Eribulin in the Management of Advanced Breast Cancer: Implications of Current Research Findings

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ABSTRACT: The search for cytotoxic agents from marine natural products ultimately led to the production of eribulin, which is a synthetic macrocyclic ketone analog of halichondrin B. Eribulin binds to tubulin to induce mitotic arrest and gained approval in Japan in May 2010; it was approved by the US Food and Drug Administration in November 2010 and the European Medicines Agency in March 2011 and was reimbursed by the Taiwan National Health Insurance in December 2014 for patients with metastatic breast cancer who had received at least one anthracycline and one taxane. The recommended regimen for eribulin mesylate comprises intravenous administration of 1.4 mg/m^2 (equivalent to 1.23 mg/m^2 eribulin) over two to five minutes on days 1 and 8 of a three-week cycle. Since 2011, various clinical investigations of eribulin monotherapy with dose or schedule modifications, combined use with other antineoplastic therapeutics, or head-to-head comparisons with specific agents have been performed in the management of advanced breast cancer. Ethnic-specific data from Japan and Korea indicate higher rates (>85%) of grade 3 or 4 neutropenia. Some anecdotal evidence suggests that eribulin can shrink brain and retinal metastases, which warrants further detailed studies. In this review, current observations of the effects of eribulin monotherapy are summarized and eribulin-backbone combination (bio-) chemotherapy is investigated.

KEYWORDS: eribulin, metastatic breast cancer, triple-negative breast cancer, chemotherapy, medical oncology

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Introduction

Extensive research has been performed to isolate candidate new-generation antineoplastic cytotoxic drugs from marine natural products, including sponges and sea squirts.[1,2] Among numerous sponge-derived cytotoxic compounds, only cytarabine and eribulin have received approval for clinical use. Although the former drug has been extensively used for the treatment of hematologic malignancies for decades, eribulin only gained approval in Japan in May 2010;[3] it was approved by the US Food and Drug Administration (FDA) in November 2010[4] and the European Medicines Agency (EMA) in March 2011.[5] The drug has only been reimbursed by the Taiwan National Health Insurance since December 2014 for patients with locally advanced or metastatic breast cancer who had received at least an anthracycline and a taxane.

Eribulin is a completely synthetic macrocyclic ketone analog of halichondrin B, which was initially isolated from the Japanese sponge *Halichondria okadai* in 1986 by Uemura and Hirata.[6] In 1991, Pettit et al subsequently reported the isolation of halichondrin B from the Western Pacific marine sponge *Axinella* sp.[7] Eribulin binds to tubulin and microtubules, inducing mitotic arrest and cell death. Moreover, eribulin exhibited growth inhibitory effects on stem cells (CD44/CD24/epithelial cell adhesion molecule) of both estrogen receptor (ER)-positive and ER-negative cell lines,[8] warranting further research into these anticancer stem cell properties.

During the past four years, the therapeutic effects and adversities of eribulin monotherapy and eribulin-based combination therapies have been investigated in numerous studies. Hitherto, the purpose of this review is to assimilate all the relevant information from this literature to form the background knowledge for the incorporation of this agent into the current anti-breast cancer armamentarium.

Literature Review Methodology and Research Strategy

Four and a half years have passed since a survival benefit was demonstrated in women with heavily pretreated advanced breast cancer assigned to eribulin mesylate (median overall survival [mOS], 13.1 months; 95% confidence interval [CI], 11.8–14.3) versus the control arm of patients receiving the treatment of physician's choice (mOS, 10.6 months; 95% CI, 9.3–12.5) with a 19% reduction in risk representing as hazard ratio at 0.81 (95% CI, 0.66–0.99; $P = 0.041$) in a global Phase III trial, and breast oncologists around the globe have been willing to accept eribulin mesylate as one

of their major antineoplastic armamentaria.[9] The main purpose of this review is to present the state of knowledge on eribulin after 2011. Literature search using PubMed and the American Society of Clinical Oncology meeting abstracts databases until September 2015 was performed to retrieve articles for review. Exclusion criteria included review articles, secondary assessment reports of prior clinical trials, and most case reports. In addition, the results of eribulin monotherapy given in the first-line, late-line, heavily pretreated settings and schedule-modified monotherapy are presented. The subtleties of different treatment efficacy among all the tubulin-targeted agents for breast cancer including eribulin, ixabepilone, taxanes, and vinorelbine will be highlighted. Finally, some of the results of eribulin in combination with other antineoplastic agents including targeted agents are presented.

