pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Eribulin (Halaven) for Metastatic Breast Cancer

August 2, 2012

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effect of eribulin monotherapy on patient outcomes compared to specific chemotherapeutic regimens without eribulin in the treatment of patients who have previously received at least two chemotherapeutic regimens for metastatic breast cancer or incurable locoregionally recurrent breast cancer, and who have previously received both anthracyclines and taxanes in the adjuvant and/or advanced-stage disease setting.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One multi-centre, open-label, randomized trial (EMBRACE), met the inclusion criteria for the pCODR systematic review.[1] The EMBRACE study randomized 762 women with locally recurrent or metastatic breast cancer who had received between two and five previous chemotherapy regimens, including an anthracycline and a taxane, in a 2:1 ratio to receive eribulin mesylate (n=508) or treatment of physician's choice (TPC) (n=254).[1] The agents most commonly administered to patients in the TPC arm included vinorelbine, gemcitabine, capecitabine, taxanes, anthracyclines, and hormone therapy.[1]

The primary outcome of the EMBRACE study was overall survival, defined as the time from randomization to the date of death or the last date the patient was known to be alive (date of censoring) and was analysed using an intention-to-treat population.[1] The final analysis, with a data cut-off of May 12, 2009, demonstrated a statistically significant difference in overall survival for eribulin (median 13.1 months) compared to TPC (median 10.6 months), with HR 0.81, 95% confidence interval (CI) 0.66-0.99, p=0.041.[1] Secondary outcomes in the EMBRACE study included progression-free survival, objective response rate, and duration of response. Quality of life was not measured.

1.2.2 Additional Evidence

pCODR received input on eribulin from two patient advocacy groups, Canadian Breast Cancer Network and Canadian Cancer Survivor Network. Provincial Advisory Group input was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

1.2.3 Interpretation and Guidance

Breast cancer is the most commonly diagnosed malignancy in Canadian women and it is the second leading cause of cancer deaths in woman. Although novel systemic agents have been introduced over the past 10-15 years for the treatment of metastatic breast cancer, there remains the need for new and improved chemotherapeutic agents, both in terms of efficacy and tolerability.

One open-label randomized trial, the EMBRACE study, met the inclusion criteria for the pCODR systematic review.[1] In this study, treatment with eribulin demonstrated a

statistically significant improvement in overall survival, when compared to TPC. The Clinical Guidance Panel considered that the absolute improvement in median survival of 2.7 months was a modest, but clinically meaningful benefit, in a heavily pre-treated population of patients. The agents delivered on the TPC arm where noted to be in line with the available chemotherapeutic agents available and used in Canadian practice today.

The adverse event profile was similar between eribulin and the range of chemotherapy options studied in the EMBRACE trial. Serious adverse events (Grade 3 or higher) occurred in 25.0% of 503 patients in the eribulin arm and in 25.9% of 247 patients in the TPC arm.[1] Two clinically important toxicities, peripheral neuropathy and febrile neutropenia, were noted to be higher with eribulin.

There were a few limitations identified with the EMBRACE study, including the open-label nature of the trial. However, it was noted that as TPC was used as the comparator arm, the implementation of blinding in the trial design would have been extremely difficult. In addition, other limitations identified included that there is a lack of clear information in regards to the dose intensity in both the eribulin and TPC arms, and there was no quality of life information collected in the trial.

1.3 Conclusions

The pCODR Breast Clinical Guidance Panel concluded that there **is a net overall clinical benefit** to eribulin in the 3rd line or greater treatment of women with incurable locally advanced/metastatic breast cancer previously exposed to anthracyclines and taxanes, based on a single high-quality randomized controlled trial (EMBRACE)[1] that demonstrated a clinically and statistically significant benefit in overall survival for women treated with eribulin compared with those treated with physician's choice.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Metastatic breast cancer is the second leading cause of cancer death in women and there is a need for new and improved chemotherapeutic agents, both in terms of efficacy and tolerability.
- Eribulin demonstrated an improvement in overall survival in a heavily pre-treated population of patients with limited efficacious options available.
- Although the rates of peripheral neuropathy and febrile neutropenia were shown to be higher for eribulin, it was noted that these rates were comparable to other standard chemotherapeutic agents administered in the metastatic breast cancer setting, such as the taxanes. This also aligned with patient values where patients indicated that they would be willing to tolerate potential adverse effects of a treatment if it was found to prolong their survival.
- There are two clinical situations where the Clinical Guidance Panel noted there was insufficient evidence from the EMBRACE trial to make any definite conclusions regarding eribulin treatment, including whether eribulin should be used in place of, or following, capecitabine therapy and whether eribulin could be considered in patients who have not previously been treated with anthracyclines and/or taxanes due to medical contraindications.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding eribulin for metastatic breast cancer The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website,www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding eribulin for metastatic breast cancer conducted by the pCODR Breast Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on eribulin and a summary of submitted Provincial Advisory Group Input on eribulin are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Eribulin inhibits tubulin polymerization and microtubule dynamics, interfering with normal mitotic spindle formation resulting in blocks within the prometaphase portion of mitosis.[2]

Eribulin mesylate (eribulin) has a Health Canada indication for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane administered in either the adjuvant or metastatic setting.[3]

There are several commonly used and generally accepted treatments in Canada for patients with metastatic breast cancer or locally recurrent breast cancer that have previously received at least two prior chemotherapy regimens in the metastatic or incurable locally recurrent setting. Many of these patients have previously received both anthracyclines and taxanes as adjuvant or advanced-stage treatment; however, no single agent or regimen has demonstrated a clear benefit in this setting. The currently accepted chemotherapeutic treatments include: vinorelbine monotherapy; capecitabine monotherapy; gemcitabine monotherapy; gemcitabine combination therapy with a platinum agent; taxanes, or; anthracyclines.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of eribulin monotherapy on patient outcomes compared to specific chemotherapeutic regimens without eribulin in the treatment of patients who have previously received at least two chemotherapeutic regimens for metastatic breast cancer or incurable locoregionally recurrent breast cancer, and

who have previously received both anthracyclines and taxanes in the adjuvant and/or advanced-stage disease setting.

See Section 6.2.1 for more details on the pCODR systematic review protocol.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

Trial Characteristics

One open-label randomized trial (EMBRACE) was identified that compared the use of eribulin monotherapy to treatment of physician's choice (TPC) in patients with metastatic breast cancer or incurable locally recurrent breast cancer who have previously received at least two chemotherapeutic regimens for metastatic breast cancer or incurable locally recurrent breast cancer, and who have previously received both anthracyclines and taxanes in the adjuvant and/or advanced-stage disease setting.[1] A summary of key trial characteristics can be found in Table 1.

The primary outcome was overall survival. Secondary outcomes included progression-free survival, objective response rate, and duration of response. Tumour response was assessed using the Response Evaluation in Solid Tumours (RECIST). Analyses of progression-free survival, objective response rate, and duration of response were based on independent masked review of tumour assessments.

The required sample size, based on the primary outcome of overall survival, was originally 630 patients, randomized in a 2:1 ratio to eribulin:TPC, to achieve 411 events. With an estimated median overall survival of nine months in the TPC arm and 12 months in the eribulin arm (hazard ratio [HR] of 0.75), the study would have a two-sided alpha of 0.05 and a power of 80%.[4] Due to a lower than expected overall death rate, the sample size requirement was increased to 1000 patients; however, no change was made to the number of events required for the final analysis. The death rate was calculated for both trial arms combined and the data were not unmasked at this time.

The baseline demographic and disease characteristics were balanced between the two treatment arms. The mean age (minimum to maximum; standard deviation) was 54.8 (28-85; 10.34) years in the eribulin arm and 55.9 (27-81; 10.43) years in the TPC arm. Of 762 patients in the EMBRACE trial, 6.7% were less than 40 years of age, 73.5% were between 40 years and 65 years of age, and 19.8% were 65 years or older. The median number of previous chemotherapy regimens was four (range, 1-7). Of 762 patients, 99% previously received chemotherapy with a taxane, 99% previously received an anthracycline, and 73% previously received capecitabine. Of 762 patients, 81% were refractory (defined as progression on or within six months of receiving treatment) to a taxane, 68% were refractory to capecitabine, and 58% were refractory to an anthracycline.[1]

A total of 762 patients were randomized in a 2:1 ratio to receive eribulin monotherapy (1.4 mg/m^2 on days 1 and 8 of a 21-day cycle; n=508) or to TPC (defined as any single-agent chemotherapy, hormonal, or biological treatment

approved for the treatment of cancer; n=254). At the time of the final analysis (data cut-off of May 12, 2009), a total of 334 (43.8%) of 762 patients were alive, 422 (55.4%) had died, and six (0.8%) were lost to follow-up.

One potential limitation of the study was the lack of blinding; however, given the choice of TPC as the comparator arm, the implementation of blinding in the trial design would have been extremely difficult. Nonetheless, the lack of blinding of the study treatment personnel and patients had the potential to impact the results of the trial.

Table 1. Summary of EMBRACE Study[1]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study E7389-G000-305 **EMBRACE study** 135 centres in 19 countries in North America, Western Europe, Australia, Eastern Europe, Latin America, and South Africa Patients enrolled from November 16, 2006 to November 17, 2008. Enrolled: n=762 Randomized: n=762 Open-label, RCT Randomized in a 2:1 ratio (eribulin:TPC) Randomization was stratified by: A) Geographical region.[A] B) Previous capecitabine C) HER2 (ERBB2) status	Diagnosis of breast cancer with measurable or evaluable disease. Between 2-5 previous chemotherapy regimens including an anthracycline and a taxane, and two or more regimens for locally recurrent or metastatic breast cancer. Progression within 6 months or less of latest chemotherapy. Age ≥18 years ECOG PS ≤2 Adequate bone marrow, liver and renal function. Exclusion criteria: Previously enrolled in an eribulin trial. Use of investigational drug within 4 weeks of study. Treatment with chemotherapy, radiation, trastuzumab, or hormone therapy within 3 weeks of study. Known brain metastases unless treated and stable. Pre-existing neuropathy higher than Grade 2.	Two arms: Eribulin mesylate 1.4 mg/m^2 i.v. over 2-5 min on day 1 and 8 of a 21-day cycle. (n=508) Or TPC (defined as any single-agent chemotherapy, hormonal, or biological treatment approved for the treatment of cancer; n=254)	Primary Overall survival Secondary Progression-free survival Objective response Duration of response Adverse events were also reported as summary statistics

Notes: ECOG PS=Eastern Cooperative Oncology Group Performance Status; TPC=treatment of physician's choice.
[A]Region 1—North America, Western Europe, Australia; Region 2—Eastern Europe; Region 3—Latin America, South Africa.

Outcome Data and Summary of Outcomes

The primary efficacy analysis was based on the ITT population which comprised all randomized study subjects (eribulin arm, n=508; TPC arm, n=254).[1] The safety population consisted of all randomized patients who had received treatment on-study according to the arm to which they were assigned (eribulin arm, n=503; TPC arm, n=247).[1] A summary of key efficacy and harms outcomes can be found in Table 2 below.

Table 2. Summary of Key Trial Outcomes from EMBRACE[1]

Efficacy	Analysis	Intervention	Median [months] (95% CI)	HR (95% CI)	p-value	Median follow-up [months]
Overall Survival	Final (data cut-off: May 12, 2009)	Eribulin TPC	13.1 (11.8-14.3) 10.6 (9.3-12.5)	0.81 (0.66-0.99)	p=0.041	14[A]
	Updated (data cut-off: March 3, 2010)	Eribulin TPC	13.2 (12.1-14.4) 10.5 (9.2-12.0)	0.81 (0.67-0.96)	p=0.014	24[A]
Progression-free survival	Independent assessment	Eribulin TPC	3.7 (3.3-3.9) 2.2 (2.1-3.4)	0.87 (0.71-1.05)	p=0.137	-
	Investigator assessment	Eribulin TPC	3.6 (3.3-3.7) 2.2 (2.0-2.6)	0.76 (0.64-0.90)	p=0.002	-

Harms	Eribulin (N=503)	TPC (N=247)
Deaths from AE, n (%)	20 (4.0)	18 (7.3)
Any AE, n (%)	497 (98.8)	230 (93.1)
SAE, n (%)	126 (25.0)	64 (25.9)
AE leading to discontinuation, n (%)	67 (13.3)	38 (15.4)
Peripheral neuropathy Any Grade Grade 3/4	 174 (34.6) 41 (8.2)	 40 (16.2) 5 (2.0)
Febrile neutropenia	23 (4.6)	4 (1.6)
Neutropenia-Grade 3/4	227 (45.1)	52 (21.1)

Notes: AE=adverse event; CI=confidence interval; HR=hazard ratio; SAE=serious adverse event; TPC=treatment of physician's choice.

