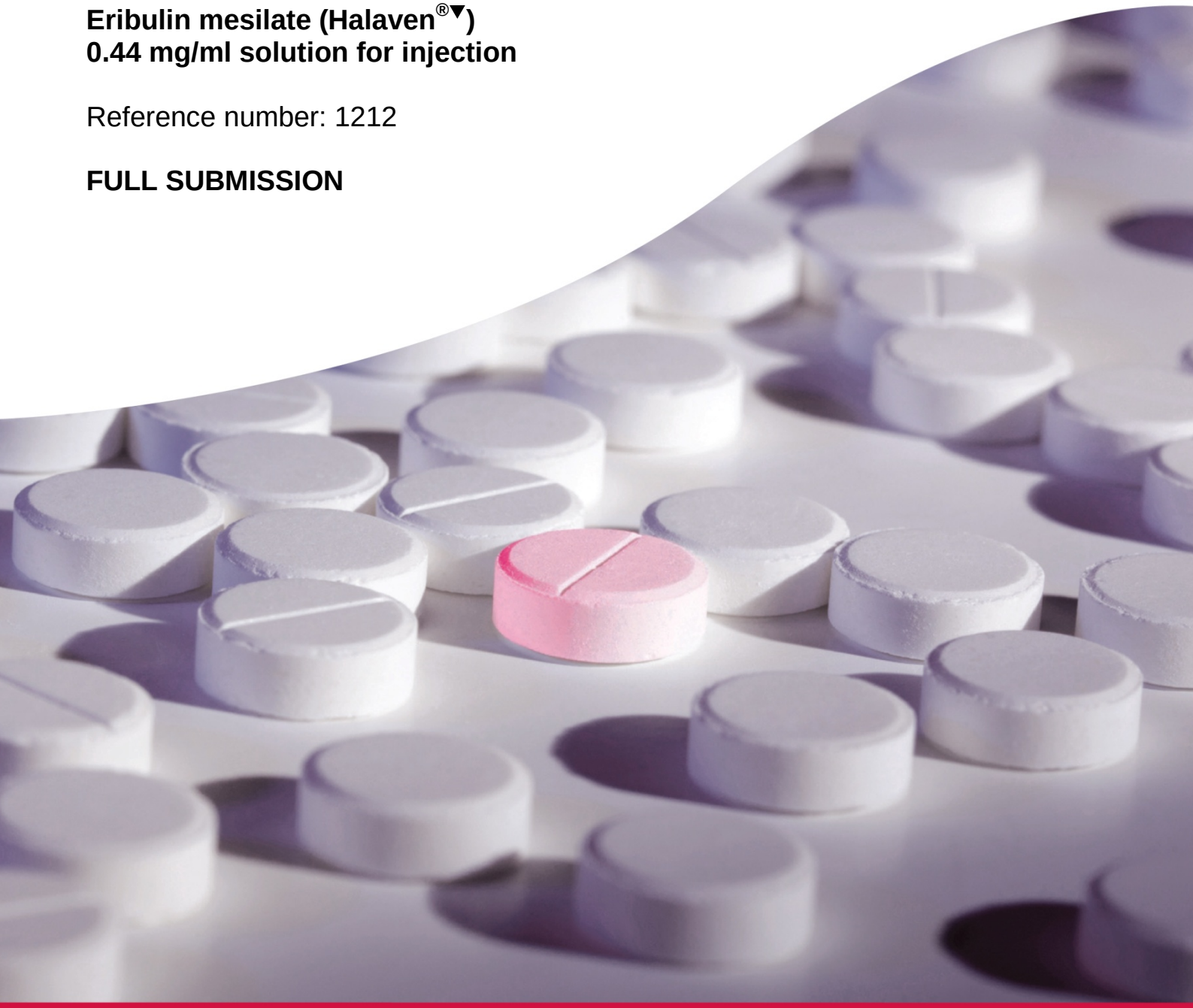
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Eribulin mesilate (Halaven®▼)
0.44 mg/ml solution for injection

Reference number: 1212

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Eribulin mesilate (Halaven®▼) 0.44 mg/ml solution for injection

This assessment report is based on evidence submitted by Eisai Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Eribulin mesilate (Halaven®▼) for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments[2].
Dosing	The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 administered intravenously over two to five minutes on days one and eight of every 21-day cycle. One ml contains 0.44 mg of eribulin as eribulin mesilate. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	27 June 2014[3] (previously licensed for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease on 17 March 2011. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments[2,4]).

2.0 DECISION CONTEXT

2.1 Background

Breast cancer is the most common cancer in women in England and Wales. A small proportion of new cases are diagnosed in the advanced stages and a significant number of women, who have been previously treated, subsequently develop either local recurrence or metastases[5]. The estimated prevalence of breast cancer and metastatic breast cancer in Wales is 4,431 and 339 respectively[1]. While there is no cure for metastatic disease, palliative treatment with radiotherapy, chemotherapy, hormonal and biologic therapy can reduce tumour symptoms and/or prolong life[4]. Clinical guidelines issued by the National Institute for Health and Care Excellence (NICE) in February 2009 advise that in patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), docetaxel (a taxane) should be offered first-line, followed by capecitabine or vinorelbine[5]. Eribulin is a simplified analogue of halichondrin B, a natural product isolated from a marine sponge. It has shown in vitro activity against medicine-resistant cells that harbour beta-tubulin mutations associated with taxane resistance[4].

