

REVIEW ARTICLE

Patient Management with Eribulin in Metastatic Breast Cancer: A Clinical Practice Guide

Jungsil Ro, Fiona Tsui-Fen Cheng¹, Virote Sriuranpong², Antonio Villalon³, B. K Smruti⁴, Janice Tsang⁵, Yoon Sim Yap⁶, Asian Working Group for Eribulin Clinical Guide

Center for Breast Cancer, National Cancer Center, Goyang, Korea; ¹Breast Cancer Center, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan; ²Division of Medical Oncology, Department of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand; ³Department of Internal Medicine, Manila Doctor Hospital, Manila, Philippines; ⁴Division of Medical Oncology, Bombay Hospital Institute of Medical Sciences & Lilavati Hospital, Mumbai, India; ⁵Department of Clinical Oncology, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China; ⁶Department of Medical Oncology, National Cancer Centre Singapore, Singapore

Eribulin, an antimicrotubule chemotherapeutic agent, is approved for the treatment of pretreated metastatic breast cancer (mBC) based on the positive outcomes of phase II and phase III clinical trials, which enrolled mainly Western patients. Eribulin has recently been approved in an increasing number of Asian countries; however, there is limited clinical experience in using the drug in certain countries. Therefore, we established an Asian working group to provide practical guidance for eribulin use based on our clinical experience. This paper summarizes the key

clinical trials, and the management recommendations for the reported adverse events (AEs) of eribulin in mBC treatment, with an emphasis on those that are relevant to Asian patients, followed by further elaboration of our eribulin clinical experience. It is anticipated that this clinical practice guide will improve the management of AEs resulting from eribulin treatment, which will ensure that patients receive the maximum treatment benefit.

Key Words: Asians, Breast neoplasms, Chemotherapy, Eribulin mesylate

INTRODUCTION

Improving overall survival (OS) remains an important treatment goal in metastatic breast cancer (mBC) patients. Despite the introduction of several novel therapies in recent years, mBC remains incurable; therefore, research continues to focus on developing treatments that could potentially improve survival [1-3].

Treatment approaches in the second- and later-line disease settings vary according to multiple factors, and no chemotherapeutic agent has clearly demonstrated superiority over the others [4]. In view of the palliative aim of mBC treatment, there is a trade-off between the benefits of chemotherapy and its associated toxic side effects. In everyday clinical practice, treatment choice is, therefore, determined based on the individual patient's condition and tumor characteristics [5]. With

this in mind, physicians need to be familiar with the available therapies, in addition to the management of side effects associated with such therapies.

Eribulin is a synthetic analog of halichondrin B, which is a naturally occurring molecule with antitumor properties that was originally isolated from a marine sponge (*Halichondria okadaei*) found in the Pacific Ocean close to the coast of Japan [6]. Eribulin is a microtubule-targeted chemotherapeutic agent that belongs to the halichondrin class of molecules. It inhibits mitotic spindle formation by selectively targeting the microtubule growth phase, without affecting the shortening phase, which results in decreased cell proliferation and increased apoptosis [7]. This mode of action is distinct from those of other tubulin-targeting agents such as vinblastine and paclitaxel [7,8]. Eribulin induces an irreversible mitotic blockade, an action that is uncommon among microtubule inhibitors [9]. In addition to its antimitotic effects, eribulin may cause tumor vasculature remodeling and the reversal of epithelial-mesenchymal transition, which may decrease the invasiveness and metastasis of tumor cells [10-12].

The pharmacokinetic profile of eribulin is characterized by a rapid distribution phase, followed by a prolonged elimination phase; its average terminal half-life is approximately 40 hours

Correspondence to: Jungsil Ro

Center for Breast Cancer, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 10408, Korea

Tel: +82-31-920-1610, Fax: +82-31-903-0455

E-mail: jungstro@ncc.re.kr

This article was financially supported by Eisai.

Received: December 10, 2015 Accepted: February 18, 2016

[13,14]. Eribulin is weakly bound to plasma proteins; at a concentration between 100 and 1,000 ng/mL, the plasma protein binding in human plasma ranged from 49% to 65% [15]. Eribulin has a low clearance rate (range of means, 1.16–2.42 L/h/m²), with no significant accumulation upon weekly administration. When the dose of eribulin falls between 0.22 and 3.53 mg/m², the pharmacokinetic properties are not dose- or time-dependent [15]. Eribulin is mainly eliminated through biliary excretion. Based on a pharmacokinetic study, approximately 82% of the eribulin administered was eliminated in the feces, and 9% in the urine, which indicate that renal clearance is not a significant elimination route in the case of eribulin [15].

The approval of eribulin for the treatment of patients with locally advanced breast cancer (LABC) or mBC pretreated with an anthracycline and a taxane was based on the results of its phase II and III clinical trial that enrolled patients mainly from Western countries. In many Asian countries, eribulin has only recently been approved, and Asian clinicians in certain countries have limited experience of using it in their clinical practice. In this paper, we summarize the key clinical information associated with eribulin for the treatment of mBC, and provide practical guidance for its use, including the management of its adverse events (AEs) based on our clinical experience in Asian patients.

