Breast Cancer Aotearoa Coalition Inc

Eribulin in Advanced and Metastatic Breast Cancer

21 August 2022

Eribulin in Advanced and Metastatic Breast Cancer

Background and Overall Summary

- A report by the New Zealand Breast Cancer Foundation in 2018 found that median survival after a diagnosis of metastatic/advanced breast cancer in New Zealand is 16 months, considerably worse than overseas. Survival varies greatly by subtype, from 27.3 months for Luminal A patients down to 6.6 months for triple negative breast cancer. Five-year survival after metastatic diagnosis is only 5% in Māori populations, compared to 15% in non-Māori populations (Breast Cancer Foundation New Zealand 2018).
- Eribulin mesylate (Halaven®) is a non-taxane inhibitor of microtubule dynamics and belongs to the halichondrin class of antineoplastic drugs. In contrast to other tubulin-targeting agents like taxanes and vinca alkaloids, eribulin has a distinct mode of action. Therefore, it could be effective for patients who do not respond to or have developed resistance to tubulin-targeting agents.
- Eribulin monotherapy significantly improves overall survival compared with treatment of physician's choice in heavily pre-treated women with metastatic breast cancer (MBC). Subgroup analyses show that it is particularly suitable for treatment of women with MBC who are HER-2 receptor negative including those who have TNBC (Cortes, O'Shaughnessy et al. 2011, Tanni, Truong et al. 2021, Zhao, Hughes et al. 2021).
- Eribulin is recommended among treatment options in current ESMO Guidelines for women with triple negative breast cancer (TNBC) or as a treatment of HR+HER2- breast cancer where other options have failed (Chabot, Zhao et al. 2020, Gennari, André et al. 2021, Tanni, Truong et al. 2021).
- Its proposed use in New Zealand would be as a last line therapy for women who have failed earlier treatments. This is consistent with clinical evidence and the proposed MEDSAFE approval.
- Since many of the options suggested by international guidelines (such as ESMO) for women with metastatic breast cancer, particularly after earlier lines of therapy have failed, are not available (let alone funded) in New Zealand, the availability of eribulin could contribute to useful treatment options, particularly until such treatments become available here (Gennari, André et al. 2021).
- Breast Cancer Aotearoa Coalition is making a submission to Pharmac to have eribulin available on the Pharmaceutical Schedule as soon as it is registered in New Zealand, a process that is currently underway with MEDSAFE.

Summary of Published Clinical Data for Eribulin in Advanced and Metastatic Breast Cancer

Trials that supported original registration of eribulin were carried out in a heavily pre-treated population of patients with advanced or metastatic breast cancer. These populations were treated with eribulin as monotherapy. This is the target population for New Zealand, because of the clinical need in this population and the expected registration wording.

(Note that other trials have evaluated eribulin in combination with other agents and/or at an earlier therapy line. These are specifically excluded from the summary below as they are not consistent with the expected use in New Zealand. For example, eribulin has been evaluated in combination with pembrolizumab, with pertuzumab and trastuzumab and with pemetrexed.)

The pivotal trials of eribulin monotherapy were as follows:

EMBRACE – Study 305 Monotherapy versus physician's choice in heavily pre-treated patients
NCT00388726

Citations

- Cortes, J., et al. (2011). "Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study." Lancet **377**(9769): 914-923. – main publication (Cortes, O'Shaughnessy et al. 2011)

- Miyoshi, Y., et al. (2020). "High absolute lymphocyte counts are associated with longer overall survival in patients with metastatic breast cancer treated with eribulin-but not with treatment of physician's choice-in the EMBRACE study." Breast Cancer **27**(4): 706-715. – sub publication (Miyoshi, Yoshimura et al. 2020)

Study 305/EMBRACE included women after two-to-five lines of chemotherapy for advanced breast cancer who were randomised to 2:1 to eribulin mesylate (1.4 mg/m^2 on days 1 and 8 every 21 days) or treatment of physician's choice (TPC). Randomisation was stratified by geographical region, previous capecitabine treatment, and HER-2 status. The primary endpoint was overall survival in the intention-to-treat population. A total of 762 women were included (508 eribulin, 254 TPC).

Patients in this trial had received a median of 4 prior chemotherapies, mainly including taxanes (99%), anthracyclines (99%) and capecitabine (73%).

Overall survival was significantly improved in women assigned to eribulin (median 13·1 months, 95% CI 11·8-14·3) compared with TPC (10·6 months, 9·3-12·5; HR 0·81, 95% CI 0·66-0·99; p=0·041). The Kaplan-Meier curve for OS is shown below.

The most common adverse events in both groups were asthenia or fatigue (270 [54%] of 503 patients on eribulin and 98 [40%] of 247 patients on TPC at all grades) and neutropenia (260 [52%] patients receiving eribulin and 73 [30%] of those on TPC at all grades). Peripheral neuropathy was the most common adverse event leading to discontinuation of eribulin, occurring in 24 (5%) of 503 patients.

It was concluded that eribulin showed a significant and clinically meaningful improvement in overall survival compared with TPC in women with heavily pre-treated metastatic breast cancer. This finding challenged the notion that improved overall survival is an unrealistic expectation during evaluation of new anticancer therapies in the refractory setting (Cortes, O'Shaughnessy et al. 2011).

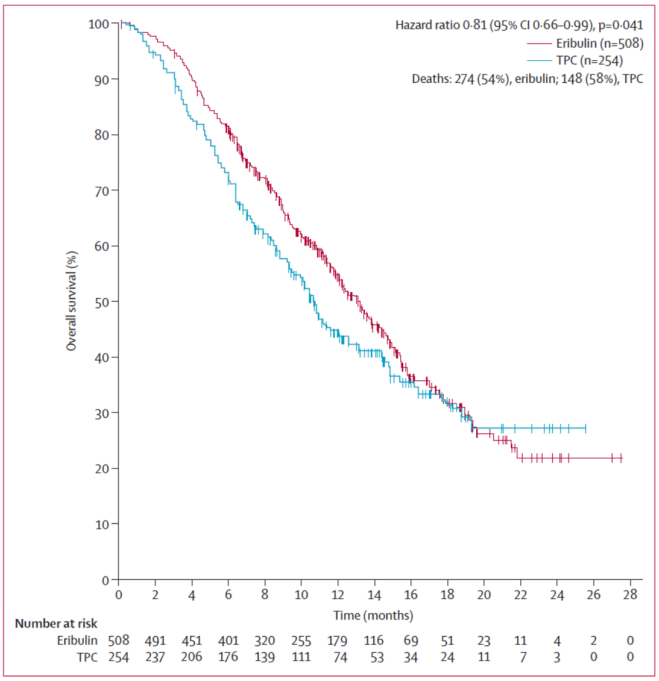

Figure 2: Kaplan-Meier graph of overall survival
Analysis was protocol prespecified and included the intention-to-treat population. Tickmarks show censored data.
TPC=treatment of physician's choice.