[A]Median follow-up data were obtained from the submitter at the checkpoint meeting.[5]

The final study analysis (data cut-off May 12, 2009) demonstrated a statistically significant difference in overall survival for eribulin (median 13.1 months) compared to TPC (median 10.6 months), with a HR of 0.81, 95% confidence interval (95% CI) of 0.66-0.99, p=0.041.[1] There were a total of 422 deaths (55.4% of 762 patients) in the trial. One-year survival rates were 53.9% of 508 patients in the eribulin arm and 43.7% of 254 patients in the TPC arm. The median follow-up was 14 months in both treatment arms.[5]

An updated overall survival analysis (data cut-off March 3, 2010) was conducted at the request of the European Medicines Agency (EMA) when more than 75% of the randomized patients had died.[1] At the data cut-off the analysis included 589 deaths (77.3% of 762 patients). A statistically significant difference in overall survival was found for eribulin (median 13.2 months) compared to TPC (median 10.5 months), with a HR 0.81, 95% CI of 0.67-0.96, p=0.014. One-year survival rates were 54.5% in the eribulin arm and 42.8% in the TPC arm. The median follow-up was 24 months in both study arms.[5]

No statistically significant difference in independently-assessed progression-free survival was demonstrated for eribulin (median 3.7 months) compared to TPC (median 2.2 months), with a HR of 0.87, 95% CI 0.71-1.05, p=0.137.[1] The investigator-assessed progression-free survival demonstrated a statistically significant difference for eribulin (median 3.6 months) compared to TPC (median 2.2 months), with a HR of 0.76, 95% CI 0.64-0.90, p=0.002.[1]

Adverse events of all Grades occurred in 98.8% of 503 patients in the eribulin arm and in 93.1% of 247 patients in the TPC arm.[1] Peripheral neuropathy of any Grade occurred in 34.6% of 503 patients in the eribulin arm and in 16.2% of 247 patients in the TPC arm.[1] Serious (Grades 3 or 4) adverse events occurred in 25.0% of 503 patients in the eribulin arm and in 25.9% of 247 patients in the TPC arm. Grade 3 or 4 peripheral neuropathy occurred in 8.2% of 503 patients in the eribulin arm and in 2.0% of 247 patients in the TPC arm. Febrile neutropenia occurred in more patients in the eribulin arm (4.6%) than in the TPC arm (1.6%) as did Grade 3 or 4 neutropenia (eribulin 45.1%; TPC 21.1%). Adverse events leading to discontinuation occurred in 13.3% of patients in the eribulin arm and in 15.4% of patients in the TPC arm. Lastly, 20 of 503 (4.0%) patients in the eribulin arm and 18 of 247 (7.3%) patients in the TPC arm died due to adverse events.[1]

No quality of life data were reported for the EMBRACE trial.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

No supplemental issues were identified during the development of this report.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, access to additional therapies that will increase life expectancy is an important aspect when consideration is given to treatment. Patients are also looking for treatments with manageable side effect profiles, that will not negatively affect their quality of life, especially as their disease progresses. However, patient input also indicated that many patients would be willing to tolerate the potential adverse effects of a treatment if it was found to prolong their survival, even for a short period of time.

PAG Input

Input on the eribulin (Halaven) review was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, there is currently no standard of care in this treatment setting (i.e. new line of therapy), so issues surrounding the additional costs relating to eribulin as well as additional implementation costs, such as the need for chemotherapy chair time, would be of importance. PAG also identified that there is a potential for wastage with this drug therapy which would need to be included in the economic evaluation. In addition, it was noted that the use of eribulin may be extended to other patient populations, such as those with earlier stages of metastatic disease, and PAG would appreciate any clinical evidence to support this use.

Other

The product monograph for eribulin (Halaven) provided by the manufacturer (Eisai Limited) provides the following warnings:[3]

Cardiovascular

Halaven is associated with QT/QTc interval prolongation. Many drugs that cause QT/QTc prolongation are suspected to increase the risk of torsade de pointes. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death. Use of Halaven in patients with congenital long QT/QTc syndrome should be avoided. The concomitant use of Halaven with another QT/QTc-prolonging drug should be avoided to the extent possible.

The safety of Halaven has not been established in patients with significant cardiovascular impairment (history of congestive heart failure New York Association >Grade 2, unstable angina or myocardial infarction within the previous 6 months, or serious cardiac arrhythmia).

Hematologic

Myelosuppression is dose dependant and primarily manifested as neutropenia. Febrile neutropenia occurred in 5% of patients receiving Halaven. Fatal outcome has been observed due to complications with neutropenia. Patients should have Absolute Neutrophil Count (ANC) values ≥1,500 cells/mm3 and platelets >100,000/mm3 at the initiation of treatment with Halaven. Frequent monitoring of complete blood counts should be performed on

all patients receiving Halaven. Patients should only be retreated with Halaven when ANC is ≥1,000 cells/mm3, platelets are ≥75,000/mm3, and any other toxicity of a previous cycle has recovered to Grade ≤2 (except anemia). Patients experiencing febrile neutropenia, severe neutropenia, or thrombocytopenia may require a subsequent reduction of the dose of Halaven. Patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x the upper limit of normal (ULN) or bilirubin >1.5 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Reduction of the starting dose for patients with ALT or AST>3 x ULN or bilirubin >1.5 x ULN should be considered. These patients should be monitored closely for toxicity.

Neurologic

Monitor patients closely for signs of peripheral neuropathy. Dosage in patients experiencing peripheral neuropathy should be adjusted according to the recommendations in Table 4 [in Dosage and Administration section of Product Monograph]. Halaven may aggravate existing neuropathy and should be used with caution in patients with pre-existing neuropathy.

Halaven has not been studied in patients with severe hepatic or renal impairment

2.2 Interpretation and Guidance

Burden of Metastatic Breast Cancer

Breast cancer deaths are the second most common cause of cancer mortality in women in Canada, with an estimated 5,100 deaths in 2011. Breast cancer deaths also contribute to the greatest potential life years lost from any illness in Canadian women. Though many end-points are clinically important in the treatment of metastatic breast cancer, an improvement in overall survival is considered to be one of the most important to strive for by women with breast cancer, health care professionals and regulatory bodies. This is reinforced by the input from the patient advocacy groups on this submission (see section 4).

Effectiveness of Eribulin

EMBRACE is an open-label randomized controlled trial that compared the use of eribulin monotherapy (1.4 mg/m^2 i.v. day 1 and 8 on a 21 day cycle) to treatment of physician's choice (TPC) in patients with metastatic breast cancer (MBC) or incurable locally recurrent breast cancer.[1] The study population (n=762) included women who had previously received at least two chemotherapeutic regimens for MBC/incurable locally recurrent breast cancer, and who had previously received both anthracyclines and taxanes in the adjuvant and/or advanced-stage disease setting.

The primary clinical end-point was overall survival with a number of secondary endpoints including progression free survival , objective response rates and duration of response. The study demonstrated a statistically significant improvement in OS (median improvement from 10.5 months TPC vs. 13.2 months eribulin; HR 0.81 with 95% CI 0.67-0.96 p=0.014). With a relative improvement in overall survival of approximately 20% and an absolute improvement in median survival of 2.7 months, this magnitude of benefit is statistically significant and has a modest but still clinically meaningful benefit. The magnitude of clinical benefit was maintained at data cut-offs with 14 and 24 months of follow-up. In the

latest analysis (24 months of follow-up), with greater than 75% of events (deaths) having occurred, it is unlikely these results will change.

The study was conducted in the appropriate patient population (MBC with a median of 4 prior chemotherapy regimens and prior exposure to anthracyclines and taxanes) with appropriate comparators in the vast majority of cases. The open label manner of the study is reasonable with the primary end-point of overall survival. The lack of collection of quality of life measures is a significant short-fall of the study; gains in clinical outcome need to be balanced against alterations in quality of life.

Safety of Eribulin

Adverse events of all grades occurred in 98.8% of 503 patients in the eribulin arm and in 93.1% of 247 patients in the TPC arm. Peripheral neuropathy of any grade occurred in 34.6% of 503 patients in the eribulin arm and in 16.2% of 247 patients in the TPC arm.[1] Serious (Grades 3 or 4) adverse events occurred in 25.0% of 503 patients in the eribulin arm and in 25.9% of 247 patients in the TPC arm. Grade 3 or 4 peripheral neuropathy occurred in 8.2% of 503 patients in the eribulin arm and in 2.0% of 247 patients in the TPC arm. Febrile neutropenia occurred in more patients in the eribulin arm (4.6%) than in the TPC arm (1.6%), as did grade 3 or 4 neutropenia (eribulin 45.1%; TPC 21.1%). Adverse events leading to discontinuation occurred in 13.3% of patients in the eribulin arm and in 15.4% of patients in the TPC arm. Lastly, 20 of 503 (4.0%) patients in the eribulin arm and 18 of 247 (7.3%) patients in the TPC arm died due to adverse events.

In terms of the toxicity spectrum, the number of deaths from an adverse event, the number of serious adverse events and the number of adverse events leading to discontinuation of study treatment were similar (if not numerically less) for eribulin versus the chemotherapy comparators in EMBRACE. Two clinically important toxicities however were higher for eribulin: the rates of peripheral neuropathy (any grade [34.6%] as well as grade 3-4 [8.2%]) as well as the rate of febrile neutropenia (4.6% for eribulin).[1] These rates are comparable to other standard chemotherapy agents prescribed in metastatic breast cancer (e.g. taxanes).

The safety profile and adverse event rate was similar between eribulin and the comparator drugs studied.

Limitations of the Evidence

The limitations are: there is only one study (EMBRACE) to rely upon, there is lack of clear information in regard to dose intensity of both the eribulin and the TPC arms, and there was no collection of quality of life on the trial. In regard to the dose intensity, from the publication it is stated that there was greater use of granulocyte colony stimulating factor in the eribulin arm (18%) compared to the TPC arm (8%). While not necessarily a limitation, the Clinical Guidance Panel did note that progression-free survival was not statistically different between the two arms of the study upon independent assessment (though it was on investigator assessment) and the median differences in progression-free survival was more limited than the median differences in overall survival.[1] It is recognized that progression-free survival does not completely correlate with overall survival in metastatic breast cancer, and that the hazard ratio is a better reflection of the

differences between the efficacy of the arms on a trial. In EMBRACE, the hazard ratio for progression-free survival and overall survival were in similar ranges.

The Clinical Guidance Panel determined that there are at least two subgroups in which there may be insufficient evidence from the EMBRACE trial to extrapolate from that has clinical implications in the Canadian environment. The first is whether eribulin should be used in place of, or following capecitabine. The majority of the study population (73 %) had prior exposure to capecitabine, but in the TPC arm only 18% were prescribed capecitabine as the study treatment. Until the results of the phase III trial comparing eribulin to capecitabine in the treatment of metastatic breast cancer is known (see section 6.4, Ongoing Trials), it would be reasonable to consider eribulin either after or in place of capecitabine with the assumption that the magnitude of clinical benefit would be the same as seen in EMBRACE.