Pharmacokinetic and Pharmacodynamic Characteristics of Eribulin

The recommended dose of eribulin mesylate is 1.4 mg/m^2, which is equivalent to 1.23 mg/m^2 eribulin administered intravenously over two to five minutes on days 1 and 8 of a three-week treatment cycle (Table 1).

Eribulin is eliminated in feces with little chemical modification, and in patients with liver cirrhosis of Child–Pugh grades A or B, the recommended initial starting dose of eribulin is reduced to 1.1 and 0.7 mg/m^2, respectively.[10] Renal clearance represents <10% of total clearance of the drug. However, eribulin may induce minor endurance of cardiac repolarization, which is manifested as corrected QT (the time from the start of the Q wave to the end of the T wave) interval (QTc), although this effect is clinically insignificant.[11]

Because eribulin is a unique microtubule-depolymerizing drug and has similar effects as microtubule-targeting agents such as taxanes, vinca alkaloids, and epothilones, peripheral neuropathy and neutropenia are the most important adverse effects. Accordingly, grade 3 peripheral neuropathy occurs in ~5% of eribulin-treated patients, and few clinical studies report grade 4 toxicity. The incidence of peripheral neuropathy is similar across all ethnic populations. However, higher rates of neutropenia have been reported in East Asian patients as highlighted in the next section.

Grade 3/4 Neutropenia may be more Pronounced in East Asian Populations

Neutropenia is a common adverse reaction following weekly treatments with eribulin. In global trials, the frequency of neutropenia is reportedly 82% and is 57% for grade 3/4 neutropenia.[9,12] The nadir of neutropenia occurs on approximately day 14 and recovery takes eight days. However, two retrospective observational studies from Korea and Japan demonstrate much higher rates of grade 3/4 neutropenia.[13,14] Specifically, in the Korean observational study, the rate of neutropenia was 88.5% with grade 3/4, 86.5%. Moreover, most patients in the Japanese study had been pretreated, leading to grade 3/4 neutropenia in 95.1% of the entire cohort. We also observed similar rates in Taiwanese patients with heavily pretreated metastatic breast cancer (data unpublished). Hence, these rates of grade 3/4 neutropenia may apply to all East Asian patients receiving the recommended dose of weekly eribulin mesylate chemotherapy. The author of this study speculates that this high rate of neutropenia reflects the use of eribulin as a late-line treatment in heavily pretreated patients. Accordingly, clinicians responsible for heavily pretreated metastatic breast cancer patients should carefully inform patients and their families of self-care options for the neutropenic phase.

Efficacy of Eribulin Monotherapy in Locally Advanced Breast Cancer (LABC) and Advanced Breast Cancer (ABC)

Eribulin registration was intended for marketing as a sequential monotherapy to be administered after anthracycline and taxane treatments, as discussed in the following section.

Table 1. Notable features of eribulin mesylate (E7389).