Source: Cortes et al. 2011

A post hoc analysis assessed predictors for overall survival (OS) in the EMBRACE study. Baseline absolute lymphocyte counts (ALCs) and neutrophil-to-lymphocyte ratio (NLR) were evaluable in 751 and 713 patients, respectively. Eribulin prolonged OS versus TPC in patients with baseline ALC ≥ 1500/µl (HR 0.586; 95% confidence interval [CI] 0.437-0.784; p< 0.001). There was no significant difference by treatment for ALC < 1500/µl (HR 1.002; 95% CI 0.800-1.253; p=0.989). Univariate and multivariate analyses were performed and identified baseline ALC as a potential predictor of OS in eribulin-treated patients. Interaction analysis of OS supported 1500/µl as a potentially differential cut-off value. NLR at a cut-off value of 3 was associated with prolonged OS (eribulin group). However, similar results were also observed in the TPC group, without apparent interaction effect, suggesting that NLR may be a general prognostic marker rather than a specific predictor of OS for eribulin. This hypothesis-generating study speculates that baseline ALC may be an independent predictor for longer OS in eribulin-treated MBC patients and could be clinically impactful because it can be evaluated without the need for additional invasive procedures (Miyoshi, Yoshimura et al. 2020).

ERIBULIN versus CAPECITABINE – Study 301 - LA and MBC treated with up to 2 prior lines
NCT00337103

In Study 301, patients who had received up to two prior chemotherapy regimens for advanced disease were randomised to eribulin (as above) or capecitabine (1.25 g/m^2 b.i.d. on days 1-14 every 21 days).

Citations

- Kaufman, P. A., et al. (2015). "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 Oncol **33**(6): 594-601. – main publication (Kaufman, Awada et al. 2015)

- Cortes, J., et al. (2015). "Health-related quality of life in patients with locally advanced or metastatic breast cancer treated with eribulin mesylate or capecitabine in an open-label randomized phase 3 trial." Breast Cancer Res Treat **154**(3): 509-520. – publication on QoL results (Cortes, Hudgens et al. 2015)

- Pivot, X., et al. (2018). "Subgroup analysis of patients with HER2-negative metastatic breast cancer in the second-line setting from a phase 3, open-label, randomized study of eribulin mesilate versus capecitabine." Breast Cancer **25**(3): 370-374. – sub publication (Pivot, Im et al. 2018)

Study 301 compared eribulin with capecitabine in patients with locally advanced or metastatic breast cancer (MBC). Women with MBC who had received prior anthracycline- and taxane-based therapy were randomly assigned to receive eribulin or capecitabine as their first-, second-, or third-line chemotherapy for advanced/metastatic disease. Stratification factors were HER-2 status and geographic region. Coprimary end points were overall survival (OS) and progression-free survival (PFS).

Median OS times for eribulin (n = 554) and capecitabine (n = 548) were 15.9 and 14.5 months, respectively (HR 0.88; 95% CI, 0.77 to 1.00; p=0.056). Median PFS times for eribulin and capecitabine were 4.1 and 4.2 months, respectively (HR, 1.08; 95% CI, 0.93 to 1.25; p=0.30). Objective response rates were 11.0% for eribulin and 11.5% for capecitabine. Global health status and overall quality-of-life scores over time were similar in the treatment arms. Both treatments had manageable safety profiles consistent with their known adverse effects; most adverse events were grade 1 or 2. It was concluded that, eribulin was not superior to capecitabine with regard to OS or PFS.

HRQoL was assessed using the EORTC QLQ-C30 and breast module-23 questions (QLQ-BR23), administered at baseline through 24 months, until disease progression or other antitumour treatment initiation. Minimally important difference (MID) and time to symptom worsening (TSW) were investigated. A total of 1062 (96.4 %) patients completed the EORTC questionnaire at baseline; overall, compliance was ≥80 %. Patients receiving capecitabine versus eribulin had significantly worse symptoms (higher scores) for nausea/vomiting (MID 8; $p<0.05$) and diarrhoea (MID 7; $p<0.05$). Treatment with eribulin versus capecitabine, led to worse systemic therapy side-effects (dry mouth, different tastes, irritated eyes, feeling ill, hot flushes, headaches, and hair loss; MID 10; $p<0.01$). Clinically meaningful worsening was observed for future perspective (MID 10; $p<0.05$) with capecitabine and for systemic therapy side-effects scale (MID 10; $p<0.01$) with eribulin. Patients receiving capecitabine experienced more-rapid deterioration in body image (by 2.9 months) and future perspective (by 1.4 months; $p<0.05$) compared with those on eribulin; the opposite was observed for systemic side-effects where patients receiving eribulin experienced more-rapid deterioration than those receiving capecitabine (by 2 months; $p<0.05$). Eribulin and capecitabine were found to have similar impact on patient functioning with no overall difference in HRQoL. Patients receiving eribulin reported worse systemic side-effects of chemotherapy but reduced gastrointestinal toxicity compared with capecitabine (Cortes, Hudgens et al. 2015).

A post-hoc subgroup analysis included 392 patients from Study 301 and compared the efficacy and safety of eribulin versus capecitabine in patients with HER2-negative metastatic breast cancer who received second-line treatment. Median overall survival was longer in patients receiving eribulin compared with capecitabine (16.1 vs 13.5 months, respectively: HR 0.77, p= 0.026). Median progression-free survival and response rates were similar between arms. Both treatments had

manageable safety profiles (Pivot, Im et al. 2018). These results are therefore consistent with ESMO 2021 guidelines for metastatic breast cancer that suggest eribulin for use in patients (after failure of other treatments) with ER+/HER2- and triple negative (TN) breast cancer (Gennari, André et al. 2021).

ERIBULIN vs VINORELBINE - LA and MBC in Chinese women
NCT02225470

Citations

- Yuan, P., et al. (2019). "Eribulin mesilate versus vinorelbine in women with locally recurrent or metastatic breast cancer: A randomised clinical trial." Eur J Cancer **112**: 57-65. – main publication (Yuan, Hu et al. 2019)

- Wu, Y., et al. (2020). "Incidence of peripheral neuropathy associated with eribulin mesylate versus vinorelbine in patients with metastatic breast cancer: sub-group analysis of a randomized phase III study." Support Care Cancer **28**(8): 3819-3829. (Wu, Wang et al. 2020)

This study compared efficacy and safety of eribulin monotherapy and vinorelbine, in Chinese women with locally recurrent/metastatic breast cancer (MBC). It was a Phase III open-label, randomised, parallel-group, multicentre clinical trial that enrolled patients with locally recurrent or MBC who had had 2-5 prior chemotherapy regimens, including an anthracycline and taxane). Women were randomised 1:1 to receive eribulin (1.4 mg/m^2, intravenously, on day 1 and day 8) or vinorelbine (25 mg/m^2, intravenously, on day 1, day 8 and day 15) every 21 days. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), duration of response and overall survival (OS). Five hundred and thirty women were randomised to receive eribulin (n = 264) or vinorelbine (n = 266). Improvement in PFS was observed with eribulin compared with vinorelbine (hazard ratio [HR]: 0.80, 95% confidence interval [CI]: 0.65-0.98, p=0.036); median PFS was 2.8 months in both treatment arms. The median OS was 13.4 months with eribulin and 12.5 months with vinorelbine (HR: 1.03, 95% CI: 0.80-1.31, p=0.838). The ORR was 30.7% (95% CI: 25.2%-36.6%) with eribulin and 16.9% (95% CI: 12.6%-22.0%) with vinorelbine (p<0.001). Treatment-emergent adverse events leading to treatment discontinuation were less frequent with eribulin (7.2%) than with vinorelbine (14.0%). It was concluded that eribulin achieved statistically significantly superior PFS (and response rate) compared with vinorelbine in previously treated women with locally recurrent or MBC. Eribulin appeared to be better tolerated than vinorelbine, with no new safety signals observed (Yuan, Hu et al. 2019).