NICE technology appraisal (TA) guidance does not recommend eribulin (on the basis of cost-effectiveness) for treatment of locally advanced or metastatic breast cancer (LABC/MBC) after two or more chemotherapies for advanced disease[6]. AWMSG are able to appraise this part of the licensed indication as eribulin is currently available for patients in England in the third- or higher-line setting via an alternative commissioning route and the company has submitted a Wales Patient Access Scheme (WPAS) which provides a further discount to NHS Wales. The applicant company has highlighted a subpopulation where they consider eribulin may be particularly advantageous, i.e. post-capecitabine (after two or more chemotherapies for advanced disease)[1].

There is currently no NICE guidance on the remaining part of the licensed indication (i.e. the licence extension for after one chemotherapeutic regime); however, the applicant company has not provided cost-effectiveness data for this subpopulation.

2.2 Comparators

- The comparator included in the company submission was the Treatment of Physician's Choice (TPC); including any single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer, radiotherapy or best supportive care.

2.3 Guidance and related advice

- NICE pathways. Advanced breast cancer: chemotherapy and biological therapy (2015)[7].
- European Society for Medical Oncology. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2) (2014)[8,9] .
- Scottish Intercollegiate Guidelines Network SIGN 134. Treatment of primary breast cancer (2013)[10].
- NICE Technology Appraisal 250. Eribulin for the treatment of locally advanced or metastatic breast cancer (2012)[6].
- NICE. Clinical Guideline 81. Advanced breast cancer: diagnosis and treatment (2009)[5]

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of lapatinib (Tyverb®)[11], paclitaxel albumin-bound nanoparticles (Abraxane®)[12], vinorelbine (Navelbine®)[13] and trastuzumab (Herceptin®)[14,15].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included a phase III study in patients with LABC/MBC who had previously received at least two chemotherapeutic regimens for advanced disease[1]. EMBRACE[16] supported the original licensed indication which has been given a negative recommendation by NICE (see Section 3.3). This study includes a pre-planned subgroup analysis in support of the company positioning of eribulin, post-capecitabine.

3.1 EMBRACE study

EMBRACE was an international, multicentre, open-label, randomised study conducted in 762 patients with LABC/MBC, with the majority (90.6%) having Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (fully active, able to carry on all pre-disease performance without restriction; or restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, respectively)[1,16,17]. A total of 51 patients were treated in the UK, including three patients treated at a centre in Wales. For the purposes of pre-planned subgroup analyses, patients were stratified by geographical region, human epidermal growth factor receptor 2 (HER2) status and prior treatment with capecitabine, before being randomised 2:1 to receive either eribulin or TPC. Single agent chemotherapy was the most common treatment in the TPC group (n=238; 93.7%) followed by hormonal treatment (n=9; 3.5%). Combination therapies were not allowed. The most common chemotherapies were vinorelbine, gemcitabine and capecitabine received by 24.0%, 18.1% and 17.3% of patients respectively[1]. Tumour assessment was by response evaluation criteria in solid tumours (RECIST) methodology[18] and was performed every eight weeks, or sooner if there was suspicion of disease progression. The median duration of treatment for patients who received eribulin and TPC was 3.9 months and 2.1 months respectively[1,16]. The primary endpoint was overall survival (OS) determined after the death of 55% of patients (initial cut-off) and after 77% of patients' deaths

(second cut-off)[1,16]. The difference in median OS between eribulin and TPC was statistically significant at the initial and second cut-off (2.5 months and 2.7 months, respectively) and was deemed clinically relevant by the Committee for Medicinal products for Human Use (CHMP)[1,4,16]. In the subgroup of 559 (73.4%) patients who received capecitabine, the median OS was 2.9 months greater in the eribulin arm than in the TPC arm (p = 0.018; see Table 1)[1].

Table 1. Overall survival (OS) for post-capecitabine subgroup in EMBRACE study[1]

	Eribulin* (n = 370)	TPC* (n = 189)	Treatment difference	p-value	HR (95% CI)
Number of patients who died (%)	291 (78.6%)	154 (81.5%)	-	-	-
Median OS (95% CI)	13.0 months (11.7–13.8)	10.1 months (7.7–11.7)	2.9 months	p = 0.018	0.787 (0.65–0.96)
Median PFS†	3.6 months	2.1 months	1.5 months	p < 0.001	-

CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; TPC: treatment of physician's choice.
*Intention-to-treat (ITT) population; second cut-off after 77% of total study patients had died.
†Investigator review

3.2 Comparative safety

In the EMBRACE study, the eribulin and TPC arms had a similar number of serious adverse events (SAEs; 25% and 26%, respectively), and adverse events (AEs) leading to discontinuation (13% and 15%, respectively). Furthermore, the proportion of patients experiencing treatment-related fatalities was 1% in each arm[16]. No important differences in AEs were observed between the treatment arms[4]. The most common grade 3/4 AEs (with % occurrence in the eribulin:TPC arms) were neutropenia (45%:21%), leucopenia (14%:6%), asthenia/fatigue (9%:10%) and peripheral neuropathy (8%:2%)[16]. Neutropenia was managed by dose delays, reductions and granulocyte colony stimulating factor[16] and did not cause a high frequency of treatment discontinuation[4].