ERIBULIN CLINICAL TRIALS IN METASTATIC BREAST CANCER

Eribulin phase I trials

In phase I studies, eribulin demonstrated antitumor activity in a range of advanced solid tumors (Table 1) [13,14,16,17]. Although the dosing regimen differed slightly between the studies, treatment responses were observed in both Western and Asian patient populations.

Table 1. Phase I efficacy data in advanced solid tumors

Study	Patient population	No.	Types of cancer	Dose regimen	Tumor response
Goel et al. (2009) [13]	Western	32	Refractory/advanced solid tumors	0.25 mg/m ² upwards, guided by PK (MTD=1.4 mg/m ²); days 1, 8, 15 q4w by 1 hr IV infusion	PR, n=2 (NSCLC, bladder); MR, n=3 (NSCLC, breast, thyroid); SD as best response, n=10; median duration of response, 4 mo (range, 2–14 mo)
Tan et al. (2009) [14]	Western	21	Advanced solid tumors	0.25, 0.5, 1, 2, 2.8, and 4 mg/m ² (MTD=2.0 mg/m ²); day 1 of q3w by 1 hr IV infusion	PR, n=1 unconfirmed; SD as best response, n=12 (4 had prior taxane); median duration 2.8 mo (range, 1.5–12.7 mo)
Morgan et al. (2015) [16]	Western	40	Advanced solid tumors	0.125, 0.18, 0.25, 0.35, 0.5, 1.0, 1.4, and 2.0 mg/m ² (MTD=1.4 mg/m ² /wk); days 1, 8 and 15 q4w by 1–2 min IV infusion	PR, n=3 (at 1.4 and 2.0 mg/m ²); SD as best response, n=14; duration median 5.6 mo (range, 1.9–13.1 mo)
Mukohara et al. (2012) [17]	Asian	15	Advanced solid tumors	0.7, 1.0, 1.4, 2.0 mg/m ² (MTD=1.4 mg/m ²); days 1 and 8 of q3w by 5 min IV injection	PR, n=3 (at MTD); SD as best response, n=4; 2 patients has SD for 6 mo

PK=pharmacokinetics; MTD=maximum tolerated dose; q4w=every 4 weeks; IV=intravenous; PR=partial response; MR=minor response; NSCLC=non-small cell lung carcinoma; SD=stable disease; q3w=every 3 weeks.

Eribulin phase II trials

The efficacy and safety of eribulin (1.4 mg/m² on day 1 and day 8 of a 21-day cycle) have been evaluated in three phase II studies in patients with LABC or mBC pretreated with an anthracycline and a taxane (Table 2) [18–20]. In these studies, eribulin demonstrated antitumor activity with a manageable toxicity profile.

Eribulin phase III trials

The efficacy and safety of eribulin in mBC treatment have been evaluated in two phase III trials, namely the EMBRACE study and Study 301 [21,22].

The EMBRACE study was a global, multicenter, randomized (2:1) trial investigating eribulin versus a treatment of physician's choice (TPC) in 762 women with pretreated LABC or mBC. The primary endpoint of the study was OS. The TPC was used as the comparator arm to reflect the "real world" prescribing choices, since there is no standard therapy for mBC in the third-line setting. The women included in the study had received prior chemotherapy regimen, including anthracyclines and taxanes; either eribulin or TPC was subsequently administered as third- or later-line chemotherapy [21].

In the primary analysis with 422 events (55%), eribulin significantly extended the median OS compared with TPC (13.1 months vs. 10.6 months; hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.66–0.99; *p*=0.041). This represents a 23% increase in the 1-year median survival. An updated OS analysis including 589 events (77%), which was requested by the European and the United States regulatory authorities, confirmed a significant OS increase in eribulin-treated patients compared with those treated with the TPC (13.2 months vs. 10.5 months; HR, 0.81; 95% CI, 0.67–0.96; *p*=0.014) [21].

Based on an independent review, the median progression-

Table 2. Phase II studies in metastatic breast cancer

Study	Patient population	No. of patients	Setting	Key efficacy and safety findings
211 [18]	Western	291	≥3rd line, LABC/mBC	ORR (independent review)=9.3% (95% CI, 6.1%–13.4%; all PRs), SD rate=46.5% Clinical benefit rate=17.1% PFS 2.6 mo OS 10.4 mo Most common treatment-related grade 3/4 toxicities were neutropenia (54%); febrile neutropenia (5.5%); leukopenia (14%), and asthenia/fatigue (10%, no grade 4). Grade 3 neuropathy occurred in 6.9% of patients (no grade 4).
201 [19]	Western	193	≥2nd line, LABC/mBC	ORR=11.5% (95% CI, 5.7%–20.1%) Clinical benefit rate 17.2% (95% CI, 10.0%–26.8%) PFS 79 days (2.6 mo; range, 1–453 days) OS 275 days (9.0 mo; range, 15–826 days) The most common drug-related grade 3/4 toxicities were neutropenia (64%); leukopenia (18%); fatigue (5%); peripheral neuropathy (5%); and febrile neutropenia (4%)
221 [20]	Japanese*	80	1–4th line, LABC/mBC	ORR=21.3% (95% CI, 12.9%–31.8%; all PRs) Clinical benefit rate=27.5% (95% CI, 18.1%–38.6%) PFS 3.7 mo (95% CI, 2.0–4.4 mo) OS 11.1 mo (95% CI, 7.9–15.8 mo) Most frequent treatment-related grade 3/4 AEs were neutropenia (95.1%); leukopenia (74.1%); and febrile neutropenia (13.6%) Grade 3 peripheral neuropathy occurred in 3.7% of patients (no grade 4)

LABC=locally advanced breast cancer; mBC=metastatic breast cancer; ORR=objective response rate; CI=confidence interval; SD=stable disease; PFS=progression-free survival; OS=overall survival; PR=partial response; AEs=adverse events.