Anti-cancer mechanism
Synthetic macrocyclic ketone analog of the marine natural product halichondrin B
Binds to tubulin and microtubules inducing mitotic arrest
Regulatory clearance
Approved by the Japanese authority in May 2010, the US FDA in November 2010, and the EMA in March 2011, and reimbursed by the Taiwan National Health Insurance since December 2014 Recommended dose for eribulin mesylate is 1.4 mg/m^2 (equivalent to 1.23 mg/m^2 eribulin) intravenously over 2–5 min on days 1 and 8 of a 3-week cycle
Pharmacokinetic and pharmacodynamic characteristics
Reduced doses of 1.1 and 0.7 mg/m^2 are recommended for patients with Child–Pugh grades A and B, respectively[10] Eliminated in feces with limited chemical modification; renal clearance represents <10% of clearance Grade 3 peripheral neuropathy 5% (no grade 4 toxicity)
Higher rates of neutropenia in Korean (88.5%; grade 3/4: 86.5%)[14] and Japanese patients (grade 3/4: 95.1%);[13] these rates may apply to all East Asian patients
No clinical concerns regarding minor prolongation of cardiac repolarization (QTc)[11]

However, the efficacy of first-line eribulin has been investigated in numerous studies. Among these, Tei et al published a multicenter Phase II study of first-line eribulin for human epidermal growth factor receptor type 2 (HER2)-negative locally advanced and metastatic breast cancer. In this cohort of 35 Japanese women, 80% of patients had ER-positive disease, and the remaining patients had triple-negative breast cancer (TNBC).[15] The overall response rate (ORR) was 54.3%, and complete remission (CR) and partial remission were achieved by 2 and 17 patients, respectively. The clinical benefit rate (CBR), which is defined as percentiles of tumor responses qualifying as at least stable disease (SD), was ~63% in the entire cohort. Moreover, the median progression-free survival (PFS) was 5.7 months and median time to failure was 5.3 months (Table 2).

Another Phase II trial of first-line eribulin monotherapy for HER2-negative recurrent or metastatic breast cancer was reported by McIntyre et al.[16] In this study, 59% of the patient cohort had prior treatments with anthracycline and/or taxane, and the response rate (RR) was 29% (95% CI, 17.3%–42.2%) and the PFS was 6.8 months.

When trastuzumab was added to treatment regimens for women with locally recurrent or metastatic HER2-positive breast cancer, the first-line weekly eribulin led to an RR of 71.2% and remarkable PFS of 11.6 months in a multicenter, single-arm, Phase II trial.[17] This result is comparable with an earlier Cancer and Leukemia Group B 9840 study of weekly paclitaxel combined with trastuzumab in patients with HER2-positive tumors, and an RR of 42% and a median time to progression (TTP) of nine months were reported.[18]

A small Sweden retrospective review of 48 patients who were treated with eribulin as third-line (median of three lines of prior chemotherapy), a CBR (=PR plus SD ≥ 6 months) of 48% was achieved. In this group of patients, 18.8% got grade 3/4 neutropenia. Three patients developed herpes zoster reactivation.[19] Even in the setting of heavily pretreated patients with metastatic breast cancer who had failed to receive a median of four lines chemotherapy including an anthracycline and a taxane, a CBR of 17% could be achieved in two Phase II trials.[20,21]

In a Phase II trial accruing 80 Japanese women with heavily pretreated metastatic breast cancer who had received a median of three prior chemotherapy regimens, the CBR was 27.5% (95% CI, 18.1%–38.6%) and a median PFS and OS was 3.7 and 11.1 months, respectively.[13]

RR and median PFS or TTP for first-line monotherapies with chemotherapeutic drugs for metastatic breast cancer are presented in Table 3, including thrice weekly docetaxel, weekly gemcitabine, weekly intravenous vinorelbine, and thrice weekly ixabepilone.[22–25] In general, these studies show that weekly eribulin monotherapy for non-HER2-overexpressing locally advanced or metastatic breast cancer, or in combination with trastuzumab for HER2-positive disease, lead to outcomes that are comparable with other tubulin-targeted agents and gemcitabine.