CHMP has identified three treatment-emergent adverse events (TEAEs) of special interest, i.e. asthenia/fatigue, peripheral neuropathy and arthralgia/myalgia. The incidence of peripheral neuropathy was considered high (based on broad standard MedDRA query [SMQ]; EMBRACE eribulin arm: 210 [41.7%]; Study 301 eribulin arm: 149 [27.4%]; Study 301 capecitabine arm: 75 [13.7%]). The three TEAEs were clearly less frequent (7-17% lower) in the earlier disease setting, indicating that eribulin treatment may be better tolerated in this setting. The overall safety profile of eribulin was found to be better when used in first and second line metastatic treatment, compared with the previously known safety profile based on later lines of therapy in the breast cancer population[19].

CHMP concluded that the differences seen between eribulin and capecitabine with regard to TEAEs of toxicity grade ≥ 3 are consistent with the known differences in safety profiles and are perhaps smaller than expected. The incidence of peripheral neuropathy was regarded as high by CHMP. At end of follow-up, 2.8% of the Phase 2/3 breast cancer population had remaining grade 3-4 neuropathy. Overall, this is not worse than for other tubulin-acting drugs, but it has been included in the risk management plan for eribulin[19].

3.3 AWTTC critique

- NICE TA250 does not recommend eribulin (on the basis of cost-effectiveness) for treatment of LABC/MBC after two or more chemotherapies for advanced disease[6]. AWMSG are able to appraise this part of the licensed indication as eribulin is currently available for patients in England in the third- or higher-line setting via an alternative commissioning route and the company has submitted a WPAS which provides a further discount to NHS Wales. The applicant company has highlighted a subpopulation where they consider eribulin may be particularly advantageous, i.e. post-capecitabine (after two or more chemotherapies for advanced disease)[1]. NICE agreed that this subpopulation was potentially relevant to clinical practice[6].
- There is currently no NICE guidance on the remaining part of the licensed indication (i.e. the licence extension for after one chemotherapeutic regime); however, the applicant company has not provided cost-effectiveness data for this subpopulation[1]. The company submission included Study 301[20] as a phase III study in support of the licence extension. Whilst this study also included some patients who had received two or more chemotherapies in the LABC/MBC setting (original licence), no subgroup analysis was provided in the post-capecitabine subpopulation where the company has positioned eribulin[1].
- There were significant gains in median OS and PFS (2.9 months and 1.5 months, respectively) in patients receiving eribulin in the post-capecitabine subpopulation in the EMBRACE trial[1].
- NICE TA250 noted that no health-related quality of life data were collected in the EMBRACE trial[6]. In the company submission for appraisal by AWMSG, Study 301 has been used to inform the quality-adjusted life-years (QALYs) for the patients in the EMBRACE study[1,16,20,21].
- The comparator arm of the EMBRACE study consisted of a range of chemotherapies and other treatments rather than a distinct single comparator. NICE report that a clinical specialist observed that these therapies were a reasonable reflection of clinical practice in the UK and the NICE Appraisal Committee concluded that the study broadly reflected clinical practice in the UK[6]. Although best supportive care only and radiotherapy were options in the TPC arm of the study, all patients received pharmacotherapy.
- The median age of the patients included in the EMBRACE study is 55 years[16], which is younger than the median age reported in clinical practice in the UK which is 60-65 years[6].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost-utility analysis (CUA) of eribulin for the treatment of patients with LABC/MBC who have progressed after at least two chemotherapeutic regimens for advanced disease[1]. Prior therapy should have included capecitabine if indicated and an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.

A decision analytic model was used to estimate the changes in total cost, total QALYs and incremental cost-effectiveness ratios (ICERs) over a five year time horizon (base case) from a Welsh NHS perspective to compare eribulin to TPC. The company used a partition survival cost-effectiveness model. Patients were assumed to transition between the three health states of Stable, Progressive and Dead. Patients enter the model in the stable health state upon treatment initiation with eribulin or TPC where they remain until disease progression, when they enter into the progressive health state, or death. Patients in the progressive state are assumed to remain in this state until death or the end of the time horizon. The treatment cycle for eribulin and TPC is

21 days long and the duration of each Markov cycle is set to one month (30.42 days). At the end of each Markov cycle, time-dependent transition probabilities (when an event is influenced by an earlier event) derived from OS and PFS were used to calculate the proportion of patients moving from one state to another.

Treatment outcomes for eribulin and TPC (OS and PFS) and AEs were derived from the EMBRACE study[1]. Quality of life data were derived from Study 301[20,21]. The information on cost items associated with the treatment of drug-related AEs was extracted from NHS reference costs for the UK. The information on resource utilisation for the different health states of the model were obtained from clinical experts and the NICE clinical guideline for advanced breast cancer, CG81[1,5,22].

Nine one-way sensitivity analyses were undertaken to create optimistic and conservative scenarios to test the robustness of the model results. Discount rates of 0% and 5% were applied to costs only, benefits only and both. The price of eribulin was increased and decreased by 20% and similar variations were applied to the cost of the comparator drugs, administrative costs, direct health care costs and HRG costs of AEs. In the probabilistic sensitivity analysis, the utility of each health state and the time spent in each health state followed gamma (utility) or normal distributions (survival and stable disease).