*Japanese registrational phase II study to support the use of eribulin in Japanese patients with locally advanced or mBC.

free survival (PFS) was longer with eribulin treatment than with the TPC; however, this difference was not statistically significant (3.7 months vs. 2.2 months; HR, 0.87; 95% CI, 0.71–1.05; $p=0.137$) [21]. The objective response rate (ORR) was 12% (57 out of 468 patients) with eribulin treatment, including three cases with a complete response, versus 5% (10 out of 214 patients) with the TPC ($p=0.002$) [21].

In the other randomized phase III trial, Study 301, women with LABC or mBC who had received prior anthracycline- and taxane-based therapy ($n=1,102$) were randomized to receive either single agent eribulin or capecitabine as a first-, second-, or third-line chemotherapy. The co-primary endpoints of the study were OS and PFS [22].

In Study 301, there was no statistically significant difference between eribulin and capecitabine with regard to the median OS (15.9 months vs. 14.5 months; HR, 0.88; 95% CI, 0.77–1.00; $p=0.056$) and the median PFS (4.1 months vs. 4.2 months; HR, 1.08; 95% CI, 0.93–1.25; $p=0.30$) [22]. Based on an independent review, the ORRs were 11% (95% CI, 8.5%–13.9%) and 11.5% (95% CI, 8.9%–14.5%; $p=0.85$) for eribulin and capecitabine, respectively [22].

A pooled analysis of the data from these two trials, as requested by the European Medicines Agency (EMA), was performed to assess whether specific patient subgroups benefited from eribulin treatment [23]. In this pooled analysis, eribulin improved the OS significantly in various patient subgroups, notably in patients with human epidermal growth factor re-

ceptor 2 (HER2)-negative and triple-negative (TN) disease. The results of this analysis were used as supplementary information to support the license extension of eribulin for second- and later-line therapy in mBC [23].

In addition to the overall analyses, a number of post-hoc analyses from the two phase III trials have been reported, and are presented in Table 3 [21,24–28].

Eribulin in the Asian patient population

The only clinical trial data for eribulin in the Asian breast-cancer-patient population comes from a phase II, multicenter, single-arm study of 80 Japanese mBC patients who were treated with eribulin as third- and later-line chemotherapy. The ORR was 21.3% (95% CI, 12.9%–31.8%; all partial responses). Based on an independent review, 37.5% of the patients in the study had stable disease [20].

CLINICAL USE OF ERIBULIN

Eribulin was originally approved by the U.S. Food and Drug Administration Agency in 2010, and the EMA in 2011, for the treatment of LABC or mBC patients who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane, unless these treatments were not suitable for the patients. Eribulin was subsequently approved in many Asian countries as third- or later-line chemotherapy for mBC pa-

Table 3. Summary of key *post hoc* data and findings from the EMBRACE Study and Study 301

		Key findings
EMBRACE study		
Twelves et al. (2010) [24]		Predefined exploratory subgroup analyses by hormone receptor expression status, number of organs involved and sites of disease were consistent with the overall analysis, and showed that the OS benefit for eribulin versus TPC was maintained across a variety of subgroups.
Blum et al. (2010) [25]		The OS benefit with eribulin was greatest in patients who had received fewer previous therapies. The subgroup analysis identified consistently longer median OS with eribulin versus TPC in patients who received ≤ 3 prior chemotherapy regimens.
Cortes et al. (2011) [21]		No significant differences in OS and PFS were noted in eribulin patients who had dose modifications due to AEs compared with those who did not have dose modifications.
Simons et al. (2013) [26]		The sequencing of prior treatments does not provide additional OS benefit with eribulin.
Study 301		
Awada et al. (2013) [27]		Treatment with capecitabine or any other postprogression anticancer treatment after progression on eribulin did not account for the nonstatistically significant trend in OS benefit associated with eribulin in the primary analysis.
Kaufman et al. (2013) [28]		Patients in certain subgroups appeared to benefit more from eribulin treatment compared with capecitabine treatment, including those with nonvisceral disease, >2 organs involved with disease, progressive disease >6 mo after last chemotherapy, triple-negative breast cancer, and HER2-negative breast cancer.

OS=overall survival; TPC=treatment of physician's choice; PFS=progression-free survival; AEs=adverse events; HER2=human epidermal growth factor receptor 2.

tients who were pretreated with an anthracycline and a taxane. More recently, based on the results of Study 301, eribulin was approved in the European Union, Thailand, Hong Kong, South Korea, India, and the Philippines for the treatment of LABC or mBC in patients who have progressed after at least one chemotherapeutic regimen for advanced disease.