A single-centre sub-group analysis of patients in this study investigated incidence of peripheral neuropathy, time to onset of neuropathy, and safety. It included 110 women with a mean age of 50.7 (SD=10.9). The median accumulated dose of eribulin was 11.2 mg/m^2 and 125.0 mg/m^2 for vinorelbine. Among patients in the eribulin group, a performance status (ECOG PS) of 2 was correlated with peripheral sensory neuropathy (p=0.015), and accumulated eribulin dose (≥ 10 mg/m^2) was associated with all neuropathy and peripheral sensory neuropathy (p=0.003 and p=0.007, respectively). In the vinorelbine group, patient age (≥ 65 years) was positively associated with all neuropathy (p=0.043). The time to onset of neuropathy appeared to be longer for eribulin versus vinorelbine (35.3 vs. 34.6 weeks; p=0.046), with a significantly higher incidence of autonomic neuropathy at weeks 2 and 10 observed among patients receiving vinorelbine (p=0.008 and p=0.043, respectively). It was concluded that vinorelbine is associated with a higher incidence of autonomic neuropathy than eribulin in

patients with metastatic breast cancer. Furthermore, the onset of neurotoxicity appeared to occur earlier with vinorelbine than eribulin.

POOLED ANALYSES and SYSTEMATIC REVIEWS/META-ANALYSES

The body of evidence from the original registration file has been subsequently supplemented with published pooled and meta-analyses that are summarised below. These include: pooled analyses of Phase III trials, (Twelves, Cortes et al. 2014, Goodin, Barbour et al. 2015); a recent systematic review and meta-analysis of RCTs (Tanni, Truong et al. 2021); a network meta-analysis that compares eribulin with other agents (Zhao, Hughes et al. 2021) and two meta-analyses of "real world evidence" studies (Voutsadakis 2017, Chabot, Zhao et al. 2020). In addition, two published systematic reviews evaluated the use of eribulin in older people with breast cancer (Muss, Cortes et al. 2014, Pedersini, di Mauro et al. 2020).

Twelves, C., et al. (2014). "Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies." Breast Cancer Res Treat 148(3): 553-561.

Data from two phase 3 studies of eribulin (Study 305-EMBRACE and Study 301) were pooled in analyses requested by the European Medicines Agency to assess whether specific patient subgroups, previously treated with an anthracycline and a taxane, benefited from eribulin. In the pooled population, overall survival (OS), progression-free survival and response rates were analysed in the intent-to-treat population and selected subgroups.

Overall, 1,062 patients were randomised to eribulin and 802 patients to control. Median OS was 15.2 months with eribulin versus 12.8 months with control (HR 0.85; 95% CI 0.77, 0.95; p=0.003). In all subgroups assessed, OS data favoured eribulin; significant improvements occurred in some subgroups, notably in women with HER2-negative disease (HR 0.82; p=0.002). It was concluded that eribulin improves OS in various patient subgroups with advanced/metastatic breast cancer who had previously received an anthracycline and a taxane. Women with HER2-negative disease are among those who may obtain benefit from eribulin.

Goodin et al. 2015 (Pooled Analysis of Phase II and Phase III clinical trials – safety and tolerability)

This retrospective analysis used pooled safety and tolerability data from three Phase II trials and one Phase III trial of eribulin in patients with MBC. In these studies, patients with pre-treated MBC received eribulin mesylate 1.4 mg/m^2 as a 2-5 five-minute IV infusion on days 1 and 8 of a 21-day cycle. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 3.0.

Across the four trials, 908 patients received eribulin and were assessed for safety. Aside from anthracyclines and taxanes, the most common prior chemotherapy agents were capecitabine, vinorelbine, and gemcitabine. Patients had received a mean of 3.7 (range, 1-11) prior chemotherapeutic regimens. Dose delays, reductions, and interruptions due to treatment-emergent adverse events occurred in 35.0%, 17.3%, and 2.9% of patients, respectively. Treatment was discontinued in 12.3% of patients due to adverse events, regardless of whether the adverse event was considered treatment related. The most common grade 3 or 4 treatment-related adverse events were neutropenia (52.4%) and leukopenia (19.3%). Serious adverse events occurred in 26.1% of patients, with the most common being febrile neutropenia (3.6%) and pyrexia (2.3%). Peripheral neuropathy was seen in 30.6% of patients, with 6.6% experiencing grade 3 or 4 reactions. It was concluded that, despite heavy pre-treatment with anthracyclines, taxanes, and capecitabine, eribulin was well tolerated in this pooled analysis of patients with MBC.

Tanni, Trong et al. Systematic Review 2021

These authors systematically searched MEDLINE Ovid, Cochrane Library, IPA, CINAHL, Web of Science and ProQuest Dissertations for studies evaluating eribulin versus non-eribulin regimens in LABC/MBC up to January 15, 2021. Primary effectiveness and safety outcomes were overall survival (OS) and adverse events (AE), respectively. Hazard ratios (HR) and relative risks (RR) with 95 % confidence intervals (CIs) were calculated using fixed or random-effects models. Of 1183 publications identified, 13 studies were included in this review as shown in the diagram below (Fig. 1 from the published paper).

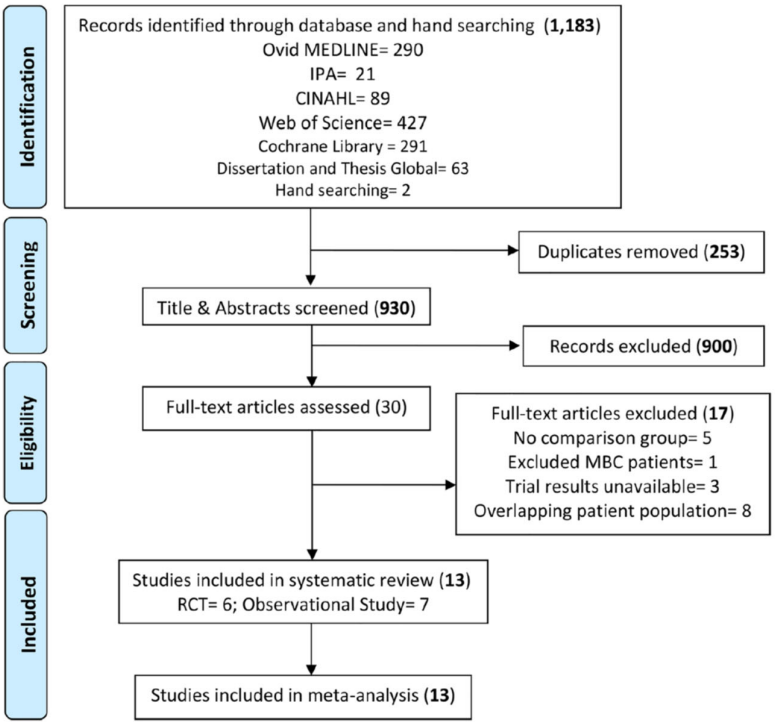

Fig. 1. Flow-chart of the study selection process.

Study characteristics are summarised in the table below (Table 1 from the published paper).

Table 1
Study Characteristics.