4.1.2 Results

The results of the base case analysis are presented in Table 2. Over the five-year horizon eribulin is more costly compared to TPC but produces a greater number of QALYs. ICERs are in the region of the £20,000 threshold when using the WPAS prices. The proportional hazard model constitutes the base case and the company uses a different model construct (the piecewise model) to validate the base case results.

Table 2. Results of analyses incorporating the WPAS

	Eribulin	TPC	Difference
Proportional hazard model (Base case)			
Total costs per patient	£18,848	£15,052	**£3,796**
Total QALYs	0.92	0.72	**0.20**
ICER (£/QALY gained)	**£18,825**		
Piecewise model			
Total costs per patient	£18,903	£14,802	**£4,100**
Total QALYs	0.92	0.71	**0.20**
ICER (£/QALY gained)	**£20,282**		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; WPAS: Wales Patient Access Scheme.

Reducing the eribulin price by 20% resulted in the largest impact to the ICER, lowering it to £13,274. Probabilistic sensitivity analysis found eribulin to be cost-effective in 62.7% of simulations at a £20,000 threshold compared to TPC.

4.1.3 AWTTC critique

Strengths of the economic analysis include:

- The company used an appropriate and comprehensive model design to address the cost-effectiveness of eribulin in comparison to TPC.
- The submission gives a very detailed and transparent account of the methods, data sources and analyses undertaken.

Limitations of the economic analysis include:

- The model is based on treatment for patients who have progressed after at least two chemotherapies for advanced disease and therefore does not reflect the full licensed indication in terms of the number of chemotherapy treatments received, prior to treatment with eribulin[1]. The cost-effectiveness of eribulin in patients who have progressed after one chemotherapy for advanced disease has not been considered.
- The company has confirmed that for treatment outcomes only patient data from the post-capecitabine subgroup were used in the cost-effectiveness analysis whereas all the patients recruited in the EMBRACE study were used to calculate risk of AEs. The company states that this was done to include all AEs related to treatment utilisation, to avoid reducing the power of the safety analysis and the risk of not incorporating important but rare AEs.
- The use of a mixed comparator approach could introduce bias; only 6.7% of the study population were from the UK and treatments may differ across countries. However, NICE TA250, concludes that this approach is a reasonable reflection of UK clinical practice.
- Office for National Statistics data indicates that on average patients in the EMBRACE trial were younger than the population of women in England diagnosed with breast cancer[23] and therefore potentially fitter, which introduces uncertainty surrounding the number of AEs identified in the study (which may be underestimated) and the survival effect reported. It would have been beneficial to explore this uncertainty through sensitivity analysis.
- Health state resource utilisation was obtained from clinical experts and the NICE clinical guideline for advanced breast cancer, CG81[5,22]. How the company addressed any discrepancies between expert opinion and the guidelines, and whether or not expert opinion reflect those of clinicians in Wales, is unclear.
- The company did not inflate costs derived from other publications (e.g. end of life costs taken directly from NICE CG81 2009[5] and cost of febrile neutropenia from NHS reference costs 2012/13)[24]. This results in an underestimation of the costs associated with palliative care and AEs more commonly observed in eribulin-treated patients, thereby introducing bias.
- The use of Study 301 to inform the QALYs for the EMBRACE patients would imply that health-related quality of life is not affected by the number of chemotherapy treatments received in the past. If this assumption is unrealistic, it adds uncertainty to the QALYs calculated and the ICERs generated. Additionally, use of these data essentially means that the model does not reflect the licensed indication in terms of the number of chemotherapy treatments received.
- The EMBRACE study did not collect QALY data. The mapping of EORTC QLQ-C30 data to EQ-5D collected from a second study with relatively healthier patients to elicit patient preferences introduces uncertainty surrounding the base case ICER[21,25].
- The disutility associated with AEs was derived from a study with a lower rate of AEs and was not derived from the EMBRACE study, which creates further uncertainty around QALY estimates[1,20].
- In the EMBRACE study, alopecia was greater for the eribulin group (45%) than the TPC group (10%)[1,16]. However, since no disutility was attached to this AE, the QALY does not take into account the distress associated with alopecia.
- No data sources are provided for the deterministic sensitivity analyses.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC identified three international published cost-effectiveness analysis of eribulin within its current licensed indication for adult patients with LABC/MBC. The clinical effectiveness of these studies was derived from the EMBRACE study. The cost-effectiveness of eribulin in Taiwan[26] and

Singapore[27] used the entire cohort of patients in the EMBRACE study, whereas the cost-effectiveness analysis conducted in Mexico[28] used only the sub group of patients treated with capecitabine. The QALY gains reported in these studies ranged from 0.12 to 0.28[26–28], compared to 0.2 reported in the company submission. The differences in health care settings and acquisition costs between these countries and Wales limit the transferability of health care costs data to NHS Wales.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on the Welsh female adult population in 2015, Cancer Research UK data and a Kantar Health report , the company estimates that 86 LABC/MBC patients in Wales will receive third-line post-capecitabine treatment[29,30]. For the budget impact analysis the company calculates the number of patients eligible for treatment with eribulin based on prevalence and mortality-based incidence. Mortality rates are based on data from the EMBRACE study[16]. Given the advanced stage of the disease and that the patients are to receive third line post-capecitabine treatment, the annual number of patients eligible for treatment with eribulin remains relatively static. The company assumes that each year 10% of the patients adopt eribulin. This translates to nine patients being treated with eribulin in year one and 43 in year five.