The National Comprehensive Cancer Network (NCCN) clinical guidelines have included eribulin as a preferred single agent for the treatment of inoperable LABC and mBC [29]. Recently, the American Society of Clinical Oncology (ASCO) clinical guidelines for HER2-negative advanced breast cancer have recommended eribulin as a second- and later-line chemotherapy, stating that “the most convincing data are for eribulin, based on survival superiority against the best standard treatment in a recent large randomized clinical trial, but there is a lack of good comparative data between these various agents” [30]. The European School of Oncology-European Society for Medical Oncology (ESO-ESMO) consensus guidelines for advanced breast cancer recommend eribulin as the preferred choice in patients pretreated with an anthracycline and a taxane (in any setting), and who do not need combination therapy [31].

In the Asian patient population, the efficacy of eribulin has been shown in a phase II trial with Japanese patients [20]. Not only is eribulin the only single agent proven to significantly extend survival in mBC patients in the third- and later-line setting, it is also a good addition to the currently available treatment options for mBC. Although eribulin has shown efficacy regardless of the tumor receptor status, we would expect greater OS benefit in patients with HER2-negative and TN breast cancer, as demonstrated in Study 301.

Although the OS was selected as the primary/co-primary end point in the EMBRACE study and Study 301 for obtaining a clinically meaningful outcome, this does not diminish the value of PFS and other surrogate endpoints as valid end points in certain clinical situations [32]. The selection of an appropriate chemotherapeutic agent for an individual mBC patient should not only be based on clinical evidence, but also on patient-associated factors, such as disease status, prior chemotherapy regimen(s), experience of toxicities, performance status, and comorbidities, in order to maximize the clinical benefit of the treatment. In addition to eribulin's current therapeutic indication as a single agent for mBC treatment, there are data available for its use in combination with other anti-cancer agents, such as trastuzumab and capecitabine [33,34].

The recommended dose of eribulin mesylate is 1.4 mg/m² (equivalent to 1.23 mg/m² eribulin [expressed as free base]), administered intravenously over 2 to 5 minutes on day 1 and 8 of every 21-day cycle. Such a short infusion regimen offers convenience from the patient's perspective by minimizing the time spent in the clinic for treatment. Some medical centers choose to administer eribulin as a diluted infusion (30 mL in 100 mL of 0.9% sodium chloride) over 10 to 30 minutes as their preferred routine practice. Eribulin is not a vesicant or an irritant [15]; therefore, it may be administered through a peripheral or central venous line.

MANAGEMENT OF ADVERSE EVENTS ASSOCIATED WITH ERIBULIN

The reported AEs in the EMBRACE study and Study 301 were consistent with the known side effect profile of eribulin

Table 4. Summary of adverse events from the EMBRACE study and Study 301

Adverse events (%)	EMBRACE		Study 301	
	Eribulin (n=503)	TPC (n=247)	Eribulin (n=544)	Capecitabine (n=546)
Overall adverse events	99	93	94	91
Serious adverse events	25	26	18	21
Adverse events leading to discontinuation	15	13	8	10
Most common hematologic adverse events*				
Neutropenia	52	30	54	16
Leukopenia	23	11	31	10
Most common nonhematologic adverse events*				
Asthenia/fatigue	54	40	83/91 [†]	79/84 [†]
Alopecia	45	10	35	4
Nausea	35	28	22	24
Peripheral neuropathy [‡]	35	16	27	14
Constipation	25	21	<10 [§]	<10 [§]
Diarrhoea	18	18	14	29
Hand-foot syndrome	1	14	0.2	45

TPC=treatment of physician's choice.

* ≥25% of patients in either treatment arm, in either EMBRACE or Study 301; [†]Asthenia/fatigue were assessed as separate adverse events in Study 301. Incidence of asthenia in Study 301 was 15.3% and 14.5% in the eribulin and capecitabine treatment groups, respectively. The incidence of fatigue was 16.7% and 15.4% in the eribulin and capecitabine treatment groups, respectively; [‡]In EMBRACE, peripheral neuropathy included neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paresthesia. Study 301 reported global peripheral neuropathy, defined as Standardized Medical Dictionary for Regulatory Activities Queries narrow and broad terms; [§]Only data for adverse events occurring in >10% of patients have been presented.

from the previous phase II studies. The overall incidences of serious AEs in the two phase III trials are shown in Table 4. The main AEs leading to treatment discontinuation in the EMBRACE study and Study 301 were peripheral neuropathy (5%) and neutropenia (1.7%), respectively [21,22]. The most common nonhematologic AEs of eribulin were asthenia/fatigue, alopecia, and nausea, while the most common hematologic AEs were neutropenia and leukopenia (Table 4).

Delays in administration and/or dose reduction are sometimes needed to manage eribulin-related grade 3/4 toxicities. These dose reductions allow most patients to continue with the treatment longer in order to gain the maximal clinical benefit. Dose modification recommendations for eribulin re-treatment are shown in Table 5 [15].