The other subgroup is patients with metastatic breast cancer not previously treated with either an anthracycline and/or taxane because of medical contra-indications (e.g. cardiac disease, contra-indication to steroids, or older physiological age). This is a patient population in which eribulin may be considered, but who did not meet the eligibility criteria for this study. There is insufficient data from EMBRACE to address this clinical cohort, for 99% of the EMBRACE population had received both prior anthracyclines and taxanes. However, there is unlikely a biological rationale as to why eribulin would not be effective in these populations. This however is speculative and there is lack of knowledge if the magnitude of improvement (if any) would be similar to that seen in EMBRACE.

Need and Therapeutic Options

The strengths of this agent, as has been studied so far and published or publicly available include: an improvement in overall survival in a heavily pre-treated population of patients with limited efficacious options available (all patients had prior anthracyclines, taxanes and the majority (73%) had prior capecitabine). In general the toxicity profile of eribulin was similar or more favorable than the treatment options in the TPC arm of EMBRACE (numerically less adverse events leading to discontinuation and less deaths on study due to adverse events from eribulin compared to TPC arm).[1] The agents delivered on the TPC arm are in keeping with the available chemotherapeutic agents available and used in Canadian practice today. Based on the schedule of delivery, toxicity profile and efficacy results, eribulin would likely replace the use of monotherapy vinorelbine and/or gemcitabine in the third-line or greater treatment of women with incurable locally advanced/metastatic breast cancer previously exposed to anthracyclines and taxanes.

Based on the currently available data, it is likely that eribulin should be considered a standard of care in the treatment of women with metastatic breast cancer/incurable locally advanced breast cancer, who have previously been exposed to anthracyclines and taxanes. It is likely eribulin will be used in place of vinorelbine and gemcitabine as monotherapy in the majority of cases as 3rd line therapy or later. In some jurisdictions in Canada, gemcitabine is given in combination with a platinum (cisplatin or carboplatin). The use of capecitabine as a requirement prior to receiving eribulin is not absolutely necessary but is likely to occur in the majority of patients (particularly if patients had received either an anthracycline or taxane in the adjuvant setting). In the EMBRACE study, 73% study population had prior capecitabine. Whether eribulin is in fact better than is clinically more efficacious than capecitabine is the focus of a fully accrued phase III clinical trial comparing these two agents head to head in the treatment of metastatic breast cancer (see section 6.4, Ongoing Trials). Future clinical studies of eribulin as

monotherapy or in combination with other systemic agents and in earlier lines of therapy will help to elucidate the specific role and benefit of this agent in the full spectrum of breast cancer treatment.

2.3 Conclusions

The Clinical Guidance Panel concluded that there ***is*** a net overall clinical benefit to eribulin in the 3rd line or greater treatment of women with incurable locally advanced/metastatic breast cancer previously exposed to anthracyclines and taxanes. This recommendation is based on a single high-quality randomized controlled trial (EMBRACE) that demonstrated a clinically and statistically significant benefit in overall survival for women treated with eribulin compared with those treated with physician's choice [in 87% of instances treatment was monotherapy vinorelbine, gemcitabine, capecitabine, taxane or anthracycline]. The adverse event profile was similar between eribulin and the range of chemotherapy options studied in the EMBRACE trial.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Metastatic breast cancer is the second leading cause of cancer death in women and there is a need for new and improved chemotherapeutic agents, both in terms of efficacy and tolerability.
- Eribulin demonstrated an improvement in overall survival in a heavily pre-treated population of patients with limited efficacious options available.
- Although the rates of peripheral neuropathy and febrile neutropenia were shown to be higher for eribulin, it was noted that these rates were comparable to other standard chemotherapeutic agents administered in the metastatic breast cancer setting, such as the taxanes. This also aligned with patient values where patients indicated that they would be willing to tolerate potential adverse effects of a treatment if it was found to prolong their survival.
- There are two clinical situations where the Clinical Guidance Panel noted there was insufficient evidence from the EMBRACE trial to make any definite conclusions regarding eribulin treatment, including whether eribulin should be used in place of, or following, capecitabine therapy and whether eribulin could be considered in patients who have not previously been treated with anthracyclines and/or taxanes due to medical contraindications.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Breast Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Breast cancer is the most commonly diagnosed malignancy in Canadian women, with an estimated incidence of 23,600 new cases in Canada in 2011. Deaths from breast cancer account for 14.4% of all annual cancer deaths (second leading cause of cancer deaths in women), with an estimated 5,100 Canadian women dying from breast cancer in 2011.[6] Deaths from breast cancer are attributable to either distant relapsed or *de novo* presentation of metastatic breast cancer, which is considered an incurable situation. In general, women with metastatic breast cancer have a quoted median life expectancy of 18-24 months, though it is recognized there is wide variability between patients and between biological subtypes of breast cancer.

The goals of systemic therapy in the treatment of metastatic breast cancer are to improve overall survival and to maintain and/or improve quality of life.[7] Despite metastatic breast cancer being such a prevalent disease, there is a lack of clinical trials to compare systemic treatment to best supportive care to demonstrate that systemic treatment in fact improves survival. Recent population based studies (including one performed in British Columbia) however have demonstrated improvements in survival in metastatic breast cancer over the course of the decade from 1991-2001 [8] – likely due to access of new systemic agents that became available during that decade.

More than in any other malignancy, over the past 10-15 years there has been the introduction and assessment of new and novel systemic agents for the treatment of metastatic breast cancer.[9] Though much hope and excitement lies with new targeted therapies, cytotoxic chemotherapy remains as a key backbone for the palliative treatment of metastatic breast cancer. Even in the subtypes of breast cancer in which targeted therapy is now considered standard of care (e.g. hormonal therapy for hormone receptor positive metastatic breast cancer; anti-HER 2 therapy for HER-2 positive metastatic breast cancer) cytotoxic chemotherapy is still potentially delivered either in combination (e.g. with trastuzumab or lapatinib) or following the targeted therapy (e.g. following hormonal agents). Thus there remains the need for new and improved chemotherapeutic agents both in terms of efficacy and tolerability for the treatment of metastatic breast cancer.

3.2 Accepted Clinical Practice

The treatment of incurable locally advanced or metastatic breast cancer generally involves systemic anti-cancer therapies (e.g. hormonal therapy, chemotherapy, and targeted therapy), supportive systemic therapies (e.g. analgesics, anti-nausea agents, anti-bone resorbtive agents, and steroids), radiation therapy, surgery (e.g. spinal cord compression, hip fractures, limited brain metastases) and the palliative care allied health service team. The prevalence of use of these various therapeutic modalities clearly vary by patient disease characteristics, patient co-medical conditions, patient preferences, physician recommendations and availability of the various treatment options. Cytotoxic chemotherapy is generally accepted by patients with incurable locally advanced or metastatic breast cancer, as evidenced by the study in British Columbia in which 90% of the cohort of women diagnosed with metastatic

breast cancer and referred to a regional cancer centre from 1999-2001 (n=525) were treated with at least one regimen of chemotherapy.[8]

Though there may not be a standard algorithm rigorously adhered to in the treatment of MBC, there are two widely accepted concepts/principles based on the totality of the published data.[10] First, sequential monotherapy (rather than combination therapy) is the preferred strategy for chemotherapy in MBC (except for rapidly progressive/symptomatic disease); second, the two most active classes of chemotherapeutic agents are the anthracyclines and the taxanes. Both are also the most commonly used chemotherapy classes used in the adjuvant treatment of early stage breast cancer. In general, for patients medically fit to receive palliative chemotherapy, the anthracyclines and taxanes are often used as either 1st or 2nd line therapy for MBC. In an era where the use of adjuvant anthracyclines and taxanes are increasing (especially for taxanes), the re-challenge with these agents in the metastatic setting varies and without firm guidelines due to the paucity of randomized data.

An improvement in overall survival is still considered the gold standard as evidence of a therapeutic benefit from any systemic agent in the treatment of breast cancer. In a recent review of randomized trials in MBC published between 1998-2007, 76 phase III trials were identified.[9] Of these 76 trials, only 15 (19.7%) demonstrated a statistical improvement in overall survival. Thus the ability to demonstrate an actual improvement in overall survival is challenging in the setting of MBC because of disease heterogeneity, cross-over (in some trials) and the ability to receive standard treatment post progression. Furthermore in a recent review of the treatment of MBC with second-line therapy and beyond, it was clear that several single agent and combination chemotherapy regimens have shown improvements in progression free survival and/or reduction in clinical symptoms of disease – however none recently have shown improvements in overall survival.[11] Thus the results of the EMBRACE study in which eribulin was compared to treatment of physician's choice (TPC) as 3rd line chemotherapy or greater and an overall survival was in fact demonstrated (HR 0.81;95% CI 0.66-0.99; p=0.041)[1] is a very important study to consider with potential impact on clinical practice.

In fact many of the chemotherapeutics agents used today in the 2nd line setting or greater were incorporated into clinical practice based simply on single-arm non-randomized studies or small randomized studies. Arguably the most commonly prescribed agent in the 2nd line or greater setting after prior anthracyclines and taxanes is capecitabine. Capecitabine received regulatory approval and subsequently became incorporated into standard clinical practice based on a phase II study of 163 patients previously exposed to both anthracyclines and paclitaxel.[12] In this study the response rate (RR) was 20%, median time to tumour progression (TTP) was approximately 3 months but the median duration of response was 8.1 months. Vinorelbine became incorporated into clinical practice (in part) based on a small RCT (n=183) comparing vinorelbine to melphalan in a heavily pre-treated population of patients with anthracycline-refractory MBC.[13] Median TTP and overall survival was significantly longer on the vinorelbine arm (12 weeks and 35 weeks respectively). Response rates however were similar between vinorelbine and melphalan (16% versus 9% respectively). Finally gemcitabine either as a single agent or in combination has demonstrated activity in MBC primarily based on phase II studies.[14,15] In the small phase II study of cisplatin and gemcitabine (n=30) a RR of 50% was seen with a median TTP of 14 weeks.

3.3 Evidence-Based Considerations for a Funding Population

The evidence based population suitable for consideration of eribulin for the treatment of MBC would essentially be the same patient population included in the clinical trial (EMBRACE).[1]

These would be women with either metastatic breast cancer or incurable locoregionally recurrent breast cancer previously exposed to both anthracyclines and taxanes (in adjuvant and/or advanced stage disease). Patients should have received at least 2 prior chemotherapy regimens in the metastatic setting (or for incurable locoregionally recurrent disease), be of good performance status (ECOG score of 0-2), and have adequate bone marrow, hepatic and renal function. Treatment with eribulin would continue until disease progression, unacceptable toxicity, or patient or physician recommendation (as was done in the EMBRACE study).

It is likely eribulin will be used in place of vinorelbine and gemcitabine as monotherapy in the majority of cases as 3rd line therapy or later (median prior number of chemotherapy regimens was 4 in EMBRACE). In some jurisdictions in Canada, gemcitabine is given in combination with a platinum (cisplatin or carboplatin). The use of capecitabine as a requirement prior to receiving eribulin is not absolutely necessary but is likely to occur in the majority of patients (particularly if patients had received either an anthracycline or taxane in the adjuvant setting) – as was in the EMBRACE study (73% study population had prior capecitabine).

It is also important to recognize that in the EMBRACE trial 54% of patients randomized to the eribulin arm in fact received further chemotherapy as the first anti-cancer therapy following progression on eribulin. It is likely in a proportion of patients in clinical practice upon progression on eribulin they would receive further chemotherapy (e.g. capecitabine, gemcitabine) – as long as there was no previous exposure to these agents in the metastatic setting. Based on its mechanism of action (tubulin targeting agent), at the very minimum eribulin should replace vinorelbine in the treatment algorithm of MBC as they both have similar mechanism of actions as well as similar toxicity profiles and schedules of administration.

3.4 Other Patient Populations in Whom the Drug May Be Used

Patients with MBC not previously treated with either an anthracycline and/or taxane because of medical contra-indications (e.g. cardiac disease, significant pre-existing neuropathy, contra-indication to steroids as examples) are likely to be a patient population in which eribulin may be considered but not meeting the eligibility criteria of those enrolled in the EMBRACE study.

Likewise another patient population where eribulin could also potentially be considered earlier in the treatment algorithm is in elderly (≥ 70 years old) patients.