The company uses four one-way sensitivity analyses to create optimistic and conservative scenarios to test the results of the budget impact analysis. The price of eribulin is increased and decreased by 20% and, similar changes are applied to the cost of the comparator drugs, direct medical costs (pre and post-progression) and AE costs.

5.1.2 Results

The estimated net budget impact is presented in Table 3. The company estimates the overall net costs, based on the WPAS, after the introduction of eribulin to be between £15,459 in year one and £78,319 in year five.

Table 3. Company-reported costs (incorporating WPAS) associated with use of eribulin in company-proposed subpopulation (post-capecitabine; after two or more chemotherapies for advanced disease)

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	86	86	86	87	87
Uptake (%)	10%	20%	30%	40%	50%
Treated patients	9	17	26	35	43
Overall net cost	**£15,459**	**£31,020**	**£46,683**	**£62,449**	**£78,319**

The sensitivity analyses on the budget impact analysis shows a large degree of change to the results. The largest impact is driven by the changes in the direct medical costs; for this parameter the optimistic scenario would generate cost savings whereas the conservative scenarios would more than double the cost of the base case.

5.1.3 AWTTC critique

- The mortality data used to estimate eligible patient numbers were not Wales-specific, which could introduce bias.
- The medical costs for TPC might not reflect Welsh standard practice and this introduces uncertainty in the budget impact estimates.
- The company does not describe the data sources used to inform the sensitivity analysis of the budget impact analysis.

- The company used a 10%/year increase in market share to reach 50% of the market in year five, but did not give any explanation of how these figures were derived. The effect of changing market share could have been explored in sensitivity analysis.
- Market shares of comparators used in the CUA and the budget impact analysis were different because they were obtained from the EMBRACE study and market research respectively[1].
- The company indicates a prevalence of breast cancer patients of 0.14% in Wales[1]. AWTTC were unable to obtain this figure from the source provided[29].
- The figure of prevalence of MBC of 7.64% of total prevalence does not appear in the section of the document supplied by the company[30].
- There is no clear information on how the figures for second, third and post capecitabine chemotherapy were determined.

5.2 Comparative unit costs

The acquisition costs reflect the cost of a cycle of chemotherapy treatment with eribulin and the TPC treatment options.

Table 4. Examples of acquisition costs of chemotherapy options for LABC/MBC

Regimens	Example doses*	Approximate costs per chemotherapy cycle
Eribulin mesilate (Halaven®)	2.10 mg IV on days one and eight	£2,166
Vinorelbine (Navelbine®) 20 mg capsules (9 capsules)	60 mg/m^2 once weekly for 3 weeks, then increased if tolerated to 80 mg/m^2 once weekly (max. per dose 160 mg once weekly)	£396
Vinorelbine (Navelbine®) 30 mg capsules (6 capsules)	60 mg/m^2 once weekly for 3 weeks, then increased if tolerated to 80 mg/m^2 once weekly (max. per dose 160 mg once weekly)	£396
Vinorelbine (Navelbine®) 80 mg capsules (3 capsules)	80mg/m^2 (Cycle 2, Day 8 onwards if nadir neutrophil count >0.5 x 10^9/l and no neutropenic sepsis)	£528
Vinorelbine (Navelbine®) 10mg/1ml solution for injection vials (10 vials)	In monotherapy the usual dose given is 25-30 mg/m² once weekly. In combination chemotherapy the usual dose (25-30 mg/m²) is usually maintained, while the frequency of administration is reduced e.g. day 1 and 5 every 3 weeks or day 1 and 8 every 3 weeks according to treatment protocol.	£297
Vinorelbine (Navelbine®) 50 mg/5ml solution for injection vials (10 vials)	Vinorelbine is usually given at 25-30mg/m² weekly	£1,400
Gemcitabine 200 mg/5.3ml concentrate for solution for infusion vials (6 vials)	1,250 mg/m^2 IV over 30 minutes on days 1 and 8 of each 21 day cycle that includes paclitaxel.	£150
Capecitabine 300 mg tablets (60 tablets)	1,250 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2,500 mg/m^2 total daily dose) for 2 weeks followed by a 1 week rest period given as 3 week cycles.	£54
Capecitabine 500 mg tablets (120 tablets)	Alternatively, a dose of 1,000 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2,000 mg/m^2 total daily dose) for 2 weeks with 1 week rest may be may be appropriate.	£146

See relevant Summaries of Product Characteristics for full licensed indications and dosing details[2,31–33].
Costs are based on BNF list prices as of 30th November 2015, assuming vial wastage.
Costs of administration are not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.
* based on average body surface area (adult female) of 1.71 m^2

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, eribulin mesilate (Halaven®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company state that eribulin mesilate (Halaven®▼) is not currently available through a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 12 November 2015.
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy on life-extending, end-of-life medicines

The applicant company has indicated that eribulin may be considered under the AWMSG policy for appraising life-extending, end-of-life medicines[34]. The AWMSG criteria for appraising life-extending, end-of-life medicines, and a discussion of the extent to which eribulin may meet these criteria, are provided in Table 5.