Yoshinami et al tested the modified schedule of eribulin monotherapy in a multicenter Phase II trial, in which 42 Japanese women with metastatic breast cancer who had failed up to three prior chemotherapy regimens including an anthracycline and a taxane underwent biweekly eribulin mesylate treatment at 1.4 mg/m^2 repeated every other week. A median time-to-treatment failure of 2.7 months and mOS of 16.0 months were achieved. Therefore, this biweekly (every other week) schedule-modified eribulin monotherapy may become a viable option for suitable patients at least for the sake of the convenience of clinic appointments (Table 2).[26]

An exploratory analysis using pooled data from prior Phase II and Phase III clinical trials was performed to investigate the effect of age in elderly women aged 70 years and older receiving eribulin monotherapy as late-line treatment.[27] The analysis demonstrated that eribulin monotherapy in these elderly patients with initially good performance status led to an outcome and efficacy similar to those of younger patients in terms of overall survival, PFS, ORR, CBR, and tolerability. The benefits and risks of eribulin monotherapy are basically similar across all age groups.[27]

Eribulin Mesylate in Combination with other Cytotoxic Agents or Targeted Therapies

Few studies report the measurements of synergistic antitumor effects of eribulin combined with other chemotherapeutic agents using indexes and isobolograms. However, Terashima et al recently demonstrated that eribulin induces the mesenchymal–epithelial transition in a TNBC cell line and that the combination treatment with S-1 (or 5-fluorouracil [5-FU]) exerted a synergistic antitumor effect.[28] Sakiyama et al also recently reported a Phase I dose-escalation study of S-1 plus eribulin in the metastatic breast cancer setting (Table 4).[29] S-1 is an oral fluoropyrimidine derivative comprising the 5-FU prodrug tegafur with the two 5-FU activity modulators gimeracil and oteracil (also known as potassium oxonate). The recommended eribulin mesylate dose for Phase II was determined as 1.4 mg/m^2 on days 1 and 8 in combination with 65 mg/m^2 oral S-1 from days 1 to 14 in a 21-day treatment cycle.

Clinical studies of eribulin mesylate in combination with other antineoplastic agents are summarized in Table 4 and include more trials for patients with TNBC than for other types of breast cancer, reflecting the paucity of hormonal manipulation therapies and well-established HER2 molecular targets against TNBC. Hence, a breakthrough treatment is eagerly awaited from the recruitment of eribulin mesylate as a key drug. The role of eribulin plus carboplatin neoadjuvant chemotherapy was investigated in patients with early-stage TNBC and eribulin plus olaparib-targeted therapy was applied to advanced or metastatic TNBC patients.[30,31] Treatments for TNBC commonly include carboplatin, and in a recent clinical trial, the poly(adenosine diphosphate ribose) poly(ADP-ribose) polymerase (PARP) inhibitor olaparib had

Table 2. Efficacy of eribulin monotherapy for breast cancer in various clinical settings.

TREATMENT SETTING	TESTED POPULATION	NUMBER OF PATIENTS	TYPE OF STUDY
First-line	First-line for HER2-negative LABC or MBC; 80% had ER-positive disease and 20% were TNBC.	35	Phase 2, multicenter
Third-line	Median of three (range 1–7) previous chemotherapy lines	48 Swedes	Retrospective review
	All patients had failed an anthracycline and a taxane. 80.2% ≥ 3rd line	96 Korean patients (TNBC 30.2%)	Phase 4
Heavily pre-treated	MBC failed a median of four lines, including an anthracycline and a taxane	103	Phase 2
	MBC failed a median of four lines, including an anthracycline, a taxane, and capecitabine	269	Phase 2
	Japanese pts with heavily pretreated MBC who had received a median of three prior chemotherapy regimens	80	Phase 2
	Locally recurrent or metastatic failed ≥2 chemotherapy regimens for advanced disease	Total 762 (503 eribulin, 254 TPC)	Phase 3 open-label (EMBRACE)
Head-to-head comparison with capecitabine	Prior anthracycline and taxane-exposed; randomized as the first-, second-, or third-line for advanced or MBC	Total 1,102: eribulin (n = 554) vs capecitabine (n = 548)	Phase 3 head-to-head comparison with capecitabine
Schedule-modified monotherapy	Both anthracycline and taxane and up to three prior chemotherapy regimens for MBC	86 enrolled (42 received bi-weekly)	Phase 2 Japanese multicenter (JUST-STUDY)