Author (year)	Country	Study design	Intervention and comparator	Therapy line	Sample size[a]		Receptor status		Primary (1) and secondary (2) outcomes	Author's conclusion
					Erb	Non-Erb	Erb	Non-Erb		
Cortes et al. (2011)	Global*	Phase III RCT, open-label	Erb vs. TPC	3rd & later	508	254	HER2- (73 %) HER2+ (16 %) TNBC (18 %)	HER2- (76 %) HER2+ (16 %) TNBC (20 %)	(1) OS (2) PFS, ORR, and duration of response	Significant increase in OS for Erb compared with TPC
Abraham et al. (2015)	US	Phase II RCT	Erb vs. paclitaxel	1st	30	19	HER2- (58 %) TNBC (42 %)	HER2- (70 %) TNBC (30 %)	(1) pCR (2) cCR rate, imaging response rate, and toxicity	Both regimens were equally well tolerated. pCR did not suggest higher activity with Erb than paclitaxel
Kaufman et al. (2015)	Global**	Phase III RCT, open-label	Erb vs. capecitabine	3rd & later	554	548	HER2- (68 %) HER2+ (16 %) TNBC (27 %)	HER2- (69 %) HER2+ (15 %) TNBC (25 %)	(1) OS and PFS (2) ORR, duration of response; 1-, 2-, and 3-year survival, safety, quality of life	OS and PFS in Erb group was not superior to capecitabine group
Park et al. (2017)	Korea	Phase II RCT, open-label	Erb + gemcitabine (EG) vs. paclitaxel + gemcitabine (PG)	1st	59	59	HER2- (76 %) TNBC (24 %)	HER2- (78 %) TNBC (22 %)	(1) PFS (2) OS, neuropathic scale, toxicity, and clinical benefit rate	EG chemotherapy had similar clinical benefits in terms of PFS but less neurotoxicity compared to PG chemotherapy
Vahdat et al. (2013)	US	Phase II RCT, open-label	Erb vs. ixabepilone	2nd & later	52	52	HER2- (84 %) HER2+ (8%) TNBC (8%)	HER2- (64 %) HER2+ (14 %) TNBC (22 %)	(1) Incidence of neuropathy AEs (2) ORR, CBR, PFS, DCR overall safety, and tolerability	No difference in the incidence of neuropathy was observed between Erb and ixabepilone groups
Yuan et al. (2019)	China	Phase III RCT, open-label	Erb vs. vinorelbine	3rd & later	264	266	HER2- (76 %) HER2+ (20 %) TNBC (24 %)	HER2- (75 %) HER2+ (20 %) TNBC (26 %)	(1) PFS (2) OS, ORR and duration of response, CBR, pR, and DCR,	Erb was significantly superior to vinorelbine in PFS (and response rates)
Dranitsaris et al. (2015)	US	Retrospective cohort study	Erb vs. capecitabine, gemcitabine & vinorelbine	Not available	90	321	HER2- (68 %) HER2+ (18 %)	HER2- (63 %) HER2+ (34 %)	(1) Drug-related toxicities and the associated health care resource use	Erb demonstrated a comparable patient safety profile to gemcitabine and vinorelbine
Jacot et al. (2019)	France	Retrospective cohort study	Erb vs. TPC	2nd & later	1481	9248	HER2- (75 %) HER2+ (7%) TNBC (18 %)	HER2- (58 %) HER2+ (22 %) TNBC (20 %)	(1) OS (2) PFS	Erb as a third- or fourth-line therapy improved survival compared to other chemotherapy, but as a second line therapy, Erb only benefited patients with HER2- disease.
Kazmi et al. (2020)	US	Retrospective cohort study	Erb. vs. gemcitabine/ capecitabine	3rd	229	214	HER2- (62 %) HER2+ (9%) TNBC (29 %)	HER2- (54 %) HER2+ (20 %) TNBC (26 %)	(1) OS	Patients with MBC and visceral metastases demonstrated that landmark OS was significantly higher with Erb at 12 and 24 months compared to gemcitabine and capecitabine
Kikuchi et al. (2018)	Japan	Prospective cohort study	Erb vs. taxanes +/- bevacizumab	1st & later	101	115	HER2- (74 %) HER2+ (26 %)	HER2- (82 %) HER2+ (18 %)	(1) OS (2) PFS, ORR, duration of treatment and safety	Erb showed a survival benefit and tolerability similar to comparison group
Pouwels et al. (2020)	Netherlands	Retrospective cohort study	Erb vs. anthracycline- and taxane-based regimens	3rd & later	45	45	HER2- (56 %) HER2+ (13 %) TNBC (24 %)	HER2- (56 %) HER2+ (13 %) TNBC (31 %)	(1) Relative effectiveness in terms of OS & PFS, (2) safety in terms of specific toxicity and any toxicity causing hospitalization	No difference in PFS and OS was observed between Erb and non-Erb treated patients. Erb had a manageable toxicity profile
Shingaki et al. (2020)	Japan	Retrospective cohort study	Erb vs. non-Erb ***	Earlier (1st & 2nd) & later	133	93	HER2- (82 %) TNBC (18 %)	HER2- (74 %) TNBC (26 %)	(1) OS (2) PFS	Patients in the Erb cohort had a longer OS than those in the non- Erb cohort
	Japan			1st & later	66	227			(1) OS (2) safety	
Watanabe (2012)		Retrospective cohort study	Erb vs. anthracycline- and taxane-based regimens				All patients were ER+/HER2-			Erb therapy has a survival benefit in women with ER+/ HER2 – MBC in routine clinical practice, with no unexpected AEs.

Erb = Eribulin; TPC = Treatment of Physician's Choice, defined as any single-agent chemotherapy or hormonal or biological treatment for the treatment of cancer and to be administered according to local practice; OS = Overall Survival; PFS = Progression-Free Survival; ORR = Objective Response Rate; CBR = Clinical Benefit Rate; DCR = Disease Control Rate; AE = Adverse Event; pCR = Pathologic Complete Response; cCR = Clinical Complete Response; pR = partial response; HER2= Human Epidermal Growth Factor Receptor; ER = Estrogen receptor; TNBC = Triple negative breast cancer.

[a] Sample size in intention-to-treat (ITT) analysis in randomized controlled trials or matched cohorts in retrospective cohort studies.

* (North America/western Europe/Australia [region 1], eastern Europe [region 2], and Latin America/South Africa [region 3].

** Latin America, Western Europe/Australia, Eastern Europe, North America, Asia, or South Africa.

*** non-Erb users was defined as those who never received eribulin.

Among the 13 included studies, 6 were RCTs and the rest (7) were cohort studies. Four studies were conducted in the US while the other 9 studies were conducted in different regions of the world. The study population involved LABC or MBC patients or both. A total of 15,073 patients from the 13 studies were included in this review, with 3612 patients receiving eribulin-based and 11,461 patients receiving non-eribulin-based regimens. In all the included studies (except for Park et al. 2017) eribulin was administered as monotherapy. The comparison group receiving non-eribulin regimens varied across studies and mostly involved TPC approved for LABC/MBC including anthracyclines (e.g., doxorubicin), taxanes (paclitaxel) or antimetabolites (capecitabine, gemcitabine), etc. Among 10 (4 RCTs and 6 cohort studies) out of the 12 studies assessing effectiveness, OS was reported as the outcome measure. Additional effectiveness measures included PFS, ORR, and CBR. Treatment safety was assessed in 8 studies.

Most RCTs were considered to have low risk of bias.