Table 5. End-of life considerations for New Medicines Group (NMG)/AWMSG

AWMSG Criteria for application of the EoL policy (all must apply)[34]	Eribulin considerations
The most plausible ICER estimate exceeds £30,000 per QALY	The EMBRACE study did not collect QALY data. These were generated from a second study with relatively healthier patients (Section 4). The higher values of the ICERs presented from the company vary between £18,825 (base case) to £24,375 (worst case scenario of a 20% increase in the price of eribulin). In the absence of primary data on the QALYs generated by patients heavily pre-treated as in the EMBRACE study it is not possible to make estimates of the probability of exceeding £30,000 per QALY.
The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).	The EMBRACE study reported median OS of 13.1 months in the eribulin arm and a median OS of 10.6 months in the TPC arm. The study used to calculate QALYs reported median OS of 15.9 months in the eribulin arm and 14.5 months in the capecitabine arm. Median OS would therefore seem likely to be less than 24 months based on treatment with eribulin, capecitabine and TPC.
There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life-years gained) should be robust and shown (or reasonably inferred) from either progression-free survival or overall survival.	The EMBRACE study estimated a statistically significant gain in median OS of 2.5 months when eribulin was compared to TPC at first cut-off point (after the death of 55% of the patients). At the second cut-off point (after the death of all the patients) there was a statistically significant gain in OS of 2.7 months compared to TPC. In the post-capecitabine subgroup, a statistically significant gain in median OS of 2.9 months was observed with eribulin compared to TPC. The study used to calculate the QALYs (Study 301) did not show any statistically significant gain in OS when eribulin was compared to capecitabine. This would suggest that there is not sufficient evidence to indicate that eribulin offers an extension of life of at least three months.
AWMSG/NMG will consider the cumulative population of each licensed indication of the medicine to be small.	NICE assumes a “small” population is equivalent to 7,000 patients in England. This would equate to around 406 patients in Wales. The company estimates 219 patients would be eligible for eribulin. The population of the licensed indication would therefore plausibly be small.
EoL: End-of-life; ICER: incremental cost-effectiveness ratio (incremental cost per QALY gained); OS: overall survival; QALY: quality-adjusted life years; TPC: Treatment of Physicians Choice.	

Should NMG/AWMSG conclude that eribulin should be considered under the AWMSG policy for appraising life-extending, end-of-life medicines[34], NMG/AWMSG will need to consider:

- The impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age.
- The magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the medicine to fall within the current threshold range.

In addition, NMG/AWMSG will need to be satisfied that:

- The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review) and;
- The assumptions used in the economic modelling are plausible, objective and robust.

6.6 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

The applicant company has suggested that the AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases may apply to use of eribulin[35]. Whilst eribulin has not been designated as an orphan medicine by European Medicines Agency (EMA), AWMSG will apply the same process and principles of consideration to a medicine developed specifically to treat an equivalent size population irrespective of whether it is designated by the EMA as an orphan medicine i.e. if the full population of the licensed indication(s) is equal to, or less than, 5 in 10,000 persons (equivalent to 1,500 patients in Wales) which is consistent with the prevalence definition of an orphan medicine[35].

Eribulin is currently licensed for the treatment of adult patients with LABC/MBC who have progressed after at least one chemotherapeutic regimen for advanced disease. Based on data from the Kantar Health report, the applicant company estimates this equates to 219 patients in Wales. The company has highlighted a subpopulation of patients with LABC/MBC who have progressive disease after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine if indicated, for which the estimated Welsh patient population is 86. However, for all relevant medicines including orphan, ultra-orphan and medicines developed specifically for rare diseases the definitions apply to the full population of the licensed indication(s), rather than any subpopulations[35].

AWTTC considers that eribulin may be eligible to be considered under the policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases[35] as the full population of the licensed indication is likely to be less than the 5 in 10,000 persons (or 1,500 patients in Wales) threshold. For medicines developed specifically to treat a rare disease, NMG/AWMSG may consider, if the cost per QALY is above the normal thresholds applied, additional criteria for appraising these medicines (see Table 6).

Table 6. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases, considerations for NMG/AWMSG