Abbreviations: CBR, clinical benefit rate (=PR plus SD ≥ six months); CI, confidence interval; CR, complete response; HR, hazard ratio; mo, months; ORR, overall response rate; OS, overall survival; PR, partial response; PFS, progression-free survival; pt(s), patient(s); SD, stable disease; TPC, treatment of physician's choice; TNBC, triple-negative breast cancer.

synthetic lethal efficacy in breast cancer patients with breast cancer (BRCA) mutations that were commonly associated with TNBC.[32] Although combination chemotherapy using eribulin as the backbone requires further investigation, various qualities, including its ease of combination and administration with carboplatin and S-1, are attractive to practicing oncologists engaged in difficult-to-treat settings such as TNBC.

Future Development of Eribulin in Breast Cancer

A number of ongoing clinical trials actively investigate the role of eribulin for breast cancer patients from adjuvant to palliative settings. An interesting multicenter, single-arm Phase II feasibility study tested eribulin mesylate (1.4 mg/m^2) given on day 1 and day 8 plus capecitabine (900 mg/m^2) orally twice daily on days 1 to 14 of a 21-day cycle for four cycles as adjuvant chemotherapy for patients with stage I or II, HER2-normal, ER-positive breast cancer (ClinicalTrials.gov identifier: NCT01439282). The final report of this trial is still pending. NCT02513472 is a multicenter, single-arm, Phase Ib/II study to evaluate the efficacy and safety of eribulin mesylate in combination with pembrolizumab in subjects with metastatic TNBC previously treated with up to two lines

TREATMENT RESPONSE RATE	PFS OR TTF OR OS	TOXICITIES	FIRST AUTHOR/ YEAR (REFERENCE)
ORR was 54.3% (CR 2: PR 17) and CBR was 62.9%.	Median PFS was 5.7 mo. and median TTF was 5.3 mo.	Grade 3/4 neutropenia: 63% and febrile neutropenia 5.7%. Hair loss, fatigue, sensory neuropathy, and fever: frequent.	Tei S/2015[15]
CR in one patient; PR = 33.3%. CBR = 48%.		Grade 3/4 Fatigue (6.3%). Grade 4 neurotoxicity (1 pt). Grade 3/4 neutropenia 18.8%. Grade 3 infection (3 pts). Herpes zoster reactivation (3 pts).	Kessler L/2015[19]
		Neutropenia (88.5%), decreased appetite (39.6%), and alopecia (37.5%). Grade 3/4 neutropenia (86.5%). Febrile neutropenia (1.0%). Neuropathy (24.0%). Grade 2/3 neuropathy (6.3%).	Park YH/2015[14]
ORR, 11.5% (95% CI, 5.7–20.1) and CBR, 17.2% (95% CI, 10.0–26.8). Median duration of response was 5.6 mo. (range, 1.4–11.9 mo.).	Median PFS, 2.6 mo; range, 1 day–14.9 mo., and the median OS, 9.0 mo; range, 0.5–27.1 mo.	Grades 3/4 toxicities: neutropenia, 64%; leukopenia, 18%; fatigue, 5%; peripheral neuropathy, 5%; and febrile neutropenia, 4%.	Vahdat LT/2009[20]
PR, 9.3% (95% CI, 6.1–13.4) and CBR, 17.1%. Median duration of response was 4.1 mo.	Median PFS, 2.6 mo (95% CI 0.03–13.1 mo), and the median OS, 10.4 mo (95% CI 0.6–19.9 mo).	Grade 3/4 toxicities: neutropenia, 54%; leukopenia, 14%; fatigue 10%; peripheral neuropathy, 6.9% (no grade 4); febrile neutropenia, 5.5%.	Cortes J/2010[21]
PR, 21.3% (95% CI, 12.9–31.8) and CBR, 27.5% (18.1–38.6); Median duration of response was 3.9 mo.	Median PFS, 3.7 mo, and the median OS, 11.1 mo.	Grade 3/4 toxicities: neutropenia, 95.1%; leukopenia, 74.1%; peripheral neuropathy, 3.7% (no grade 4); febrile neutropenia, 13.6%.	Aogi K/2012[13]
	Median OS, 13.1 mo (95% CI, 11.8–14.3) in eribulin compared with 10.6 mo (9.3–12.5) in TPC arm. HR = 0.81 (0.66–0.99, *P* = 0.041). In TNBC subgroup analysis, OS benefit noted with HR at 0.71 (0.46–1.10).	Most common adverse event leading to discontinuation from eribulin is peripheral neuropathy (5% of eribulin pts).	Cortes J/2011[9]
Eribulin equals capecitabine in efficacy. ORR were 11.0% for eribulin and 11.5% for capecitabine.	Median PFS for eribulin and capecitabine were 4.1 and 4.2 mo, respectively (HR, 1.08; 95% CI, 0.93–1.25). Median OS for eribulin and capecitabine were 15.9 and 14.5 mo., respectively (HR, 0.88; 95% CI, 0.77–1.00).	Global peripheral neuropathy grade III/IV (7.0% vs 0.9%).	Kaufman PA/2015[35]
	Median TTF was 2.7 mo., and median OS was 16.0 mo. in the bi-weekly group (1.4 mg/m^2 repeated every other week).		Yoshinami T/2015[26]