Neutropenia and febrile neutropenia

The most commonly reported AEs associated with eribulin treatment in clinical trials are hematological effects attributed to bone marrow suppression (i.e., neutropenia) [21,22]. This is consistent with our clinical experience of treating Asian patients with eribulin. In the EMBRACE study and Study 301, there was no prophylactic use of growth factors to prevent eribulin-induced neutropenia. Patients who developed neutropenia during eribulin treatment were managed with treatment delays, dose reductions, and granulocyte colony-stimulating factor (G-CSF), which was used in 18% and 14.6% of patients in the EMBRACE study and Study 301, respectively. Only 0.6% and 1.7% of patients discontinued eribulin treatment

Table 5. Eribulin dose modification recommendations [15]

Adverse reaction after previous administration	Recommended eribulin dose
Hematologic	1.1 mg/m ²
ANC <0.5 × 10 ⁹ /L lasting more than 7 day	
ANC <1 × 10 ⁹ /L neutropenia complicated by fever or infection	
Platelets <25 × 10 ⁹ /L thrombocytopenia	
Nonhematologic	1.1 mg/m ²
Any grade 3 or 4 in the previous cycle	
Reoccurrence of any hematologic or non-hematologic adverse reactions as specified above	
Despite reduction to 1.1 mg/m ²	0.7 mg/m ²
Despite reduction to 0.7 mg/m ²	Consider discontinuation

ANC=absolute neutrophil count.

due to neutropenia in the EMBRACE study and Study 301, respectively [21,22]. The median time to recovery from grade 3/4 neutropenia to grade 2 or lower was 8 days, but in some cases, this was extended up to 51 days [21,22]. In the EMBRACE study and Study 301, febrile neutropenia (FN) occurred in 5% and 2% of patients, respectively [21,22].

In the Asian population, based on the phase II trial of eribulin in Japanese patients, neutropenia was reported at a relatively higher incidence of 98.8% (all grades; 95.1% for grade 3/4) than in the Western population in the phase III trials. There was also a higher incidence of FN (13.6%), and G-CSF was administered to 25.9% of the patients to manage symptomatic neutropenia. However, only one patient (1%) discon-

tinued eribulin treatment due to neutropenia [20].

Neutropenia and FN are the major dose-limiting toxicities of some of the systemic cancer chemotherapies, including eribulin and other myelosuppressive chemotherapeutic agents such as paclitaxel, docetaxel, vinorelbine, and anthracycline-containing regimens. Advanced age, poor performance status, comorbidities, and low baseline blood cell counts have been identified as significant predictors for neutropenic complications, including FN [35]. However, eribulin-associated neutropenia is reversible and not cumulative; in most cases, it can be managed with dose delays or modification alone, or with the use of growth factors [15]. Eribulin should not be initiated in patients with an absolute neutrophil count (ANC) $< 1,000/\text{mm}^3$, or with other hematologic toxicity at grade 2 or higher. If neutropenia occurs, a dose delay of 3 to 7 days should be considered in order to allow the ANC to recover, followed by a reduced dose schedule as specified in the dosing recommendations for eribulin (Table 5). Eribulin is associated with a low risk of FN, and primary prophylaxis with growth factors was not permitted in the aforementioned phase III trials of eribulin. However, maintaining adequate dose intensity is recognized as a key factor influencing a tumor's response to cytotoxic drugs. Therefore, primary or secondary prophylactic use of G-CSF may be considered, if needed, to maximize treatment benefit.

The prophylactic use of growth factors can reduce the risk, severity and duration of both severe and FN. The use of G-CSF or equivalent to manage eribulin-induced severe neutropenia is at the discretion of the treating physician, and in accordance with the relevant clinical practice guidelines, such as the guidelines of the European Organisation for Research and Treatment of Cancer (EORTC) [36], NCCN [37], and ESMO [38]. In general, these guidelines recommend that FN risk factors, including disease, dose density, age, neutrophil count, and treatment intent, should be evaluated before administering each cycle of chemotherapy. These guidelines also recommend not to consider growth factor use for primary prophylaxis in patients with a low risk of FN ($< 10\%$), unless they are at a significant risk of serious medical consequences of FN, or if a chemotherapy dose reduction would be detrimental to the clinical outcome [37]. The NCCN recommendation for growth factor use in the prophylaxis and treatment of FN, and the maintenance of scheduled dose delivery, is the administration of 5 $\mu\text{g}/\text{kg}$ daily of filgrastim until post-nadir ANC recovery to normal or near normal levels. It is initiated on the next day, after more than 24 hours up to 3 to 4 days after the completion of chemotherapy and throughout post-nadir recovery [37]. The ESMO guidelines suggest using 5 $\mu\text{g}/\text{kg}$ daily of G-CSF, administered subcutaneously 24 to 72 hours after the last

day of chemotherapy, until sufficient or stable post-nadir ANC recovery is achieved (achieving a target ANC of $> 10 \times 10^9/\text{L}$ is not necessary) [38]. Pegfilgrastim is generally not recommended by the NCCN guidelines for use with weekly chemotherapeutic regimens (such as eribulin) owing to insufficient supporting data, although, it may be administered if chemotherapy is given every 2 weeks or more [37].

A higher incidence of eribulin-associated neutropenia was reported by a clinical trial with Japanese patients [20], as well as from individual clinicians treating Asian patients in their daily practice who received eribulin; although, there is no published report, to our knowledge, so far. Currently there is evidence that the pharmacogenomics of eribulin in Asian breast cancer patients differ from that in the Western population. Another potential reason for the higher neutropenia rate in Asian patients may be related to the use of eribulin as a very late-line therapy in heavily pretreated patients; using G-CSF may help to reduce the neutropenia rate in such patients.