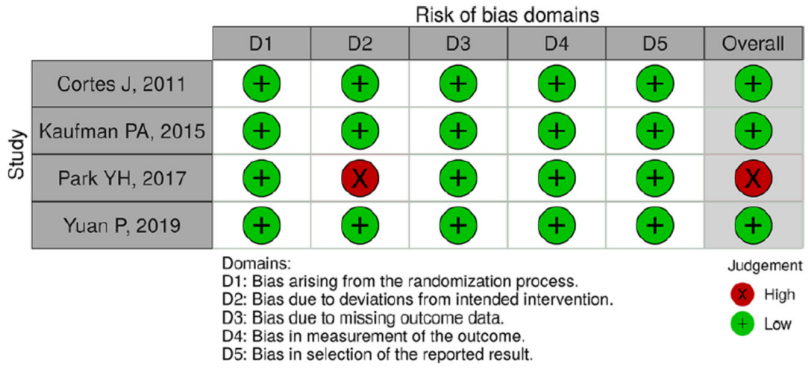

Fig. 2. Risk of bias in randomized controlled trials reporting overall survival using the Cochrane Collaboration's risk of bias assessment tool.

Results showed the following

Overall Survival

Eribulin based therapy showed significantly increased OS (HR 0.77, 95 % CI 0.67-0.88) compared to non-eribulin in the main analysis (10 studies), which included both RCTs and observational studies. See Forest plot below (Fig. 3 from published paper). Statistical heterogeneity was high (I2 = 73 %) in the overall effect and 95 % PI was not significant (0.50–1.17).

The hazard ratio for overall survival for RCTs alone (n=4) for eribulin versus non-eribulin was 0.88 (95%CI 0.80-0.97). See Forest plot below (Fig. 3 from published paper).

The hazard ratio for overall survival for cohort studies (n=6) for eribulin was 0.68 (95%CI 0.54-0.86). See Forest plot below (Fig. 3 from published paper). Although the magnitude of effect on improved OS was significantly higher in cohort studies compared to RCTs (p-value for subgroup difference = 0.05), the meta-analyses results were consistent.

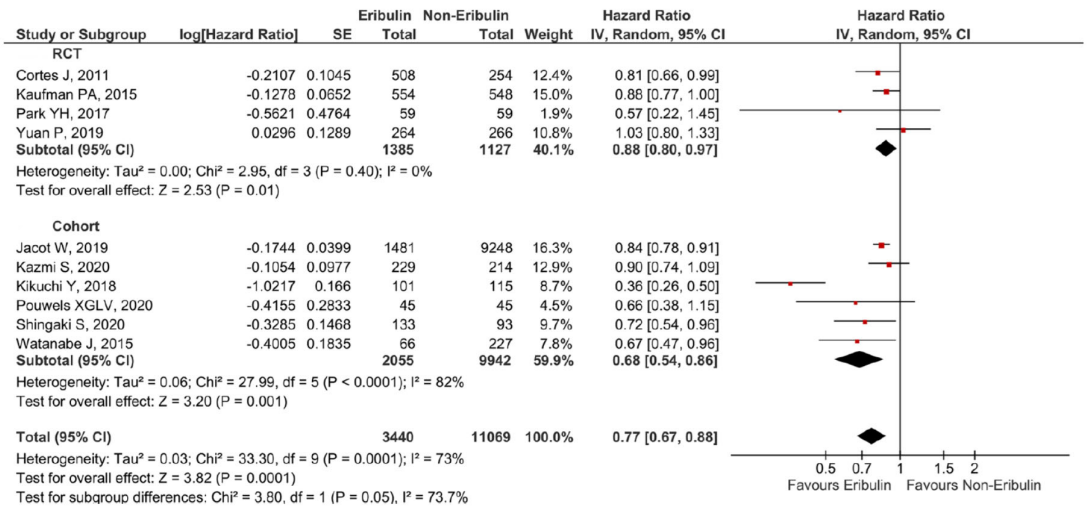

Fig. 3. Forest plot of meta-analysis of overall survival.

Subgroup Analyses and Other Outcomes

The results of the random-effects meta-regression analyses investigating heterogeneity from the proportions of HER2-positive, HER2-negative or TNBC patients found that most (70.02 %) of the between-study variance was explained by the covariate of proportion of TNBC patients, but not proportion of HER2-negative or HER2-positive patients (9.02 % and 0%, respectively). Eribulin-based regimens also showed significant OS versus non-eribulin-based regimens in the meta-analysis limiting to patients with HER2-negative tumour type (HR= 0.81, 95%CI 0.76-0.86; I2 = 0%).

When categorised by line of chemotherapy, OS with eribulin as first/second line treatment demonstrated non-significantly improved (p = 0.06) OS versus non-eribulin [HR (95 % CI) = 0.90 (0.80–1.00); I_2 = 0%], and eribulin as third/later line therapy showed significantly increased OS over non-eribulin therapy (HR = 0.86, 95%CI 0.81-0.90; I2 = 0%).

Sensitivity analysis was conducted omitting one study from the meta-analysis at a time and the results remained robust in all cases. Again, when two studies identified as having high risk of bias were removed from the analysis, the meta-analysis results remained consistent. Influence analysis revealed that one study overly contributed to the overall heterogeneity in the meta-analysis. Omitting this study led to the absence of overall heterogeneity (I2 = 0%) without significantly affecting the summary effect size.

Meta-analyses performed for 3 secondary effectiveness outcomes: PFS, ORR and CBR using a random effects model showed statistically significant benefit in PFS (HR = 0.81 95 % CI 0.67-0.98) and ORR RR = 1.84 (95%CI 1.19–2.85) for eribulin users versus non-users. In contrast, results of CBR revealed similar results for eribulin and non-eribulin regimens (RR = 1.09, 95%CI 0.87–1.64).

Adverse Effects

Among the 5 AEs of interest, neutropenia and neuropathy were most commonly reported among the included studies (n = 8).

- In random effects meta-analysis, risk of all-grade neutropenia was significantly higher among patients receiving eribulin compared to non-eribulin RR = 1.68 (95%CI 1.04–2.73; I_2 = 98 %).

However, risk was different when limiting to studies with RCT [RR 1.66, 95%CI 0.92–2.99; I_2 = 99 %) and cohort (RR=1.77, 95 % CI 1.24–2.53; I_2 = 56 %).