Both these patient populations may be reasonable to consider for eligibility for eribulin because current treatment options for these cohorts of patients include either vinorelbine, gemcitabine and/or capecitabine as the mostly likely agents.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy groups provided input on eribulin (Halaven) for advanced breast cancer and their input is summarized below:

- Canadian Breast Cancer Network
- Canadian Cancer Survivor Network

The Canadian Breast Cancer Network conducted one-on-one interviews with patients using current therapies for breast cancer and knowledge from previous breast cancer focus groups to gather information about the patient and caregiver experience related to the medical condition. In addition, they also obtained information through printed sources and survey reports of patients with metastatic breast cancer. Information on the drug under review was obtained through Eisai Limited and information from the clinical trials of eribulin.

The Canadian Cancer Survivor Network utilized professional experience of their CEO and some directors, as well as printed sources, to gather information about the patient and caregiver experience related to the medical condition and drug under review

From a patient perspective, access to additional therapies that will increase life expectancy is an important aspect when consideration is given to treatment. Patients are also looking for treatments with manageable side effect profiles, that will not negatively affect their quality of life, especially as their disease progresses. However, patient input also indicated that many patients would be willing to tolerate the potential adverse effects of a treatment if it was found to prolong their survival, even for a short period of time.

Please see below for a summary of specific input received from the patient advocacy groups.

4.1 Condition and Current Therapy Information

4.1.1 Experiences patients have with advanced breast cancer

Patients with advanced/metastatic breast cancer may experience a number of debilitating symptoms, stemming from the disease itself and also from the various therapies used to treat the disease, including pain, fatigue, nausea, vomiting, cognitive problems, depression, hair loss, sleep disturbance, lymphedema, loss of appetite, anxiety or sexual dysfunction. Many of these symptoms can have an impact on the patient's daily life and negatively affect their quality of life.

Although there is no cure at this stage of the disease, patient input indicated that patients lives may be extended due to continuous treatments given in this setting. If the treatment is successful, these patients can go through periods of time in remission where their quality of life is relatively good. However, these treatments tend to work for increasingly shorter periods of time and with a lower effectiveness, and eventually, the cancer will return. It was noted that some patients may live for years with metastatic breast cancer while others may succumb to their disease more quickly.

The diagnosis of metastatic breast cancer and the knowledge that this is an incurable disease can have a great impact on the patient's emotional well-being, and patients, as well as their family and friends, can experience significant anxiety and stress.

In addition, many patients are unable to work during this time which can cause serious financial impacts on their day to day lives. In addition, some treatments are not covered by hospitals, cancer centers or government formularies, which can also add to the financial burden experienced by patients.

Patient input indicated that the limitations of metastatic breast cancer are similar to other episodic diseases, which are marked by unpredictable and fluctuating periods of wellness and disability, and the challenges are also the same, such as struggling with unpredictability; the ongoing need for care, treatment and support; depression and lack of self-esteem; difficulties remaining in the workforce, with part-time work and flex time often not available; and a loss of income and forced reliance on health or disability benefits.

From a patient perspective, it is extremely important for patients to have access to therapies that will extend their life expectancy without increasing side effects that will negatively impact their daily lives.

4.1.2 Patients' Experiences with Current Therapy for advanced breast cancer

Input from patient advocacy groups indicated that there are currently a variety of different therapies available for the treatment of metastatic breast cancer, depending upon the particular subset the patient has. However, these therapies eventually stop working and patients require access to new therapies to manage the progression of the disease, with some patients receiving an average of four to six lines of chemotherapy and some receiving more. Patient groups noted that the disease is no longer considered curable at this stage. Although access to the best care and new therapies can make a difference in both the survival time and quality of life, patients indicated a pressing need for better information and treatments.

Patient input indicated that nausea, vomiting, fatigue and pain are the most difficult side effects experienced with treatment. However, many patients are willing to tolerate the potential adverse effects of treatment if it prolongs their survival, even if they only see short-term benefits.

Access to certain treatments can be uneven, and women who live in rural, remote or Northern regions of Canada will typically have to travel to receive treatment. In addition, the financial impact of cancer treatment can be stressful to patients. Some patients are unable to afford certain treatments, including supportive treatments for nausea or anemia. In addition, as many patients can no longer work, they lose income and require the use of their savings or take on debt due to the disease.

4.1.3 Impact of advanced breast cancer and Current Therapy on Caregivers

Input from the patient advocacy groups indicated that the impact of this cancer on caregivers can be quite significant.

Caregivers spend a great amount of time taking care of patients, especially as the disease progresses. In order to do this, caregivers who work must take vacation or sick days, cut back to part-time hours, or even quit their jobs, which can lead to increased financial

burdens. Compassionate care benefits are only available for six weeks if a caregiver has to be absent from work to provide care or support to a gravely ill family member at risk of dying within 26 weeks, which greatly limits the number of caregivers who are eligible for this benefit.

Caregivers may also have to help cover financial costs associated with the disease that are not covered under public or private health benefits, including some medications and non-medical expenses, such as hospital parking.

In addition, caregivers often experience anxiety and stress due to the additional responsibility of looking after a loved one and also dealing with the emotional aspect of a loved one dying.

As breast cancer primarily affects women, there is usually a very large impact on the family unit as a whole because women are often the primary caregivers for the family, and spouses end up having to assume the caretaker responsibilities for the patient as well as for the rest of the family.

Patient advocacy input indicated that increasing the life expectancy of women with breast cancer while minimizing side effects would help to ease some of the psychosocial burden assumed by caregivers.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to date with Eribulin (Halaven)

Input from patients without direct experience with eribulin indicated that patients are seeking treatments which can extend their life expectancy, even if only for a short period of time. In addition, treatments with manageable side effect profiles that would not affect a patient's daily life would also be considered favorable to patients.

Based upon the positive results of a phase III trial of eribulin (EMBRACE) and the fact that there are limited options currently available to these patients, it is expected that the lives of patients, families, and caregivers will be improved with this medication.

There was no input provided from patients who have had direct experience with eribulin, but information from the EMBRACE trial was presented, which provides information on the effectiveness and side effects associated with eribulin. As seen in the clinical trial, eribulin was shown to significantly increase the median overall survival when compared to treatment of physician's choice, which is an important consideration for patients. In addition, eribulin appeared to have a manageable toxicity profile. Side effects that were noted with eribulin included fatigue, neutropenia, leukopenia, and peripheral neuropathy,

It was noted that eribulin has a convenient dosing schedule compared to other existing therapies for metastatic breast cancer. In addition, there is no need for special tubing for IV administration, which would make it easier to use when compared to other IV treatments.

4.3 Additional Information

No additional comments were received.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for eribulin (Halaven) for the treatment of locally advanced or metastatic breast cancer . The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the eribulin (Halaven) review was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, there is currently no standard of care in this treatment setting (i.e. new line of therapy), so issues surrounding the additional costs relating to eribulin as well as additional implementation costs, such as the need for chemotherapy chair time, would be of great importance. PAG also identified that there is a potential for wastage with this drug therapy which would need to be included in the economic evaluation. In addition, it was noted that the use of eribulin may be extended to other patient populations, such as those with earlier stages of metastatic disease, and PAG would appreciate any clinical evidence to support this use.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

PAG identified that there is no specific standard of care in this treatment setting and physicians may have a number of potential options available to treat their patients; however, it was noted that the evidence to support the use of eribulin in this clinical setting appears to be more robust than that available for the other available treatment options, which would be an enabler to eribulin funding.

PAG was interested in knowing the cost-effectiveness of eribulin in comparison to some of the other available alternatives in this treatment setting.

5.2 Factors Related to Patient Population

PAG noted that there may be considerable numbers of patients with locally advanced or metastatic breast cancer who would be eligible for this therapy and as a result, budget impact would likely be significant, which would be a barrier for jurisdictions to implement funding for eribulin.

Although there is currently only clinical evidence to support the use of eribulin in heavily pre-treated populations with at least 2 lines of prior therapy, PAG noted that there is the potential for off-label use in earlier stages of metastatic disease, such as those patients who have not received prior treatment with an antracycline or a taxane, which would also be a barrier to eribulin funding.

5.3 Factors Related to Accessibility

PAG recognized that eribulin will need to be administered intravenously and as a result, there would be an impact on chemotherapy centers; however, it was also noted that the

eribulin infusion is given over a short period of time in comparison with other agents used in this clinical setting, which would be an enabler for eribulin therapy.

Some jurisdictions noted that if the cost of eribulin is high and there is a potential for wastage, treatment in rural locations outside of tertiary cancer centers may be limited and treatment would have to be given at specialized centers, which may have an impact on the patient.

5.4 Factors Related to Dosing

It was noted that eribulin is administered as an intravenous infusion on Days 1 and 8 every 21 days and would require the patient to make frequent treatment visits to the chemotherapy center. This may be difficult for patients having to travel far distances for chemotherapy treatment.

Eribulin is only known to be available in one vial size (1mg vial) and PAG noted that there may be a potential for drug wastage using the dosage of 1.4mg/m^2.

5.5 Factors Related to Implementation Costs

As eribulin would represent an additional 'line of therapy' in this clinical setting, PAG noted that there would be additional costs associated with its implementation, including costs for the drug itself and costs relating to increased workload on chemotherapy centers administering the treatment. PAG noted that it would be valuable to have these costs included in the economic evaluation.

PAG noted that eribulin would require chemo chair time for administration, which would be a barrier to its implementation; however, PAG also noted that the associated chair time would be minimal as eribulin is administered as a rapid IV infusion, which would be an enabler to eribulin implementation.

PAG recognized that not all jurisdictions have had experience with administering this product since only two provinces reported being involved with clinical trials to date, which may have an implication on implementation in jurisdictions naïve to this treatment.

PAG noted that there may be a potential for drug wastage with eribulin if it is only available in a 1mg vial size as seen in the United States. At the standard recommended dose of 1.4mg/m^2, an average adult at 1.7m^2 would require a dosage of approximately 2.4mg, meaning that 3 vials total would be required. As these are single-use vials without preservatives, drug wastage would be a concern and a barrier to implementation. In addition, it was noted that there would be increased workload on healthcare workers as they would have to withdraw medication from multiple vials.

5.6 Other Factors

PAG noted that eribulin is a non-taxane microtubule inhibitor with a unique mechanism of action.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of eribulin monotherapy on patient outcomes compared to specific chemotherapeutic regimens without eribulin (see Table 1 in Section 6.2.1) in the treatment of patients who have previously received at least two chemotherapeutic regimens for metastatic breast cancer or incurable locoregionally recurrent breast cancer, and who have previously received both anthracyclines and taxanes in the adjuvant and/or advanced-stage disease setting. Outcomes of interest can be found in Table 1 in Section 6.2.1.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 3 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCT	Patients who have previously received at least two chemotherapeutic regimens for incurable locally advanced or MBC, including an anthracycline or a taxane in the adjuvant and/or advanced-stage disease setting.	Eribulin mesylate monotherapy at 1.4 mg/m^2 i.v. over 2-5 minutes on days 1 and 8 of a 21-day cycle.	Vinorelbine monotherapy; capecitabine monotherapy; gemcitabine monotherapy or combination therapy with a platinum agent; Taxane, or; Anthracycline.	**Overall survival** Progression-free survival Adverse events *Specific AE's:* Febrile neutropenia Peripheral neuropathy **QOL**
Abbreviations: AE=adverse event; i.v.=intravenous; MBC=metastatic breast cancer; QOL=quality of life; RCT=randomized controlled trial.				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-April Week 4, 2012 [May 7]) with in-process records & daily updates via Ovid; EMBASE (1980-2012 Week 18 [May 7]) via Ovid; The Cochrane Central Register of Controlled Trials (2012, Issue 4) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were eribulin mesylate (Halaven) and breast cancer.

Methodological filters were not applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was not limited by language.