of chemotherapy. The Phase Ib part accruing up to 12 subjects will aim to determine the recommended Phase II dose (RP2D). The Phase II part will evaluate the tumor responses in ~83 subjects with metastatic TNBC. In addition to immunotherapy and add-on therapy, other targeted agents such as everolimus plus eribulin are being tested in a dose-finding Phase I/IB trial in subjects with metastatic TNBC (NCT02120469). The rationale of this trial of combining eribulin mesylate and everolimus is based upon the preclinical research findings that the combination may suppress the growth of cancer cells by blocking some of the enzymes needed for cell growth.[33]

At present, there is no standard for the second-line treatment for metastatic breast cancer. The trial registered as NCT02175446 is going to evaluate the efficacy including PFS after being treated with the combination of eribulin 1.23 mg/m^2 on days 1 and 8 every three weeks intravenously plus an anti-vascular endothelial growth factor monoclonal antibody, bevacizumab at either 15 mg/kg every three weeks intravenously or 10 mg/kg every two weeks intravenously.

An open-label, randomized, Phase III multicenter study will compare eribulin and vinorelbine in Chinese women with locally recurrent or metastatic breast cancer, previously

Table 3. RR, median PFS, and TTP or TTF of eribulin and other chemotherapeutic agents given as first-line for locally advanced and metastatic breast cancer.

REGIMEN	HER2-TARGETED TREATMENT	RR (95% CONFIDENCE INTERVAL)	MEDIAN PFS OR TTP OR TTF	REF.
Weekly paclitaxel	Yes	42% (37–47%)	9.0 mo (TTP)	18
Docetaxel, Q3W	No	68%	7.2 mo (TTP)	24
Weekly gemcitabine	No	37.1% (21.5–55.1%)	5.1 mo (95% CI, 3.5–8.8 mo) (TTP)	22
Weekly vinorelbine	No	50% (CR 2%)	5.0 mo (TTF)	25
Ixabepilone, Q3W	All HER2-negative	47% (29–65%)	9.0 mo (4–14 mo) (PFS)	23
Weekly eribulin	Yes	71.2% (56.9–82.9%)	11.6 mo (9.1–11.3 mo) (PFS)	17
Weekly eribulin (29% of pts received prior anthracycline and/or taxane)	All HER2-negative	54.3% (CR 5.7%)	5.8 mo (PFS) 5.4 mo (TTF)	15
Weekly eribulin (59% of pts received prior anthracycline and/or taxane)	All HER2-negative	29% (17.3–42.2%)	6.8 mo (4.4–7.6 mo) (PFS)	16

