type:	Randomized, open-label
Accrual:	300
Primary outcome:	Progression-free survival
Sponsorship:	Hoffmann-La Roche
Status:	Ongoing, not accruing

A randomized, open-label study to compare time to disease progression in patients with HER2 positive metastatic breast cancer who continue or discontinue Herceptin in combination with 2nd line chemotherapy, having progressed on 1st line chemotherapy in combination with Herceptin.

Protocol ID:	NCT00444587
Last date modified:	June 16, 2009
Accrual:	274
Trial type:	Randomized, open-label
Primary outcome:	Time to disease progression
Sponsorship:	Hoffmann-La Roche
Status:	Accruing

A randomized, multicentre, phase III open-label study of the efficacy and safety of tratuzumab-MCC-DM1 vs. capecitabine + lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab-based therapy.

Protocol ID:	NCT00829166
Last date modified:	March 3, 2009
Trial type:	Randomized, open-label
Accrual:	580
Primary outcome:	Progression-free survival, adverse events
Sponsorship:	Genentech; Hoffmann La-Roche
Status:	Accruing

A randomized study of weekly vinorelbine (Navelbine®) alone or in combination with trastuzumab (Herceptin®) (NSC-688097) for patients with HER-2-positive metastatic breast cancer whose tumours have progressed after taxane + trastuzumab combination therapy – phase III.

Protocol ID:	NCT00103233
Last date modified:	February 6, 2009
Accrual:	292
Trial type:	Randomized, open-label
Primary outcome:	Progression-free survival
Sponsorship:	Southwest Oncology Group; National Cancer Institute (NCI)
Status:	Completed