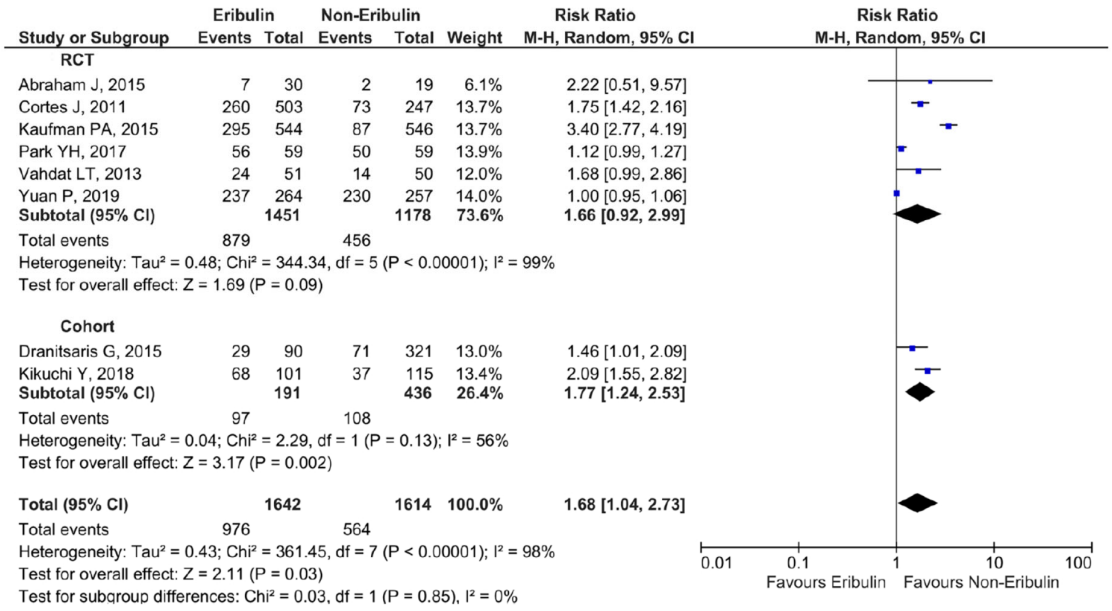

Fig. 4. Forest plot of meta-analysis of all-grade neutropenia.

- Risk of all-grade neuropathy was similar between eribulin and non-eribulin groups (RR 1.10, 95%CI 0.58–2.03; I_2 = 95 %).
- There were no differences in all-grade anaemia, asthenia and nausea between eribulin and non-eribulin treated patients RR 0.95, 95 % CI 0.78–1.15), 0.94 (0.67–1.32), and 1.02 (0.89–1.16) respectively.

Overall, the conclusions of this analysis were that eribulin has a manageable toxicity profile and provides significant survival benefit in LABC/MBC patients (Tanni, Truong et al. 2021).

Zhao 2021 Network Meta-analysis

This network meta-analysis compared the efficacy and safety of eribulin (ERI) versus other chemotherapies based on systematic searches conducted in MEDLINE, Embase, and the Cochrane Central Register of Clinical Trials to identify RCTs of locally advanced breast cancer/metastatic breast cancer chemotherapies in second- or later-line settings. Efficacy assessment included pre-specified subgroup analysis of breast cancer subtypes. Included studies were assessed for quality using the Centre for Reviews and Dissemination tool. Bayesian network meta-analysis estimated primary outcomes of overall survival and progression-free survival using fixed-effect models. Comparators included: capecitabine (CAP), gemcitabine (GEM), ixabepilone (IXA), utidelone (UTI), treatment by physician's choice (TPC), and vinorelbine (VIN). The network meta-analysis included seven trials. The network diagram for the base case analysis (overall survival) is shown below.

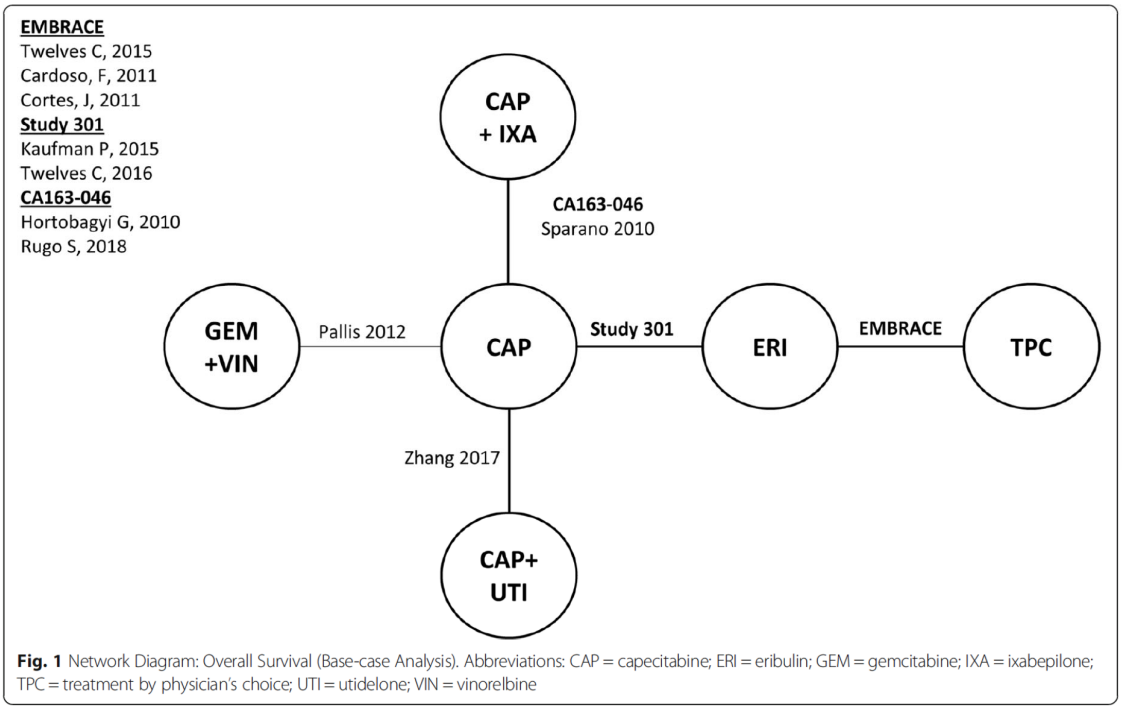

Fig. 1 Network Diagram: Overall Survival (Base-case Analysis). Abbreviations: CAP = capecitabine; ERI = eribulin; GEM = gemcitabine; IXA = ixabepilone; TPC = treatment by physician's choice; UTI = utidelone; VIN = vinorelbine

Results showed that second- or later-line patients treated with eribulin had statistically longer overall survival versus treatment by physician's choice (TPC) (HR 0.81; credible interval [CrI]: 0.66-0.99) or GEM+VIN (0.62; 0.42-0.90) and statistically longer progression-free survival versus TPC (0.76; 0.64-0.90), but statistically shorter progression-free survival versus CAP+IXA (1.40; 1.17-1.67) and CAP+UTI (1.61; 1.23-2.12). (See Figure 10 from the published paper, below).

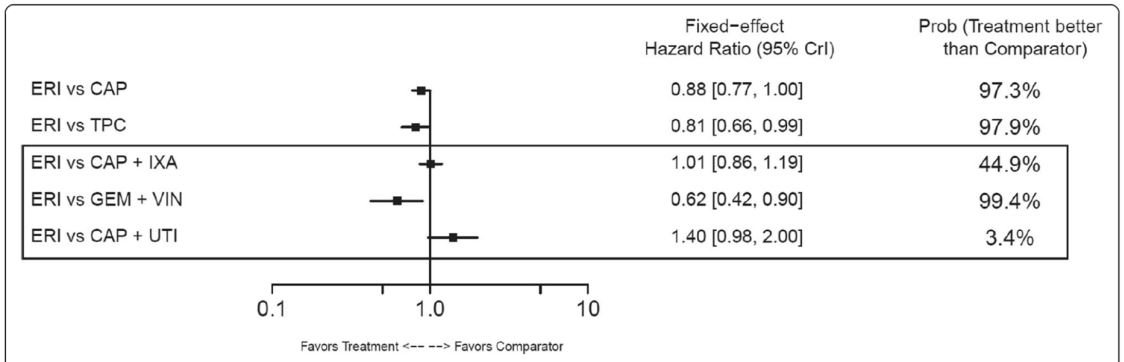

Fig. 10 Forest Plot of Overall Survival Treatment Comparison. Estimates derived only from indirect comparisons shown in black box. Included references: Study 301 (Kaufman 2015; Twelves 2016), EMBRACE (Twelves 2015; Cardoso 2011; Cortes 2011), CA163–046 (Hortobagyi 2010; Rugo 2018), Sparano 2010, Pallis 2012, Zhang 2017. Abbreviations: CAP = capecitabine; CrI = credible interval; ERI = eribulin; GEM = gemcitabine; IXA = ixabepilone; TPC = treatment by physician's choice; UTI = utidelone; VIN = vinorelbine

In triple negative breast cancer, ERI had statistically longer overall survival versus CAP (0.70; 0.54-0.90); no statistical differences in progression-free survival were observed in triple negative breast cancer.