The initial search was completed on March 5, 2012 and was updated during the review. The search is considered up to date as of May 7, 2012.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies, clinical trial registries and conference abstracts from the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS). Searches of conference abstracts were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

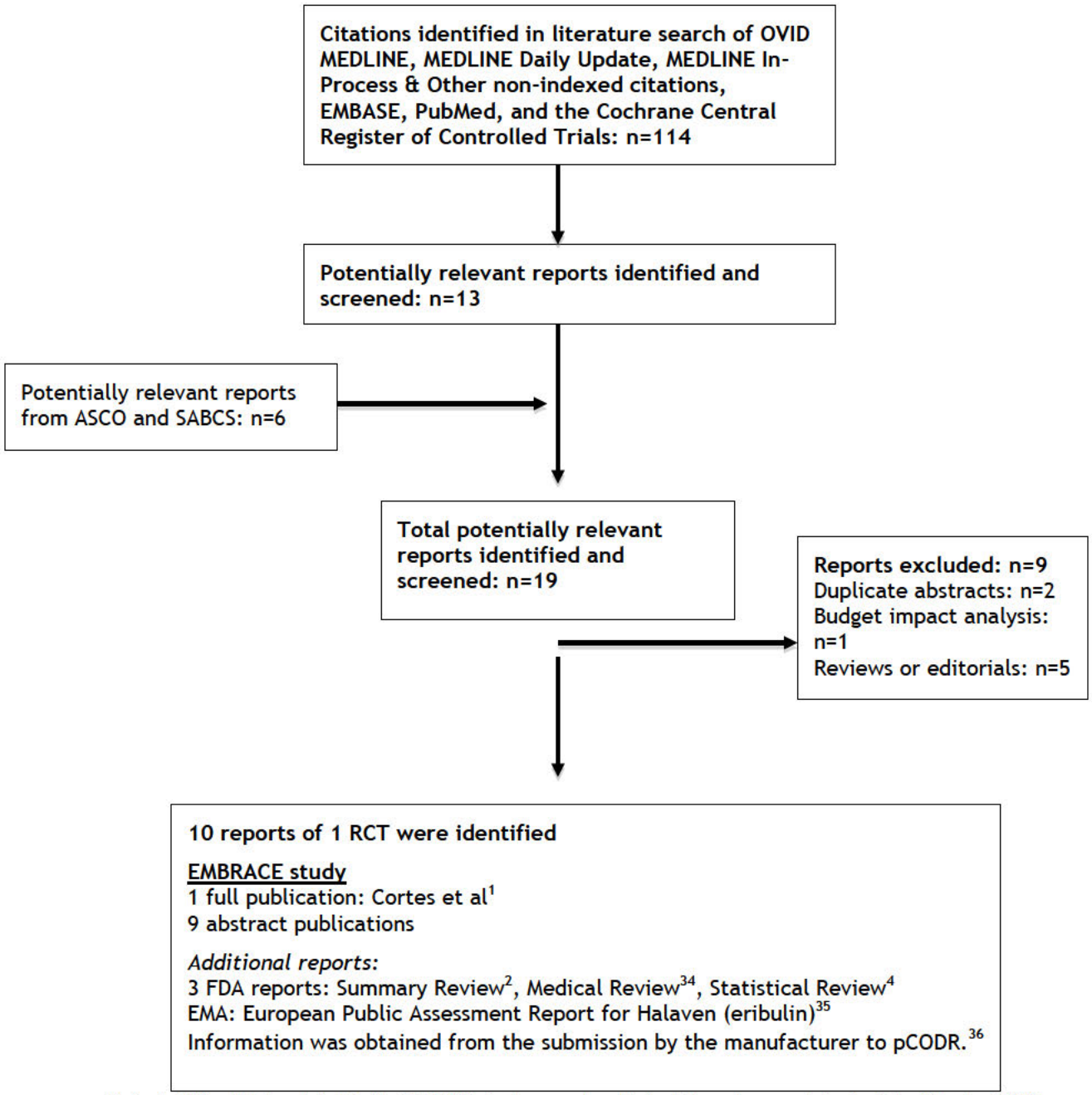
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 18 potentially relevant reports identified, 10 reports of one study were included in the pCODR systematic review[1,16-24] and eight studies were excluded. Studies were excluded because they were duplicate citations of abstracts[25,26], budget impact analyses[27], or they were reviews or editorials.[28-33] Additional reports were included from the United States Food and Drug Administration (US FDA)[2,4,34], and the European Medicines Agency (EMA).[35] Additional information was obtained from the submission from the manufacturer to pCODR.[36]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the EMBRACE study were also obtained through requests to the Submitter by pCODR.

6.3.2 Summary of Included Studies

One open-label randomized trial (EMBRACE) was identified that compared treatment with eribulin to treatment of physician's choice (TPC) in women with locally recurrent or metastatic breast cancer who had received between two and five previous chemotherapy regimens including an anthracycline and a taxane.[1]

6.3.2.1 Detailed Trial Characteristics

a) Trials

One open-label RCT (EMBRACE) met the inclusion criteria for this systematic review (Table 1).[1] Patient eligibility criteria included all of the following:

1. Women with incurable locally recurrent or metastatic breast cancer;
2. Disease progression within six months of the most recent chemotherapy;
3. Patients previously received chemotherapeutic regimens that included an anthracycline and a taxane, in either the adjuvant and/or advanced-stage disease setting;
4. Patients previously received at least two chemotherapeutic regimens for incurable locally recurrent or metastatic breast cancer;
5. Patients had previously received a maximum of five chemotherapeutic regimens.

The study was conducted in 135 centres in 19 countries in North America, Latin America, Western Europe, Eastern Europe, Australia, and South Africa.[1] The study was sponsored by the manufacturer. The study was open-label, that is neither the patients or investigators were masked to treatment allocation. A total of 762 patients were randomized by a centralized voice-recognition system in a 2:1 ratio to receive eribulin or TPC. The randomization was stratified by geographical region, previous capecitabine treatment, and HER2 (ERBB2) status. The procedures for randomization and allocation concealment were considered appropriate. Given that the control arm was decided by the treating physician, it would have been impossible to blind the treating physician to the treatment allocation. Blinding of the patients may have been possible, but it would have been difficult to accomplish given the many possible treatment options that patients in the TPC-arm could receive.

The primary outcome of the study was overall survival (defined from the date of randomization to the date of death or the last date the patient was known to be alive [date of censoring]).[1] Secondary outcomes included progression-free survival (defined from the date of randomization to the date of disease progression, death, or the date of censoring), objective response rate, and duration of response (defined as time from first documented response until disease progression, death from any cause, or the date of censoring). Tumour response was assessed using Response Evaluation Criteria in Solid Tumours (RECIST) every eight weeks or sooner if disease progression was suspected. Analyses of progression-free survival, objective response rate, and duration of response were based on independent masked review of tumour assessments.

The required sample size, based on the primary outcome of overall survival, was originally 630 patients, randomized 2:1 to eribulin:TPC, to achieve 411 events. With an estimated median overall survival of nine months in the TPC arm and 12 months in the eribulin arm (hazard ratio [HR] of 0.75), the study would have a two-sided alpha of 0.05 and power of 80%.[4] The authors estimated an average accrual rate of 35 patients per month and an accrual period of 18 months. Fifteen months after the first patient was enrolled, the overall death rate in the trial was evaluated, with the data remaining masked. That evaluation suggested that deaths were occurring slower than expected, therefore the sample size was increased to 1000 patients (with 2:1 randomization), but no change was made to the number of events required for the final analysis. The final study protocol stated that sample size re-assessment would be done on an ongoing basis and that as soon as it became apparent that the required number of events would be reached within a reasonable timeframe, recruitment would cease.[4] The re-assessments were conducted by an in-house statistician blinded to treatment assignment. As no formal comparison was made between the two treatment arms, no alpha adjustment was made.[4] The final study protocol stated that in addition to the final overall survival analysis, one interim analysis would be conducted when 50% of the events (206 deaths) occurred. The trial could be stopped early for superiority or lack of efficacy on overall survival.[4] In order to maintain an overall significance level of 0.05, the authors utilized the O'Brien and Fleming alpha spending function to create a stopping rule for superior efficacy. The significance level of the first interim test was 0.003 and the significance level of the final analysis was 0.049.[4] The interim overall analysis was conducted on August 23, 2008.[2] The Data Monitoring Committee noted that although a statistically significant difference in overall survival in favour of eribulin was detected, the Data Monitoring Committee concluded that the study should continue without modification due to the lack of mature data.[2]

b) Populations

The baseline demographic and disease characteristics were balanced between the two treatment arms.[1] Patients from North America, Western Europe, and Australia accounted for 64% of 762 patients in the trial, with similar proportions in both treatment arms. Eastern Europeans made up 25% of the trial population and patients from Latin America or South Africa accounted for the remaining 11%. Again, the proportions of patients from each geographical region were similar in both treatment arms. Of the 762 patients in the trial, 92% were white, 4% were black, 1% were Asian, and 3% were other. The mean age (minimum to maximum; standard deviation) was 54.8 (28-85; 10.34) years in the eribulin arm and 55.9 (27-81; 10.43) years in the TPC arm. Of 762 patients in the trial, 6.7% were less than 40 years of age, 73.5% were between 40 years and 65 years of age, and 19.8% were 65 years or older. Of 762 patients, 16% were HER2 positive, 74% were HER2 negative, 1% HER2 unknown, and 9% did not have HER2 testing. The most common metastatic sites for all 762 patients included bone in 61% of patients, liver in 60%, lymph nodes in 44%, and lung in 38%. The median number of previous chemotherapy regimens was four (range, 1-7). Of 762 patients, 99% previously received chemotherapy with a taxane,

99% previously received an anthracycline, and 73% previously received capecitabine. Of 762 total patients, 81% were refractory (defined as progression on or within six months of receiving treatment) to a taxane, 68% were refractory to capecitabine, and 58% were refractory to an anthracycline.

c) Interventions

Eribulin mesylate was administered at 1.4 mg/m^2 intravenously over 2-5 minutes on days 1 and 8 of a 21-day cycle.[1] TPC was defined as: any single-agent chemotherapy, hormonal, or biological treatment approved for the treatment of cancer and administered according to local practice; radiotherapy; or symptomatic treatment alone. Treatment continued until disease progression, unacceptable toxic effects, patient or physician request to discontinue, or serious protocol non-compliance.

Grade 3 or 4 toxic effects were managed by dose modifications. Concomitant treatments that did not interfere with the evaluation of eribulin or the relevant TPC agent could be given at the investigator's discretion, including palliative radiotherapy, but excluding other investigational antitumour treatments.

The agents most commonly administered to patients in the TPC arm included vinorelbine, gemcitabine, capecitabine, taxanes, anthracyclines, and hormone therapy (see Table 4). The number of cycles of therapy received by patients in the EMBRACE study and the mean and median duration of therapy can be found in Table 5. Dose interruptions, delays, and reductions can be found in Table 6. The mean dose intensity in the eribulin arm, for the 503 patients who received eribulin, was 0.781 mg/m^2/week (standard deviation [SD] of 0.166) and the median was 0.846 mg/m^2/week (minimum-maximum, 0.237-1.008) (Table 5).(ref-FDA Medical Review) The relative dose intensity can be found in Table 5. The expected dose intensity was 0.91 mg/m^2/week.[34]

Table 4. Proportion of patients assigned to treatment regimens in EMBRACE[1,4]

Treatment	No. patients assigned to treatment (%)	No. patients that actually received treatment (%)
Eribulin	508 (100)	503 (99.0)
TPC-total	254 (100)	247 (97.2)
Vinorelbine	65 (25.6)	61 (24.0)
Gemcitabine	46 (18.1)	46 (18.1)
Capecitabine	45 (17.7)	44 (17.3)
Taxanes	41 (16.1)	38 (15.0)
Anthracyclines	24 (9.4)	24 (9.4)
Hormone therapy[A]	8 (3.1)	9 (3.5)
Other chemotherapies[B]	25 (9.8)	25 (9.8)
Other therapies	NR	NR

Notes: No.=number of; TPC=treatment of physician's choice.
[A]Hormonal therapies included: fulvestrant (n=4), letrozole (n=3), exemestane (n=1), and tamoxifen (n=1).