Abbreviations: mo, months; PFS, progression-free survival; RR, response rate; TTF, time-to-treatment failure; TTP, time to progression.

treated with two to five prior chemotherapy regimens, including an anthracycline and a taxane (NCT02225470). This study may give us an answer on whether eribulin will outperform vinorelbine as a preferred tubulin-targeting agent in late-line palliative therapy for metastatic breast cancer.

Some anecdotal evidence suggests that eribulin can shrink brain and retinal metastases, which warrants further detailed studies.[34]

In the coming months, we will expect more and more clinical trials to be conducted evaluating eribulin in the management of breast cancer particularly on TNBC subtype. For example, eribulin mesylate combined with carboplatin with or without a PARP inhibitor should first be tested in patients with TNBC on the setting of either front-line or subsequent line of therapy. Further studies on eribulin mesylate monotherapy or combining eribulin mesylate with stereotactic ablative radiotherapy for TNBC oligo-cerebrometastases are highly recommended.

Conclusions

Recent research trends emphasize the microtubule-depolymerizing drug, eribulin mesylate, whether as monotherapy, combination chemotherapy, or combined with targeted agents, such as a PARP inhibitor, in the management of patients with TNBC. Certainly, eribulin monotherapy in combination with trastuzumab or bevacizumab has been regarded as the treatment of choice for the management of a variety setting of advanced breast cancer. Out of clinical trial settings, eribulin plus another chemotherapy doublet is currently not recommended. The most common adverse reaction of clinical significance is grade 3/4 neutropenia, particularly in East Asian population which should be efficiently managed to prevent the development of sepsis and further deterioration of quality of life.

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Table 4. Eribulin mesylate in combination with other antineoplastic agents.

COMBINATION	DOSAGE	AUTHORS	PUBLISHED
Eribulin + S-1	Eribulin 1.4 mg/m^2 D1 and D8; S-1 65 mg/m^2 PO D1–D14 in a 21-day cycle.	Sakiyama, T. et al[29]	2015
Eribulin + trastuzumab for HER2+/MBC	Eribulin 1.4 mg/m^2 D1 and D8 in a 21-day cycle; trastuzumab 8 mg/kg loading followed by 6 mg/kg tri-weekly doses or 4 mg/kg loading followed by 2 mg/kg weekly doses.	Study 1 Wilks, S. et al[17] Study 2 Mukai, H. et al[36]	Study 1 2014 Study 2 2015
Neoadjuvant eribulin + carboplatin for early stage TNBC	Eribulin 1.4 mg/m^2 day 1 and day 8; carboplatin AUC 6 iv in a 21-day cycle for four cycles.	Kaklamani, V. G. et al[30]	2015
Neoadjuvant sequential eribulin × 3 followed by AC × 3 for LABC	Eribulin 1.4 mg/m^2 day 1 and day 8 every 3 weeks for 4 cycles followed by AC every 3 weeks for 4 cycles before surgery.	Abraham, J. et al[37] for NSABP Foundation Study FB-9	2015
Triple-negative ABC or MBC previously treated with anthracyclines and taxanes	Eribulin 1.4 mg/m^2 day 1 and day 8; olaparib 300 mg PO BID.	Yasojima, H. et al[31] Phase I results	2015

multidisciplinary shared-care approaches toward the management of our breast cancer and other patients, through which the author accumulated experience on the use of eribulin.

Author Contributions

Conceived the concepts: VCK. Analyzed the data: VCK. Wrote the first draft of the manuscript: VCK. Developed the structure and arguments for the paper: VCK. Made critical revisions: VCK. The author has reviewed and approved the final manuscript.

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