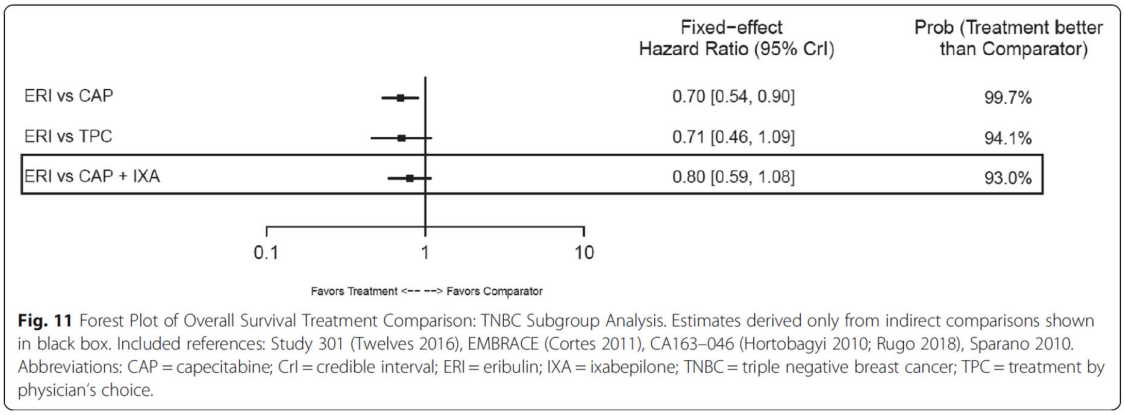

Fig. 11 Forest Plot of Overall Survival Treatment Comparison: TNBC Subgroup Analysis. Estimates derived only from indirect comparisons shown in black box. Included references: Study 301 (Twelves 2016), EMBRACE (Cortes 2011), CA163–046 (Hortobagyi 2010; Rugo 2018), Sparano 2010. Abbreviations: CAP = capecitabine; CrI = credible interval; ERI = eribulin; IXA = ixabepilone; TNBC = triple negative breast cancer; TPC = treatment by physician's choice.

The analysis also showed superiority for the HER2- subgroup, versus other agents.

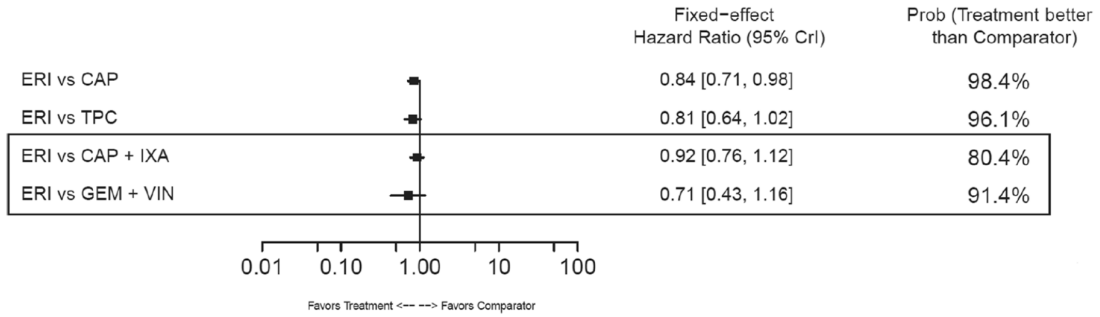

Fig. 12 Forest Plot of Overall Survival Treatment Comparison: HER2– Subgroup Analysis. Estimates derived only from indirect comparisons shown in black box. Included references: Study 301 (Twelves 2016), EMBRACE (Cortes 2011), CA163–046 (Hortobagyi 2010; Rugo 2018), Sparano 2010, Pallis 2012. Abbreviations: CAP = capecitabine; CrI = credible interval; ERI = eribulin; GEM = gemcitabine; HER2 = human epidermal growth factor receptor 2; IXA = ixabepilone; TPC = treatment by physician's choice; VIN = vinorelbine

This network meta-analysis of available RCTs suggests that eribulin may provide a favourable OS benefit in overall LABC/MBC populations and TNBC subgroups compared to standard treatments. Specifically, the network meta-analysis suggests that eribulin provides a statistically significant OS benefit compared with treatment of physician's choice, and gemcitabine and vinorelbine (GEM+VIN) in second line and beyond treatment of patients with LABC/MBC and compared with capecitabine in TNBC and HR+ /HER2-negative subgroups. Eribulin shows significantly lower rates of discontinuation due to AEs than CAP+IXA, CAP+UTI, and IXA.

Meta-analyses of Observational Studies

Pedersini Efficacy in Older Patients with Breast Cancer (Cohort Studies)

In this pooled analysis of retrospective studies, the efficacy and toxicity profile of eribulin in older patients with breast cancer in the real-world setting was evaluated. A systematic database search for studies (to March 2019), reporting outcome and adverse events with eribulin in older patients (≥70 years) was carried out. Overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) were described and aggregated in a pooled analysis. Main toxicity rates (G1-2 and G3-4) were also described.

The analysis included five studies for a total of 301 patients. The median age was 71 to 74 years. Pooled ORR, median PFS and OS were 23.2%, 4.8 and 13.1 months, respectively. The disease control rate was 47%. Grade 3-4 neutropenia was 0 to 49%, G3-4 anaemia and thrombocytopenia were rare. The most frequent G3-4 adverse events among non-haematological toxicities were fatigue (5-16.5%) and neurotoxicity (0-10.1%). Dose reduction rate was reported in three studies and carried out in 40% of patients (18.6-84%). This pooled analysis shows that the median OS in older patients with breast cancer is 13 months, with an ORR of 23%. Control of disease was achieved in about 50% of patients. Dose reduction was relatively frequent and severe toxicities were rare. Eribulin treatment of older patients with breast cancer is feasible and reflects the outcomes for the general population.

Voutsadakis 2017 -Systematic Review of Retrospective Studies

This paper presents a pooled analysis of retrospective series to obtain efficacy and toxicity data for eribulin in metastatic breast cancer patients treated off trials. Thirteen series with a total of 1095 patients were identified. Pooled estimates of response rate and clinical benefit rate were 20.1% (95% confidence interval: 16.3-23.9%) and 46.3% (95% confidence interval: 39.4-53.2%) respectively. These were somewhat higher than the response rate and clinical benefit rate observed in a pooled analysis of two randomised phase III trials (14.9 and 30.9%, respectively, conducted using ITT analysis). However, overall survival was longer in the phase III trials (median 15.2 months) than in the retrospective studies (pooled estimate 9.8 months). All grades toxicities were similar in practice compared with trials with slightly higher grade 3 toxicities (46.1 vs. 38.7%) but lower grade 4 toxicities (17.2 vs. 27.7%) in patients off trials (Voutsadakis 2017).