[B]Other chemotherapies included: cisplatin (n=9), carboplatin (n=4), cyclophosphamide (n=4), etoposide (n=4), mitomycin (n=3), fluorouracil (n=1), and methotrexate (n=1).

Table 5. Number of cycles of therapy received by patients in EMBRACE[34]

	Eribulin n=503 (%)	TPC n=247 (%)
Number of cycles completed		
1-2	81 (16)	93 (38)
3-4	127 (25)	65 (26)
5-6	110 (22)	46 (19)
>6	185 (37)	43 (17)
Median number of cycles completed (range)	5 (1-23)	3 (1-31)
Mean number of cycles completed (standard deviation)	6 (4)	4 (4)
Duration (days)		
Mean (standard deviation)	137 (92.6)	98 (94.3)
Median (minimum-maximum)	118 (21-497)	63 (1-644)
Dose Intensity of eribulin (mg/m^2/week)		
Mean (standard deviation)	0.781 (0.166)	-
Median (minimum-maximum)	0.8458 (0.2366-1.0077)	-
Relative dose intensity of eribulin (mg/m^2/week)		
Mean (standard deviation)	0.837 (0.178)	-
Median (minimum-maximum)	0.907 (0.254-1.080)	-

Table 6. Number of patients with dose interruptions, delays or reductions in EMBRACE[1]

	Eribulin n=503 (%)	TPC n=247 (%)
Dose interruptions	28 (5.6)	21 (8.5)
Dose delays	248 (49.3)	98 (39.7)
Dose reductions	145 (28.8)	63 (25.5)

d) Patient Disposition

A total of 762 patients were enrolled and randomized on the study.[1] The analysis of overall survival included the intention-to-treat (ITT) population (all randomized patients). Please see Table 7 for patient disposition in the EMBRACE study.[1] A total of 12 patients discontinued the study prior to receiving treatment (Table 7). At the data cut-off on May 12, 2009, a total of

422 patients had died (55.4% of 762 patients) and six patients (0.8%) were lost to follow-up.[34]

Data on post-trial treatments were not well-reported. Cortes et al[1] reported that this data were not required to be collected per the trial protocol; however, the authors did report the following: chemotherapy was received by 274 (54.5%) of 503 patients who received eribulin, and 123 (49.8%) of 247 patients who received TPC; hormonal therapy was received by 52 (10.3%) of patients on eribulin and 30 (12.1%) of patients on TPC; and radiotherapy by 34 (6.8%) of patients on eribulin and eight (3.2%) of patients on TPC.[1]

Table 7. Patient Disposition in the EMBRACE study[4]

	Eribulin (%)	TPC (%)	Total (%)
Randomized	508	254	762
Not treated (Discontinued Study)	6 (1.2)	6 (2.4)	12 (1.6)
Progressive disease (RECIST)	1 (0.2)	1 (0.4)	2 (0.3)
Clinical progression	1 (0.2)	0	1 (0.1)
Adverse events	1 (0.2)	0	1 (0.1)
Physician's decision	1 (0.2)	1 (0.4)	2 (0.3)
Withdrew consent	1 (0.2)	2 (0.8)	3 (0.4)
Other reasons	1 (0.2)	2 (0.8)	3 (0.4)
Treated	502[A] (98.8)	248[A] (97.6)	750 (98.4)
Discontinued study treatment	479 (94.3)	238 (93.7)	717 (94.1)
Progressive disease (RECIST)	335 (65.9)	152 (59.8)	487 (63.9)
Clinical progression	60 (11.8)	36 (14.2)	96 (12.6)
Adverse events	49 (9.6)	24 (9.4)	73 (9.6)
Physician's decision	18 (3.5)	11 (4.3)	29 (3.8)
Withdrew consent	9 (1.8)	5 (2.0)	14 (1.8)
Death	3 (0.6)	2 (0.8)	5 (0.7)
Other	5 (1.0)	8 (3.1)	13 (1.7)
At data cut-off (final analysis)			
Patients that were alive	230 (45.3)	104 (40.9)	334 (43.8)
Patients that had died	274 (53.9)	148 (58.3)	422 (55.4)
Lost to follow-up	4 (0.8)	2 (0.8)	6 (0.8)

Notes:
[A]One patient was randomly allocated to received TPC, left the trial prior to receiving treatment, returned, and was rerandomized to the eribulin arm. That patient was included in the TPC arm for the ITT analysis, excluded from the per-protocol analysis, and included in the eribulin arm in the safety population. The numbers in this table reflect the ITT population, with the patient in question included in the TPC arm.

e) Limitations/Sources of Bias

This trial was open-label and none of the patients or treating study personnel (physicians, etc.) were blinded to treatment assignment. Given the choice of TPC as the control arm, implementing blinding in this trial design would have been extremely difficult; however, it should be noted that the lack of blinding of study treatment personnel and patients may have had an impact on the results of the trial. For example, a higher proportion of patients in the eribulin arm had dose delays (49.3%) compared to patients in the TPC arm (39.7%). This difference may have been due to the treating physician knowing that the patients in the eribulin arm were receiving the investigational agent and thus allowed a delay between treatment rather than just stopping treatment. The difference may also be due to differences in how dose delays are defined for eribulin compared to each of the many agents used in the TPC arm.

The choice of TPC as the comparator arm in the study is a potential limitation. If any treatment option has shown superior efficacy to another in the third-line treatment of locally recurrent or metastatic breast cancer previously treated with anthracyclines or taxanes (i.e., the study population in EMBRACE), then that treatment should have been the comparator. However, if the available treatment options, either currently or at the time the study started, did not demonstrate superior efficacy to any other treatment, then the choice of TPC as the comparator arm was appropriate.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The primary efficacy analysis was based on the ITT population which comprised all randomized study subjects (eribulin arm, n=508; TPC arm, n=254). The safety population consisted of randomized patients who had received treatment on-study according to the arm to which they were assigned (eribulin arm, n=503; TPC arm, n=247). Key efficacy and harms outcomes can be found in Table 3.

Efficacy Outcomes

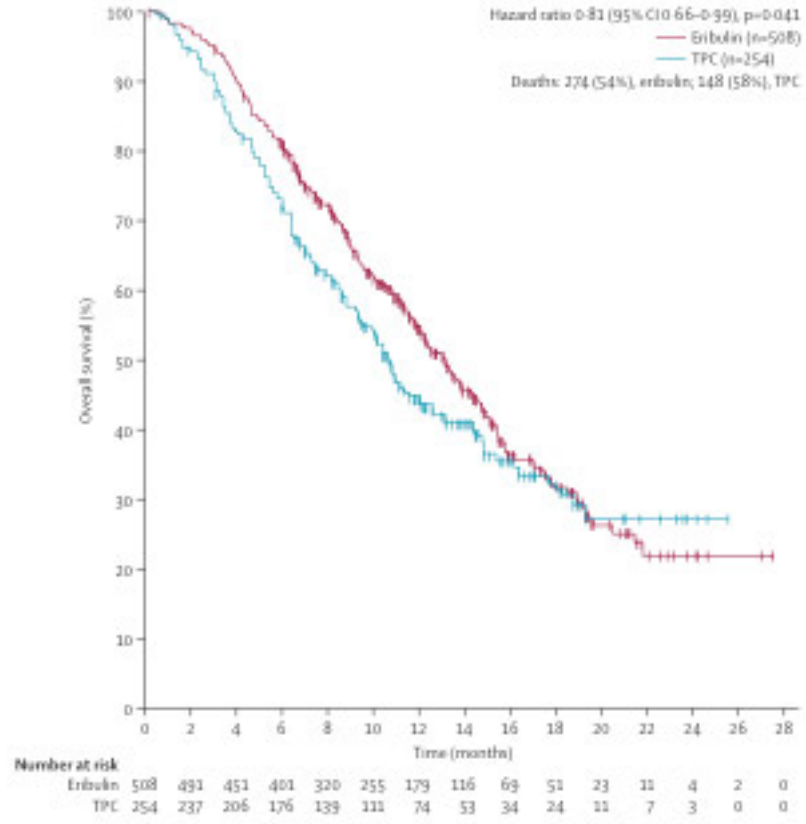
Overall Survival

The primary outcome of the EMBRACE study was overall survival which was defined as the time from randomization to the date of death or the last date the patient was known to be alive (date of censoring) and was analyzed using the ITT population. The analysis was a stratified log-rank test stratified by geographical region, previous capecitabine treatment, and HER2 (ERBB2) status. Kaplan-Meier curves were used to estimate the overall survival statistics and the hazard ratio (HR) was estimated by a stratified Cox regression model.

The final analysis, with a data cut-off of May 12, 2009, demonstrated a statistically significant difference in overall survival for eribulin (median 13.1 months) compared to TPC (median 10.6 months), with HR 0.81, 95% confidence interval (CI) 0.66-0.99, p=0.041 (Table 3 and Figure 2). There were 274 deaths

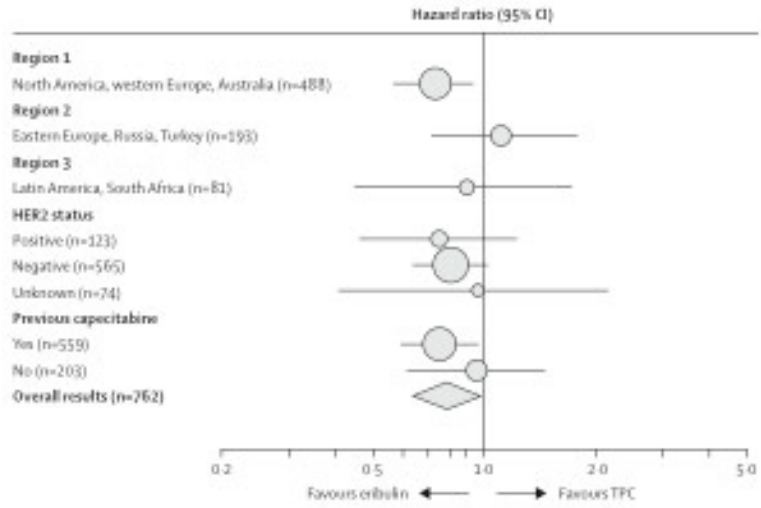
(53.9% of 508 patients) in the eribulin arm and 148 deaths (58.3% of 254 patients) in the TPC arm. One-year survival rates were 53.9% in the eribulin arm and 43.7% in the TPC arm. The median follow-up was 14 months in both treatment arms.[5] Subgroup analyses by the stratification factors showed a statistically significant difference in overall survival in the North America/Western Europe/Australia region (n=488) for eribulin (median 13.1 months) compared to TPC (median 10.1 months), with HR 0.72, 95% CI 0.57-0.92, p=0.009. No other statistically significant differences were noted (Figure 3).