In our clinical practice, although the routine use of growth factors with eribulin therapy is not always necessary in Asian patients, G-CSF may be considered as primary or secondary prophylaxis for "high-risk" patients. For example, primary prophylaxis with G-CSF might be considered for patients who experienced significant hematologic toxicities or FN during previous chemotherapeutic regimens, or for patients at risk of infective complications without good access to care. In some countries, primary prophylaxis with G-CSF is not reimbursed by their national healthcare systems. Under these circumstances, a reduced initial dose of eribulin can be considered for patients at high risk of neutropenia. This reduced dose may then be increased to the full dose if eribulin is well tolerated during the first treatment cycle. Although this may compromise dose intensity, treatment decisions should be individualized in accordance with these limitations in the clinical setting.

Peripheral neuropathy

Microtubule-targeted therapies, including taxanes, epothilones, and vinca alkaloids, are commonly associated with some forms of neuropathy; severe peripheral neuropathy (grade 3 or 4) has been reported in 30% of patients [39]. Eribulin is one such agent associated with neurotoxicity [40].

Peripheral neuropathy was reported as one of the most common grade 3/4 AEs of eribulin in the phase III trials; it occurred in about 7% to 8% of patients. However, it only resulted in treatment discontinuation in less than 5% of patients [21]. The incidence of all grades of peripheral neuropathy in the eribulin group in the EMBRACE study was 35% (8% of grade 3 or higher), compared with the 45% (17/38, 5% of grade 3 or higher) observed in the taxanes-TPC subgroup

[21]. In the pooled safety analysis from the two phase III studies and two phase II studies of patients with mBC, 7.7% of patients (116/1,503) treated with eribulin had grade 3 or higher peripheral neuropathy [41]. In patients with grade 3 or higher peripheral neuropathy who remained on eribulin, the symptoms improved to grade 2 or less after treatment delays and dose reductions. Most patients who had peripheral neuropathy at baseline did not experience a worsening of its severity during eribulin treatment [21]. Of these patients, most showed an improvement in the severity of peripheral neuropathy, and 50% of them experienced its resolution. The median time to improvement was 2.1 weeks, whereas the median time to resolution was 7.7 weeks [41]. Moreover, neuropathy lasting more than 1 year occurred in only 5% of the patients [42]. Peripheral neuropathy associated with eribulin was reversible in many, but not all, patients [42]. Collectively, the data suggest that the risk-benefit ratio for eribulin in relation to peripheral neuropathy supports the use of this drug for treating patients with breast cancer [41]. A lower incidence of peripheral sensory neuropathy (23.5% of all grades, 3.7% of grade 3, and no grade 4) was reported in the Japanese phase II trial [20]. This is consistent with our experience of treating Asian patients with eribulin, and demonstrates that neuropathy does not seem to be a major dose-limiting toxicity.

Chemotherapy-induced peripheral neuropathy (CIPN) is a common treatment-related serious AE that interferes with the efficacy of treatment and decreases patients' quality of life. Several classes of chemotherapeutic agents cause peripheral neuropathy, including platinum-based agents (cisplatin, carboplatin, and oxaliplatin), vinca alkaloids (vincristine and vinblastine), and taxanes (paclitaxel and docetaxel). The incidence and severity of neuropathy vary considerably for different agents when administered alone or in combination. The incidence of neuropathy was reported to be as high as 70% to 90% with vincristine, cisplatin, oxaliplatin, and paclitaxel treatment [43-47]. The risk of developing both short- and long-term CIPN is highly dependent on factors such as the age, single-dose intensity, cumulative dose, duration of therapy, combination of neurotoxic agents, coexisting neuropathies, genetic susceptibility, and alcohol abuse [47-53]. This neuropathy predominantly consists of sensory symptoms, rather than motor symptoms, and it is dose dependent [54,55]. The symptoms become progressively worse with chemotherapy continuation. The standards of care for patients at risk of, or experiencing, neuropathy are based on a thorough assessment of their sensory symptoms; dose adjustments for chemotherapy can be made based on these findings. There are no established agents recommended for the prevention of CIPN in cancer patients undergoing treatment with neuro-

toxic agents. When grade 3 or higher peripheral neuropathy occurs, eribulin should be delayed until recovery to grade 2 or less; eribulin should be discontinued if peripheral neuropathy higher than grade 3 reoccurs (Table 5). The symptomatic management of peripheral neuropathy should be based on physicians' assessments and clinical judgments. Available clinical guidelines, such as the ASCO clinical practice guidelines for CIPN, may serve as a useful reference [56].

Alopecia

Alopecia is another common AE associated with eribulin therapy. In the EMBRACE study and Study 301, 45% and 35% of patients experienced alopecia, respectively [21,22]. Chemotherapy-induced hair loss is common, with an estimated overall incidence rate of 65% [57]. The frequency and severity of hair loss are variable, and are related to the specific chemotherapeutic agent and the treatment protocol. Eribulin-induced hair loss cannot be reliably predicted or prevented. The treating physician should discuss the treatment plan with the patient and their family in order to establish their expectations regarding eribulin treatment, in addition to communicating the risks of potential AEs such as alopecia. From the patient's perspective, the clinical benefit of eribulin should be balanced with its potential toxicities. Treatment choice should be based on the patient's personal preference and physician's best clinical judgment. To date, no approved pharmacological option exists for the prevention of chemotherapy-induced hair loss. Scalp cooling with a cold cap in order to reduce alopecia is available in some cancer centers; however, there is limited experience in applying this method to patients with eribulin-induced alopecia.