Chabot, Zhao et al. 2020 -Systematic Review of Real-World Effectiveness

Numerous studies have evaluated eribulin in real-world (RW) breast cancer populations to assess effectiveness beyond registration randomised controlled trials (RCTs) that reported median overall survival (OS) of 13.1 and 15.9 months. This systematic literature review (SLR) was based on RW effectiveness studies in LABC/MBC located in Medline/PubMed and Embase databases between 2012 and 2019 where use was in the second- or third-line or later LABC/MBC setting. Because eribulin showed greatest OS benefits in triple negative breast cancer (TNBC) in RCTs, this tumour subtype also received special attention. OS and progression-free survival (PFS) were the effectiveness outcomes of interest. Overall, 34 journal articles or abstracts met the selection criteria. Median OS ranged between 6.9 and 28.0 months; median PFS varied from 2.3 to 14.7 months. Eight studies reported OS outcomes for TNBC patients, and median OS ranged between 3.0 and 23.0 months. It was concluded that there was high variability in OS and to a lesser extent in PFS associated with eribulin use in RW setting. Despite heterogeneity in line of use and patient subtypes, this SLR supports effectiveness of eribulin for LABC/MBC in clinical practice (Chabot, Zhao et al. 2020).

Comment: Although the studies in these reviews clearly are fraught with selection bias, it nevertheless shows that eribulin use in the real-world clinical setting has been extensively studied and documented.

References

Breast Cancer Foundation New Zealand (2018). "I'm still here" Insights into living – and dying – with Advanced Breast Cancer in New Zealand.

Chabot, I., Q. Zhao and Y. Su (2020). "Systematic review of Real-World effectiveness of eribulin for locally advanced or metastatic breast cancer." Curr Med Res Opin **36**(12): 2025-2036.

Cortes, J., S. Hudgens, C. Twelves, E. A. Perez, A. Awada, L. Yelle, S. McCutcheon, P. A. Kaufman, A. Forsythe and G. Velikova (2015). "Health-related quality of life in patients with locally advanced or metastatic breast cancer treated with eribulin mesylate or capecitabine in an open-label randomized phase 3 trial." Breast Cancer Res Treat **154**(3): 509-520.

Cortes, J., J. O'Shaughnessy, D. Loesch, J. L. Blum, L. T. Vahdat, K. Petrakova, P. Chollet, A. Manikas, V. Diéras, T. Delozier, V. Vladimirov, F. Cardoso, H. Koh, P. Bougnoux, C. E. Dutcus, S. Seegobin, D. Mir, N. Meneses, J. Wanders and C. Twelves (2011). "Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study." Lancet **377**(9769): 914-923.

Gennari, A., F. André, C. H. Barrios, J. Cortés, E. de Azambuja, A. DeMichele, R. Dent, D. Fenlon, J. Gligorov, S. A. Hurvitz, S. A. Im, D. Krug, W. G. Kunz, S. Loi, F. Penault-Llorca, J. Ricke, M. Robson, H. S. Rugo, C. Saura, P. Schmid, C. F. Singer, T. Spanic, S. M. Tolaney, N. C. Turner, G. Curigliano, S. Loibl, S. Paluch-Shimon and N. Harbeck (2021). "ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer[☆]." Annals of Oncology **32**(12): 1475-1495.

Goodin, S., S. Barbour, J. Song, E. Berrak and D. Cox (2015). "Safety and tolerability of eribulin mesylate in patients with pretreated metastatic breast cancer." Am J Health Syst Pharm **72**(24): 2150-2156.

Kaufman, P. A., A. Awada, C. Twelves, L. Yelle, E. A. Perez, G. Velikova, M. S. Olivo, Y. He, C. E. Dutcus and J. Cortes (2015). "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 Oncol **33**(6): 594-601.

Miyoshi, Y., Y. Yoshimura, K. Saito, K. Muramoto, M. Sugawara, K. Alexis, K. Nomoto, S. Nakamura, T. Saeki, J. Watanabe, J. M. Perez-Garcia and J. Cortes (2020). "High absolute lymphocyte counts are associated with longer overall survival in patients with metastatic breast cancer treated with eribulin- but not with treatment of physician's choice-in the EMBRACE study." Breast Cancer **27**(4): 706-715.

Muss, H., J. Cortes, L. T. Vahdat, F. Cardoso, C. Twelves, J. Wanders, C. E. Dutcus, J. Yang, S. Seegobin and J. O'Shaughnessy (2014). "Eribulin monotherapy in patients aged 70 years and older with metastatic breast cancer." Oncologist **19**(4): 318-327.

Pedersini, R., P. di Mauro, V. Amoroso, M. C. Parati, A. Turla, M. Ghilardi, L. Vassalli, M. Ardine, A. D. Volta, S. Monteverdi, K. Borgonovo, A. Ghidini, M. Cabiddu, E. L. Simoncini, F. Petrelli, A. Berruti and S. Barni (2020). "Efficacy of Eribulin mesylate in older patients with breast cancer: A pooled analysis of clinical trial and real-world data." J Geriatr Oncol **11**(6): 976-981.

Pivot, X., S. A. Im, M. Guo and F. Marmé (2018). "Subgroup analysis of patients with HER2-negative metastatic breast cancer in the second-line setting from a phase 3, open-label, randomized study of eribulin mesilate versus capecitabine." Breast Cancer **25**(3): 370-374.

Tanni, K. A., C. B. Truong, B. S. Johnson and J. Qian (2021). "Comparative effectiveness and safety of eribulin in advanced or metastatic breast cancer: a systematic review and meta-analysis." Crit Rev Oncol Hematol **163**: 103375.

Twelves, C., J. Cortes, L. Vahdat, M. Olivo, Y. He, P. A. Kaufman and A. Awada (2014). "Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies." Breast Cancer Res Treat **148**(3): 553-561.

Voutsadakis, I. A. (2017). "A systematic review and pooled analysis of retrospective series of eribulin in metastatic breast cancer." Anticancer Drugs **28**(5): 557-564.

Wu, Y., Q. Wang, J. Zhang, J. Cao, B. Wang and X. Hu (2020). "Incidence of peripheral neuropathy associated with eribulin mesylate versus vinorelbine in patients with metastatic breast cancer: sub-group analysis of a randomized phase III study." Support Care Cancer **28**(8): 3819-3829.

Yuan, P., X. Hu, T. Sun, W. Li, Q. Zhang, S. Cui, Y. Cheng, Q. Ouyang, X. Wang, Z. Chen, M. Hiraiwa, K. Saito, S. Funasaka and B. Xu (2019). "Eribulin mesilate versus vinorelbine in women with locally recurrent or metastatic breast cancer: A randomised clinical trial." Eur J Cancer **112**: 57-65.

Zhao, Q., R. Hughes, B. Neupane, K. Mickle, Y. Su, I. Chabot, M. Betts and A. Kadambi (2021). "Network meta-analysis of eribulin versus other chemotherapies used as second- or later-line treatment in locally advanced or metastatic breast cancer." BMC Cancer **21**(1): 758.