NMG/AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	The applicant company highlight that breast cancer is the most common malignancy among women in the UK; it accounts for approximately 1 in 3 cases of cancer in women and the lifetime risk of developing breast cancer for women is 1 in 8[29]. As many as 35% of women diagnosed with early breast cancer will eventually progress to or relapse with LABC/MBC[5]. Evidence has been provided by the applicant company highlighting symptoms can be severe including cancer-related fatigue and uncontrolled local disease, along with further complications relating to the organ(s) to which the cancer has spread[1,5]. LABC/MBC has a significant impact on quality of life[36–38], and patients commonly suffer psychological and psychiatric disturbances[39] . Due to the age of these references however, these findings may not accurately reflect current quality of life due to improvements in current clinical practice and treatments.
Whether the medicine can reverse or cure, rather than stabilise the condition.	The applicant company do not claim that eribulin can reverse or cure this condition. They do state however that (as recognised by NICE clinical guidelines [CG81[5]]), one of the key priorities for treating this advanced stage of breast cancer is to prolong survival, while controlling the symptoms experienced and improving the patient's quality of life.
The innovative nature of the medicine.	Eribulin is considered an innovative chemotherapy treatment which is a non-taxane inhibitor of microtubule dynamics, with a unique mechanism of action[40,41]. Eribulin is the first and only single agent therapy to demonstrate a significant overall survival benefit in in LABC/MBC patients previously treated with an anthracycline and a taxane, a patient population with limited treatment options and an unmet medical need.
Whether medicine addresses an unmet need.	Most patients with MBC are treated with anthracycline and taxane agents; however, the applicant company suggest patients will ultimately fail treatment as a result of disease progression or intolerable toxicity with these drugs, and for those patients no universal standard therapy exists. Furthermore, previous exposure to anthracyclines and taxanes in the adjuvant setting means that the proportion of women with MBC whose disease is resistant to these agents has increased.
Added value to the patient which may not be captured in the QALY.	The applicant company noted the patient group, Breast Cancer Now's comment that, "eribulin may give patients a few extra months at the end of their life and is well tolerated by many patients". The patient group highlighted the importance of additional good quality time to patients with terminal breast cancer and their families.
LABC: locally advanced breast cancer; MBC: metastatic breast cancer; QALY: quality-adjusted life-year.	

REFERENCES

1 Eisai Limited. Form B: Detailed appraisal submission. Eribulin mesilate (Halaven®▼). 2015.
2 Eisai Limited. Halaven®▼. 0.44 mg/ml solution for injection. Summary of Product Characteristics. Jul 2015. Available at: https://www.medicines.org.uk/emc/medicine/24382. Accessed Nov 2015.
3 European Medicines Agency. Halaven®▼. Procedural steps taken and scientific information after the authorisation. Jul 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/002084/WC500127272.pdf. Accessed Nov 2015.
4 European Medicines Agency. Assessment Report for Halaven®▼. Procedure No.: EMEA/H/C/002084. Jan 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002084/WC500105115.pdf. Accessed Nov 2015.
5 National Institute for Health and Care Excellence. Clinical Guideline 81. Advanced breast cancer: diagnosis and treatment. Feb 2009. Available at: http://guidance.nice.org.uk/CG81. Accessed Nov 2015.
6 National Institute for Health and Care Excellence. Technology Appraisal 250. Eribulin for the treatment of locally advanced or metastatic breat cancer. Apr 2012. Available at: http://guidance.nice.org.uk/TA250. Accessed Nov 2015.
7 National Institute for Health and Care Excellence. Advanced breast cancer: chemotherapy and biological therapy. 2015. Available at: http://pathways.nice.org.uk/pathways/advanced-breast-cancer#path=view%3A/pathways/advanced-breast-cancer/advanced-breast-cancer-chemotherapy-and-biological-therapy.xml&content=view-node%3Anodes-third-line-therapy. Accessed Nov 2015.
8 Cardoso F, Costa A, Norton L et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Annals of Oncology* 2014; 25: 1871-88. Available at: http://annonc.oxfordjournals.org/content/early/2014/09/17/annonc.mdu385.full.pdf. Accessed: Mar 2016.
9 Cardoso F, Costa A, Norton L et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *The Breast* 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25244983. Accessed: Mar 2016.
10 Scottish Intercollegiate Guidelines Network. SIGN 134. Treatment of primary breast cancer. 2013. Available at: http://www.sign.ac.uk/pdf/SIGN134.pdf. Accessed Nov 2015.
11 All Wales Medicines Strategy Group. Lapatinib (Tyverb®) 250 mg film-coated tablet. Reference No. 178. Appraisal information. Dec 2015. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/178. Accessed Dec 2015.
12 All Wales Medicines Strategy Group. Paclitaxel albumin-bound nanoparticles (Abraxane®) powder for suspension for infusion. Reference No. 232. Appraisal information. Dec 2015. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/232. Accessed Dec 2015.
13 All Wales Medicines Strategy Group. Vinorelbine (Navelbine®) capsule. Reference No. 330. Appraisal information. Dec 2015. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/330. Accessed Dec 2015.
14 All Wales Medicines Strategy Group. Trastuzumab (Herceptin®) powder for concentrate for solution for infusion. Reference No. 1006. Appraisal information. Dec 2015. Available at:

http://www.awmsg.org/awmsgonline/app/appraisalinfo/1066. Accessed Dec 2015.
15 All Wales Medicines Strategy Group. Trastuzumab (Herceptin®) 150 mg powder for concentrate for solution for infusion. Reference No. 1409. Appraisal information. Dec 2015. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1409. Accessed Dec 2015.
16 Cortes J, O'Shaughnessy J, Loesch D 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; 377: 914-23. Available at: http://www.sciencedirect.com/science/article/pii/S0140673611600706. Accessed: Nov 2015.
17 Oken M, Creech R, Tormey D. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5: 649-55. Available at: http://ecog-acrin.org/resources/ecog-performance-status. Accessed: Dec 2015.
18 Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92 (3): 205-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10655437. Accessed: Nov 2015.
19 European Medicines Agency. Assessment Report for Halaven®▼. Procedure No.: EMEA/H/C/002084/II/0011. May 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002084/WC500170478.pdf. Accessed Nov 2015.
20 Kaufman PA, Awada A, Twelves C et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncology* 2015; 33 (6): 594-601. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4463422/. Accessed: Dec 2015.
21 Kaufman PA, Awada A, Twelves C et al. Supplementary online appendix - quality of life. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncology* 2015; 33 (6). Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4463422/bin/supp_33_6_594__index.html. Accessed: Dec 2015.
22 Curtis L. Unit costs of Health and Social Care. Personal Social Services Research Unit, University of Kent, UK. 2013. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2013/. Accessed Dec 2015.
23 Office for National Statistics. Nearly 85% of women diagnosed with breast cancer now survive for 5 years or more. Sep 2013. Available at: http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--42--2011/sty-breast-cancer-survival.html. Accessed Dec 2015.
24 Department of Health. NHS reference costs. Jan 2014. Available at: https://www.gov.uk/government/collections/nhs-reference-costs. Accessed Dec 2015.
25 Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. *Eur J Health Econ* 2010; 11 (4): 427-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20473703. Accessed: Dec 2015.
26 Chang CJ, Chao T, Park J et al. Economic assessment of eribulin against treatment of physician's choice (TPC) in Taiwan. 2015. Available at: http://www.ispor.org/ScientificPresentationsDatabase/Presentation/60049. Accessed Dec 2015.

27 Lopes G, Gluck S, Avancha K et al. A cost effectiveness study of eribulin versus standard single-agent cytotoxic chemotherapy for women with previously treated metastatic breast cancer. *Breast Cancer Res Treat* 2013; 137 (1): 187-93. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23143283. Accessed: Dec 2015.
28 Jones T, Tremblay G, Majethia U et al. Cost effectiveness analysis of eribulin mesylate (Halaven®) as treatment for metastatic breast cancer in Mexico. *Value in Health* 2015; 18 (7): A822. Available at: http://www.valueinhealthjournal.com/article/S1098-3015(15)02344-X/pdf. Accessed: Dec 2015.
29 Cancer Research UK. Breast cancer statistics. 2012. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero. Accessed Dec 2015.
30 Kantar Health. Treatment Architecture. Breast Cancer. (reference supplied by company, not in public domain). 2015. Accessed Dec 2015.
31 Pierre Fabre Limited. Navelbine® 10 mg/ml concentrate for solution for infusion. Summary of Product Characteristics. Aug 2011. Available at: http://www.medicines.org.uk/emc/medicine/16029. Accessed Dec 2015.
32 Sun Pharmaceuticals UK Limited. Gemcitabine 1000 mg powder for solution for infusion. Summary of Product Characteristics. Mar 2014. Available at: http://www.medicines.org.uk/emc/medicine/27754. Accessed Dec 2015.
33 Actavis UK Limited. Capecitabine Actavis 500 mg film-coated tablets. Summary of Product Characteristics. Nov 2014. Available at: https://www.medicines.org.uk/emc/medicine/28428. Accessed Dec 2015.
34 All Wales Medicines Strategy Group. AWMSG policy on appraising life-extending, end-of-life medicines. Jul 2015. Available at: http://www.awmsg.org/awmsgonline/grabber?resId=File%2F858. Accessed Feb 2016.
35 All Wales Medicines Strategy Group. Process for appraising orphan and ultra-orphan medicines and medicines developed for rare diseases. Aug 2015. Available at: http://www.awmsg.org/awmsgonline/grabber?resId=File%2F1770. Accessed Mar 2016.
36 Klee M, Groenvold M, Machin D. Quality of life of Danish women population-based norms of the EORTC QLQ-C30. *Qual Life Res* 1997; 6 (1): 27-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Quality+Danish+population+norms+of+the+EORTC+QLQ-C30+Klee. Accessed: Mar 2016.
37 Aranda S, Schofield P, Weih L. Mapping the quality of life and unmet needs of urban women with metastatic breast cancer. *European J Cancer Care* 2005; 14 (3): 211-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15952965. Accessed: Mar 2016.
38 Wilson KA, Dowling AJ, Abdolell M. Perception of quality of life by patients, partners and treating physicians. *Qual Life Res* 2000; 9 (9): 1041-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Perception+of+quality+of+life+by+patients%2C+partners+and+treating+physicians. Accessed: Mar 2016.
39 Kissane DW, Grabsch B, Love A et al. Psychiatric disorder in women with early stage and advanced breast cancer: a comparative analysis. *Aust NZ Psychiatry* 2004; 38 (5): 320-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15144508. Accessed: Dec 2015.
40 Okouneva T, Azarenko O, Wilson L. Inhibition of centromere dynamics by eribulin (E7389) during mitotic metaphase. *Mol Cancer Ther* 2008; 7 (7): 2003-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Inhibition+of+centromere+dynamics+by+eribulin+(E7389)+during+mitotic+metaphase. Accessed: Mar 2016.
41 Jordan MA, Kamath K, Manna T. The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. *Mol*

Cancer Ther 2005; 4 (7): 1086-95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16020666. Accessed: Mar 2016.