Nausea and vomiting

Nausea and vomiting are among the most common gastrointestinal AEs associated with eribulin therapy. In the EMBRACE study, 35% and 18% of the patients experienced nausea and vomiting, respectively [21]. However, these AEs were usually mild, with grade 3 and 4 toxicities occurring in <1% of patients. A low incidence of both AEs was seen in Study 301 [22]. Although the emetogenic potential of eribulin is common, it is considered low in comparison to that of the other antineoplastic agents such as cisplatin, doxorubicin, and cyclophosphamide [58]. Based on our clinical experience, eribulin-induced nausea and vomiting are relatively uncommon and anti-emetic prophylaxis is usually not necessary for Asian patients. If these AEs do occur, treatment guidelines for managing chemotherapy-induced nausea and vomiting can be followed, such as the guidelines of the Multinational Association of Supportive Care in Cancer, ASCO, and NCCN [59,60].

Eribulin in patients with hepatic or renal impairment

Pharmacokinetic studies of eribulin show that drug exposure is greater in patients with hepatic impairment or severely impaired renal function [15,61]. Therefore, eribulin dose adjustments may be required for mBC patients with hepatic and renal impairment. Eribulin should be used with caution and at the discretion of the treating physician in such patients. The recommended doses of eribulin in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment are 1.1 and 0.7 mg/m², respectively [61]. Eribulin has not been studied in patients with severe hepatic impairment (Child-Pugh C), but it is expected that a more significant dose reduction may be needed if eribulin is used in these patients. Patients with impaired renal function may also require a dose reduction although the optimal dose for this patient group remains to be established.

Eribulin in elderly patients

No dose adjustment is recommended for the elderly patient population [15]. The EMBRACE study did not include sufficient numbers of patients aged ≥ 65 years in order to determine whether these patients had a different treatment response than the younger patients. Similar incidences of AEs were observed between these two groups of patients in the EMBRACE study. In Study 301, it was reported that in the patients receiving eribulin, there was a slight increase in study withdrawal among older patients (> 65 years, 10.7%) compared to that observed for younger patients (≤ 65 years, 7.4%) [62]. There was also an increased trend in the incidence of grade 3/4 leukopenia in older patients (22.6%) when compared with younger patients (13.7%); similar results were observed for the incidence of grade 3/4 neutropenia (50.0% vs. 45.0%, respectively). In contrast, a decrease in the incidence of peripheral sensory neuropathy was observed in the older population. However, a similar OS benefit of eribulin was shown in the younger (≤ 65 years) and older (> 65 years) age groups in this cohort of patients [62]. For older patients (> 65 years), we recommend careful evaluation of the patients' conditions, including their bone marrow function, prior to eribulin treatment.

CONCLUSION

Approaches for mBC management have evolved in recent years; however, chemotherapy remains the mainstay of treatment for patients with advanced disease. Eribulin is a microtubule dynamics inhibitor indicated in several Asian countries as second- and later-line chemotherapy for mBC patients pretreated with an anthracycline and a taxane. While there is

limited clinical trial data for the use of eribulin in the Asian patient population, the drug has been evaluated in two global, randomized phase III studies. In the EMBRACE study, eribulin showed a significant and clinically meaningful improvement in the OS compared with TPC in heavily pretreated mBC patients. Study 301 evaluated eribulin versus capecitabine in patients who had received prior anthracycline and taxane treatment. Although the co-primary endpoints of OS and PFS for eribulin superiority over capecitabine in this study were not met, there was a numerical difference in the median OS in favor of eribulin. Furthermore, a pooled analysis of these two studies suggests that eribulin may specifically confer OS benefits to patients with HER2-negative and TN disease when compared with the control treatment. The benefit of eribulin as a single agent in this setting suggests that this drug could become a new standard of care [21]. Eribulin is generally well tolerated although neutropenia may occur at a higher frequency among Asian patients receiving eribulin after several lines of systemic therapy. The most common AEs are manageable with the supportive measures highlighted in this paper. Collectively, the phase III trials' data and our clinical experience support the use of eribulin as a potential treatment option for mBC in Asian patients. The efficacy and safety of eribulin in combination with other agents for advanced breast cancer, including capecitabine [34]; carboplatin (NCT 01372579); poly (ADP-ribose) polymerase inhibitors such as olaparib (NCT02000622) and talazoparib (NCT01945775); the programmed death 1 immune checkpoint inhibitor, pembrolizumab (NCT02513472); and the mammalian target of rapamycin inhibitor, everolimus (NCT02120469, NCT 02616848), are currently being explored in the setting of HER2-negative, TN, and *BRCA*-mutated breast cancer. Results from ongoing clinical trials in the adjuvant setting after doxorubicin and cyclophosphamide for HER2-negative disease (NCT01328249), capecitabine for estrogen receptor-positive disease (NCT01439282), and in the neoadjuvant setting with carboplatin (NCT01372579) for TN breast cancer are also awaited.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ACKNOWLEDGMENTS

The authors wish to thank Jenny Szkolar from Virgo Health who provided editorial support through funding by Eisai.