Figure 2. Kaplan-Meier survival curves for final OS analysis of EMBRACE.[1]



Notes: CI=confidence interval; TPC=treatment of physician's choice.
Source: Cortes et al[1]

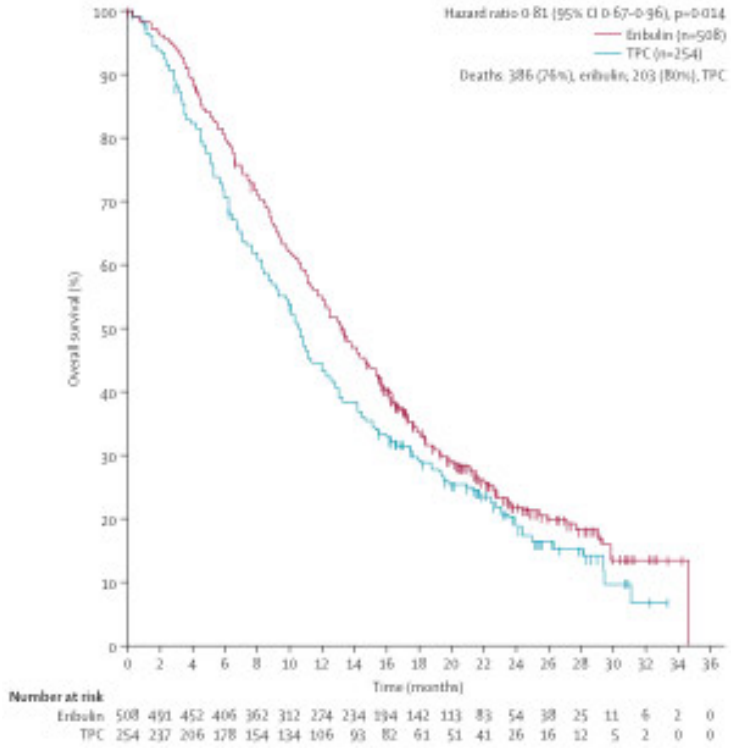
Figure 3. Subgroup analyses of overall survival in EMBRACE.[1]



Notes: CI=confidence interval.
Source: Cortes et al[1]

In addition to the study's final analysis, another overall survival analysis was reported by Cortes et al[1] that included overall survival data up to March 3, 2010. The authors reported that this analysis was requested by the European Medicines Agency (EMA) when more than 75% of the randomized patients had died. At the data cut-off the analysis included a total of 589 deaths (77.3% of 762 patients); 386 (76.0% of 508 patients) in the eribulin arm and 203 (79.9% of 254 patients) in the TPC arm. A statistically significant difference in overall survival was found for eribulin (median 13.2 months) compared to TPC (median 10.5 months), with HR 0.81, 95% CI 0.67-0.96, p=0.014 (Figure 4.). One-year survival rates were 54.5% in the eribulin arm and 42.8% in the TPC arm. The median follow-up was 24 months in both study arms.[5]

Figure 4. Kaplan-Meier survival curves for updated OS analysis of EMBRACE.[1]



Notes: CI=confidence interval; TPC=treatment of physician's choice.
Source: Cortes et al[1]

Progression-Free Survival

Progression-free survival was reported as a secondary endpoint. The primary study publication reported progression-free survival analyses for the independently reviewed tumour assessments (independent PFS) and for the investigator tumour assessments (investigator PFS).[1] Progression-free survival was defined from the date of randomization to the date of disease progression, death, or the date of censoring. The independent PFS analysis demonstrated no significant statistical difference in progression-free survival for eribulin (median 3.7 months) compared to TPC (median 2.2 months), with HR 0.87, 95% CI 0.71-1.05, p=0.137 (Table 3). The investigator PFS analysis demonstrated a statistically significant difference in progression-free survival for eribulin (median 3.6 months) compared to TPC (median 2.2 months), with HR 0.76, 95% CI 0.64-0.90, p=0.002. Cortes et al felt that the reason that the independent review was not significant was due to the fact that almost twice as many patients in the independent review were censored.[1] The authors felt that the higher proportion of censored patients in the independent review was due to study scans stopping once the investigator had declared disease progression, which lead to many censored patients in the independent review not being assessable as the independent reviewers would have only been able to assess

non-measurable disease for progression if non-target lesions progressed or new lesions appeared.

Harms Outcomes

A total of 750 patients comprised the safety population of which 503 were in the eribulin arm and 247 were in the TPC arm.

Adverse Events of Any Grade

Adverse events of any grade were reported in 98.8% of 503 patients in the eribulin arm and in 93.1% of 247 patients in the TPC arm (Table 2). The breakdown most commonly reported adverse events of any grade can be found in Table 8. Of note, a higher proportion of patients in the eribulin arm experienced the following adverse events of any grade: neutropenia, leucopenia, astenia/fatigue, alopecia, peripheral neuropathy, arthralgia/myalgia, weight loss, pyrexia, and back pain (Table 8). Peripheral neuropathy of any grade occurred in 34.6% of 503 patients in the eribulin arm and in 16.2% of 247 patients in the TPC arm.

Table 8. Adverse Events reported in EMBRACE.[1]

Harm	Eribulin n=503		TPC n=247	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Hematological				
Neutropenia	260 (51.7)	227 (45.1)	73 (29.6)	52 (21.1)
Leucopenia	116 (23.1)	70 (13.9)	28 (11.3)	14 (5.7)
Anemia	94 (18.7)	10 (2.0)	56 (22.7)	9 (3.6)
Non-hematological				
Asthenia/fatigue	270 (53.7)	44 (8.7)	98 (39.7)	25 (10.1)
Alopecia	224 (44.5)	-	24 (9.7)	-
Peripheral neuropathy	174 (34.6)	41 (8.2)	40 (16.6)	5 (2.0)
Nausea	174 (34.6)	6 (1.2)	70 (28.3)	6 (2.4)
Constipation	124 (24.7)	3 (0.6)	51 (20.6)	2 (0.8)
Arthralgia/ myalgia	109 (21.7)	2 (0.4)	29 (11.7)	3 (1.2)
Weight loss	107 (21.3)	3 (0.6)	35 (14.2)	1 (0.4)
Pyrexia	105 (20.9)	1 (0.2)	31 (12.6)	1 (0.4)
Anorexia	98 (19.5)	2 (0.4)	32 (13.0)	3 (1.2)
Headache	97 (19.3)	2 (0.4)	29 (11.7)	1 (0.4)
Diarrhea	92 (18.3)	0	45 (18.2)	0
Vomiting	91 (18.1)	5 (1.0)	44 (17.8)	3 (1.2)
Back pain	79 (15.7)	4 (0.8)	18 (7.3)	4 (1.6)
Dyspnea	79 (15.7)	18 (3.6)	31 (12.6)	7 (2.8)
Cough	72 (14.3)	0	21 (8.5)	0
Bone pain	60 (11.9)	9 (1.8)	23 (9.3)	4 (1.6)
Pain in extremity	57 (11.3)	5 (1.0)	25 (10.1)	3 (1.2)
Mucosal inflammation	43 (8.5)	7 (1.4)	25 (10.1)	5 (2.0)
Palmar-plantar erythrodysaesthesia	7 (1.4)	2 (0.4)	34 (13.8)	9 (3.6)

Notes: TPC=treatment of physician's choice.
Source: Cortes et al[1]

Serious Adverse Events (Grade 3 or Higher)

Serious adverse events (Grade 3 or higher) occurred in 25.0% of 503 patients in the eribulin arm and in 25.9% of 247 patients in the TPC arm (Table 3).[1] Grade 3 or higher peripheral neuropathy occurred in 8.2% of 503 patients in the eribulin arm and in 2.0% of 247 patients in the TPC arm. Febrile neutropenia occurred in 4.6% of patients in the eribulin arm and in 1.6% of patients in the TPC arm. Grade 3 or higher neutropenia occurred in 45.1% of patients in the eribulin arm and in 21.1% of patients in the TPC arm. Grade 3 or higher leucopenia occurred in 13.9% of patients in the eribulin arm and in 5.7% of patients in the TPC arm.

Adverse Events Leading to Discontinuation of Therapy

Cortes et al reported that 67 of 503 (13.3%) patients in the safety population that received eribulin and 38 of 247 (15.4%) patients in the safety population that received TPC discontinued therapy due to an adverse event. Cortes et al reported

that peripheral neuropathy was the most common adverse event leading to discontinuation of eribulin (24 of 503 patients or 4.8%).[1]

Time to Resolution of Peripheral Neuropathy

The median time to resolution of peripheral neuropathy was approximately eight weeks in the 34.6% of 503 evaluable patients in the eribulin arm who experienced peripheral neuropathy of any Grade.[36]

Fatal Adverse Events

There were a total of 38 deaths due to adverse events, with 20 deaths in the eribulin arm (4.0% of 503 patients) and 18 deaths in the TPC arm (7.3% of 247 patients).[1] Of the 20 deaths in the eribulin arm, five were considered to be treatment-related and were due to febrile neutropenia (n=1), lung infection (n=1), bronchopneumonia (n=1), and dyspnea (n=2).[1] Of the 18 deaths in the TPC arm, two were considered to be treatment-related and were due to febrile neutropenia (n=1) and aspergillosis (n=1).[1]

Quality of Life

Quality of life data were not reported for the EMBRACE study.

6.4 Ongoing Trials

Three ongoing trials investigating eribulin in locally recurrent or metastatic breast cancer were identified through searches of clinical trial registries: NCT00337103; NCT01534455; NCT01427933. Details of the trials can be found in Tables 9-11.

Table 9. Study NCT00337103: E7389 (eribulin) versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes.[37]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT00337103 Open-label, randomized phase III trial. Start date: June 2006 Expected completion date: September 2011 Estimated enrolment: 1100	Locally advanced or metastatic breast cancer who have received up to 3 prior chemotherapy regimens (no more than 2 prior regimens for locally advanced or metastatic disease) Prior regimens must have included an anthracycline and a taxane either in combination or in separate regimens. Patients with HER2/neu over-expressing tumours may have received trastuzumab. Patients with estrogen and/or progesterone receptor-expressing tumours may have received hormonal therapy. ECOG PS 0-2	Eribulin mesylate 1.4 mg/m^2 i.v. over 2-5 minutes on day 1 and 8 every 21 days. ***Or*** Capecitabine 2.5 g/m^2/day orally in two equal doses on days 1-14 every 21 days.	<u>Primary outcomes:</u> Overall survival Progression-free survival

Available from: http://clinicaltrials.gov/ct2/show/NCT00337103?term=e7389+capecitabine&rank=1

Table 10. Study NCT01534455: Randomized phase II study comparing two doses of eribulin plus lapatinib in trastuzumab pre-treated patients with HER2-positive metastatic breast cancer (E-VITA).[38]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01534455 Open-label, randomized phase II trial. Start date: February 2012 Expected completion date: December 2015 Estimated enrolment: 80	Locally advanced or metastatic breast cancer not suitable for surgery or radiotherapy alone. Measurable disease (RECIST). Histologically confirmed breast cancer with over-expression of HER2.	Eribulin mesylate 1.23 mg/m^2 i.v. on day 1 and 8 of 21-day cycle plus lapatinib. ***Or*** Eribulin mesylate 1.76 mg/m^2 i.v. on day 1 and 8 of a 21-day cycle plus lapatinib. Both arms receive: lapatinb 1000 mg/day	Primary outcome: Time-to-progression Safety and toxicity Secondary outcomes: Overall survival Objective response rate

Available from: http://clinicaltrials.gov/ct2/show/NCT01534455?term=nct01534455&rank=1

Table 11. Study NCT01427933: Randomized phase II study comparing ramucirumab in combination with eribulin versus eribulin monotherapy in unresectable, locally-recurrent, or metastatic breast cancer patients previously treated with anthracycline and taxane therapy.[39]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01427933 Open-label, multicenter, randomized phase II trial. Start date: November 2011 Expected completion date: October 2013 Estimated enrolment: 134	Stage III locally recurrent (not amenable to curative therapy) or Stage IV breast cancer. Measurable disease (RECIST) Prior treatment with both anthracyclines and taxanes in the metastatic, adjuvant or neoadjuvant setting.	Ramucirumab 10 mg/kg i.v. infusion on day 1 of 21-day cycle plus eribulin mesylate 1.4 mg/m^2 i.v. bolus on day 1 and 8 of 21-day cycle. ***Or*** Eribulin mesylate 1.4 mg/m^2 i.v. bolus on day 1 and 8 of a 21-day cycle.	Primary outcome: Progression-free survival Secondary outcomes: Overall survival Objective response rate Duration of response

Available from: http://clinicaltrials.gov/ct2/show/NCT01427933?term=nct01427933&rank=1

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Breast Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on eribulin for metastatic breast cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision were made in between posting of the Initial and Final Clinical Guidance Reports.

The pCODR Breast Clinical Guidance Panel is comprised of three medical oncologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature Search via OVID Platform.

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

1. (eribulin: or halaven: or b1939: or e7389: or nsc707389: or b1793: or er?86526: or 253128-41-5).ti,ab,rn,nm,sh,hw,ot.
2. exp breast neoplasms/
3. breast cancer:.ti,ab,sh,hw,ot.
4. (cancer: adj2 breast:).ti,ab,sh,hw,ot.
5. Breast carcinom:.ti,ab,sh,hw,ot.
6. (carcinom: adj2 breast:).ti,ab,sh,hw,ot.
7. Breast neoplasm:.ti,ab,sh,hw,ot.
8. Or/2-8
9. 1 and 9

Ovid EMBASE

1. *eribulin/
2. (eribulin: or halaven: or b1939: or e7389: or nsc707389: or b1793: or er?86526:).ti,ab.
3. 1 or 2
4. *breast cancer/
5. breast cancer:.ti,ab.
6. (cancer: adj2 breast:).ti,ab.
7. Breast carcinom:.ti,ab.
8. (carcinom: adj2 breast:).ti,ab.
9. Breast neoplasm:.ti,ab.
10. (neoplasm: adj2 breast:).ti,ab.
11. Or/4-10
12. 3 and 11

2. Literature Search via PubMed

PubMed

1. eribulin* or halaven* or e7389* or b1939*
2. publisher[sb]
3. 1 and 2

3. Literature Search via Cochrane Central Register of Controlled Trials (CENTRAL)

Issue 2, 2012
Three results for: eribulin* or halaven* or e7389* or b1939* AND breast cancer* in Cochrane Central Register of Controlled Trials.

4. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: eribulin, halaven, e7389, b1939

Select International Agencies:

Food and Drug Administration (FDA):
www.fda.gov

European Medicines Agency (EMA):
www.ema.europa.eu

Search terms: eribulin, halaven, e7389, b1939

Conference Abstracts:

American Society of Clinical Oncology (ASCO)
via the Journal of Clinical Oncology search portal: http://jco.ascopubs.org/search

San Antonio Breast Cancer Symposium (SABCS)
Via the SABCS Abstracts2View Portal:
2011: http://www.abstracts2view.com/sabcs11/index.php
2010: http://www.abstracts2view.com/sabcs10/index.php
2009: http://www.abstracts2view.com/sabcs09/index.php
2008: http://www.abstracts2view.com/sabcs/sessionindex.php
2007: Searched via PDF copy of abstract book for the *30th Annual San Antonio Breast Cancer Symposium*, published in: Breast Cancer Research and Treatment. 2007;106(Suppl 1).

Search terms: eribulin, halaven, e7389, b1939

REFERENCES

1. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011 Mar 12;377(9769):914-23.
2. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Summary review [Internet]. In: Halaven (eribulin mesylate) injection. Company: Eisai Incorporated. Application no.: 201532. Approval date 11/15/2010. Rockville (MD): The Center; 2011 [cited 2012 Mar 5]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201532s000_halaven_TOC.cfm.
3. Halaven (eribulin mesylate) injection: 0.5 mg/mL [product monograph]. Mississauga (ON): Eisai Limited; 2011 Dec 14.
4. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review [Internet]. In: Halaven (eribulin mesylate) injection. Company: Eisai Incorporated. Application no.: 201532. Approval date 11/15/2010. Rockville (MD): The Center; 2011 [cited 2012 Mar 5]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201532s000_halaven_TOC.cfm.
5. Eisai Limited response to checkpoint meeting questions [internal report]. Mississauga (ON): Eisai Limited.
6. Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics 2011. Toronto: Canadian Cancer Society; 2011.
7. Smith I. Goals of Treatment for Patients With Metastatic Breast Cancer. Semin Oncol. 2006;33(Suppl 2):2-5.
8. Chia SK, Speers CH, D'yachkova Y, Kang A, Malfair-Taylor S, Barnett J, et al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. Cancer. 2007;110(5):973-9.
9. Saad ED, Katz A, Buyse M. Overall survival and post-progression survival in advanced breast cancer: a review of recent randomized clinical trials. J Clin Oncol. 2010;28(11):1958-62.
10. Cardoso F, Bedard PL, Winer EP, Pagani O, Senkus-Konefka E, Fallowfield LJ, et al. International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. J Natl Cancer Inst. 2009;101(17):1174-81.
11. Roche H, Vahdat LT. Treatment of metastatic breast cancer: second line and beyond. Ann Oncol. 2011;22(5):1000-10.
12. Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol. 1999;17(2):485-93.
13. Jones S, Winer E, Vogel C, Laufman L, Hutchins L, O'Rourke M, et al. Randomized comparison of vinorelbine and melphalan in anthracyline-refractory advanced breast cancer. J Clin Oncol. 1995;13(10):2567-74.
14. Spielmann M, Llombart-Cussac A, Kalla S, Espie M, Namer M, Ferrero J-M, et al. Single-agent gemcitabine is active in previously treated metastatic breast cancer. Oncology. 2001;60(4):303-7.

15. Nagourney RA, Link JS, Blitzer JB, Forsthoff C, Evans SS. Gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed breast cancer patients. J Clin Oncol. 2000;18(11):2245-9.
16. Cardoso F, Twelves C, Vahdat LT, Dutcus C, Seegobin S, Wanders J, et al. Eribulin mesylate EMBRACE study - Survival analysis excluding patients re-challenged with therapies of the same class. Eur J Cancer. 2011 September;47(Suppl 1):S331-S2, Abstract 5006.
17. Twelves C, Loesch D, Blum JL, Vahdat LT, Petrakova K, Chollet PJ, et al. A phase III study (EMBRACE) of eribulin mesylate versus treatment of physician's choice in patients with locally recurrent or metastatic breast cancer previously treated with an anthracycline and a taxane [abstract]. J Clin Oncol (ASCO Annual Meeting). 2010 20 Jun;28(18 Suppl):CRA1004.
18. Twelves C, Akerele C, Wanders J, Cortes JA. Eribulin mesylate (e7389) vs treatment of physician's choice (TPC) in patients (pts) with metastatic breast cancer (MBC): Subgroup analyses from the embrace study. Ann Oncol. 2010 October;21(Suppl 8):viii96, Abstract 275O.
19. Cortes J, Twelves C, Wanders J, Wang W, Vahdat L, Dutcus C. Clinical response to eribulin in patients with metastatic breast cancer is independent of time to first metastatic event. EMBRACE study group. Breast. 2011 October;20(Suppl 4):S48-S9, Abstract PO107.
20. Vahdat LT, Cortes J, Twelves C, Wanders J, Seegobin S, Dutcus C, et al. Impact of eribulin on overall survival in patients with metastatic breast cancer with visceral disease [abstract]. J Clin Oncol (ASCO Breast Cancer Symposium). 2011;29(27 Suppl):239.
21. Twelves C, Vahdat LT, Cortes J, Wanders J, Dutcus CE, Seegobin S, et al. The relationship between age and survival outcomes for eribulin in metastatic breast cancer [abstract]. J Clin Oncol (ASCO Annual Meeting). 2011;29(15 Suppl):1060.
22. Blum JL, Twelves CJ, Akerele C, Seegobin S, Wanders J, Cortes J. Impact of the number of prior chemotherapy regimens on overall survival (OS) among subjects with locally recurrent or metastatic breast cancer treated with eribulin mesylate: results from the phase III EMBRACE study [abstract]. 33rd Annual San Antonio Breast Cancer Symposium; 2010 Dec 8-12; San Antonio (USA). 2010 [cited 2012 Mar 8]:Abstract P6-13-01. Available from: http://www.abstracts2view.com/sabcs10/sessionindex.php.
23. Vahdat LT, Twelves CJ, Seegobin S, Akerele C, Wanders J, Cortes J. Survival outcomes with eribulin mesylate vs. treatemnt of physician's choice (TPC) in heavily pretreated subjects with locally recurrent or metastatic breast cancer in North America, Western Europe, and Australia: results of the phase III EMBRACE study [abstract]. 33rd Annual San Antonio Breast Cancer Symposium; 2010 Dec 8-12; San Antonio (USA). 2010:Abstract P6-13-02. Availabe from http://www.abstracts2view.com/sabcs10/sessionindex.php.
24. Twelves C, Loesch D, Blum J, Vahdat L, Petrakova K, Durando X, et al. Updated survival analysis of a phase III study (EMBRACE) of eribulin mesylate versus treatment of physician's choice in subjects with locally recurrent or metastatic breast cancer previously treated with an anthracycline and a taxane [abstract]. 33rd Annual San Antonio Breast Cancer Symposium; 2010 Dec 8-12; San Antonio (USA). 2010:Abstract P6-14-8. Available from: http://www.abstracts2view.com/sabcs0/sessionindex.php.
25. Twelves C, Loesch D, Blum JL, Vahdat LT, Petrakova K, Chollet PJ, et al. A phase III study (EMBRACE) of eribulin mesylate versus treatment of physician's choice in

patients with locally recurrent or metastatic breast cancer previously treated with an anthracycline and a taxane [abstract via OVID search]. J Clin Oncol (ASCO Annual Meeting). 2010;28(18 Suppl):CRA1004.
26. Twelves C, Vahdat LT, Cortes J, Wanders J, Dutcus CE, Seegobin S, et al. The relationship between age and survival outcomes for eribulin in metastatic breast cancer. [abstract via OVID search]. J Clin Oncol (ASCO Annual Meeting). 2011 20 May;29(15 Suppl):1060.
27. Tao C, Taylor D, Parthan A, Faria C, Choe Y. Budget-impact of eribulin for third-line treatment of metastatic breast cancer in a United States managed care setting. Value in Health. 2011 May;14(3):A159, Abstract PCN25.
28. Kreutzkamp B. Advanced breast cancer: Eribulin prolongs overall survival. [German]. Medizinische Monatsschrift fur Pharmazeuten. 2011;34(11).
29. Junker A. Advanced breast carcinoma: Prolonged overall survival with eribulin. [German]. Arzneimitteltherapie. 2011 November;29(11):360-1.
30. Haussen HP. Breast carcinoma: Eribulin extends the total survival period. [German]. Deutsche Apotheker Zeitung. 2010 17 Jun;150(24):41-2.
31. Cortes J, Montero AJ, Gluck S. Eribulin mesylate, a novel microtubule inhibitor in the treatment of breast cancer. Cancer Treat Rev. 2012 Apr;38(2):143-51.
32. Cortes J, Lorca R. Eribulin mesylate: a promising new antineoplastic agent for locally advanced or metastatic breast cancer. Fut Oncol. 2011 Mar;7(3):355-64.
33. Wendling P. Eribulin monotherapy boosts survival in late metastatic disease. The Oncology Report. 2010 July-August(JULY-AUGUST):10-1.
34. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review [Internet]. In: Halaven (eribulin mesylate) injection. Company: Eisai Incorporated. Application no.: 201532. Approval date 11/15/2010. Rockville (MD): The Center; 2011 [cited 2012 Mar 5]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201532s000_halaven_TOC.cfm.
35. Committee for Medicinal Products for Human Use, European Medicines Agency. European Public Assessment Report for Halaven (eribulin) [Internet]. Procedure no.: EMEA/H/C/002084. First published: 2011 Apr 11. London (UK): 2011 [cited 2012 Mar 21]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002084/human_med_001427.jsp&mid=WC0b01ac058001d124.
36. pan-Canadian Oncology Drug Review Manufacturer Submission: Halaven (eribulin mesylate) injection: 0.5 mg/mL; Company: Eisai Limited. Mississauga (ON): Eisai Limited; 2012 Feb 9.
37. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT00337103, E7389 versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes; 2006 Jun 13 [Last updated 2012 Apr 4; cited 2012 May 7]. Available from: http://clinicaltrials.gov/ct2/show/NCT00337103?term=00337103&rank=1.
38. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01534455, Efficacy and tolerability of eribulin plus lapatinib in patients with metastatic breast cancer (E-VITA); 2012 Feb 8 [Last updated 2012 Apr 16; cited 2012 May 7]. Available from: http://clinicaltrials.gov/ct2/show/NCT01534455?term=nct01534455&rank=1.

39. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01427933, A study of ramucirumab (IMC-1121B) in combination with eribulin versus eribulin alone in patients with breast cancer; 2011 Aug 31 [Last updated 2012 May 3; cited 2012 May 7]. Available from: http://clinicaltrials.gov/ct2/show/NCT01427933?term=nct01427933&rank=1.