REFERENCES

- Giordano SH, Buzdar AU, Simth TL, Kau SW, Yang Y, Hortobagyi GN. Is breast cancer survival improving? *Cancer* 2004;100:44-52.
- Pal SK, Dehaven M, Nelson RA, Onami S, Hsu J, Waliany S, et al. Impact of modern chemotherapy on the survival of women presenting with de novo metastatic breast cancer. *BMC Cancer* 2012;12:435.
- Chia SK, Speers CH, Dyachkova Y, Kang A, Malfair-Taylor S, Barnett J, et al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer* 2007;110:973-9.
- Cardoso F, Senkus-Konefka E, Fallowfield L, Costa A, Castiglione M; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21 Suppl 5:v15-9.
- Jones SE. Considerations in treatment choice for metastatic breast cancer. *Breast Cancer* 2008;15:35-9.
- Towle MJ, Salvato KA, Budrow J, Wels BF, Kuznetsov G, Aalfs KK, et al. In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. *Cancer Res* 2001;61:1013-21.
- Jordan MA, Kamath K, Manna T, Okouneva T, Miller HP, Davis C, et al. The primary antimetabolic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. *Mol Cancer Ther* 2005;4:1086-95.
- Okouneva T, Azarenko O, Wilson L, Littlefield BA, Jordan MA. Inhibition of centromere dynamics by eribulin (E7389) during mitotic metaphase. *Mol Cancer Ther* 2008;7:2003-11.
- Towle MJ, Salvato KA, Wels BF, Aalfs KK, Zheng W, Seletsky BM, et al. Eribulin induces irreversible mitotic blockade: implications of cell-based pharmacodynamics for in vivo efficacy under intermittent dosing conditions. *Cancer Res* 2011;71:496-505.
- Agoulnik SI, Oestreicher JL, Taylor NH, Uesugi M, Muto H, Kawano S, et al. Eribulin and paclitaxel differentially affect gene expression profiling of blood vessel cells and in vitro angiogenesis in cocultures of human endothelial cells with pericytes. *Cancer Res* 2013;73(8 Suppl):Abstract #3830.
- McCracken PJ, Ito K, Yanagimachi M, Tizon X, Provent P, Xu S, et al. Eribulin alters vascular function in human triple-negative (TN) breast MX-1 and MDA-MB-231 tumor xenograft models as measured by DCE-MRI. *Cancer Res* 2013;73(8 Suppl):Abstract #4502.
- Matsui J, Toyama O, Ino M, Semba T, Uesugi M, Muto H, et al. Eribulin caused re-modeling of tumor vasculature altering gene expression profiling in angiogenesis and epithelial mesenchymal transition (EMT) signaling pathway of host cells within human breast cancer cell (BCC) xenografts in nude mice. *Cancer Res* 2013;73(8 Suppl):Abstract #1413.
- Goel S, Mita AC, Mita M, Rowinsky EK, Chu QS, Wong N, et al. A phase I study of eribulin mesylate (E7389), a mechanistically novel inhibitor of microtubule dynamics, in patients with advanced solid malignancies. *Clin Cancer Res* 2009;15:4207-12.
- Tan AR, Rubin EH, Walton DC, Shuster DE, Wong YN, Fang F, et al. Phase I study of eribulin mesylate administered once every 21 days in patients with advanced solid tumors. *Clin Cancer Res* 2009;15:4213-9.
- European Medicines Agency. Eribulin: Summary of Product Characteristics. London: European Medicines Agency; 2014.
- Morgan RJ, Synold TW, Longmate JA, Quinn DI, Gandara D, Lenz HJ, et al. Pharmacodynamics (PD) and pharmacokinetics (PK) of E7389 (eribulin, halichondrin B analog) during a phase I trial in patients with advanced solid tumors: a California Cancer Consortium trial. *Cancer Chemother Pharmacol* 2015;76:897-907.
- Mukohara T, Nagai S, Mukai H, Namiki M, Minami H. Eribulin mesylate in patients with refractory cancers: a Phase I study. *Invest New Drugs* 2012;30:1926-33.
- Cortes J, Vahdat L, Blum JL, Twelves C, Campone M, Roché H, et al. Phase II study of the halichondrin B analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine. *J Clin Oncol* 2010;28:3922-8.
- Vahdat LT, Pruitt B, Fabian CJ, Rivera RR, Smith DA, Tan-Chiu E, et al. Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol* 2009;27:2954-61.
- Aogi K, Iwata H, Masuda N, Mukai H, Yoshida M, Rai Y, et al. A phase II study of eribulin in Japanese patients with heavily pretreated metastatic breast cancer. *Ann Oncol* 2012;23:1441-8.
- Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomized study. *Lancet* 2011;377:914-23.
- Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, 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 Oncol* 2015;33:594-601.
- Twelves C, Cortes J, Vahdat L, Olivo M, He Y, Kaufman PA, et al. Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies. *Breast Cancer Res Treat* 2014;148:553-61.
- Twelves C, Akerele C, Wanders J, Cortes JA. Eribulin mesylate (E7389) vs treatment of physician's choice (TPC) in patients (pts) with metastatic breast cancer (MBC): subgroup analyses from the EMBRACE study. *Ann Oncol* 2010;21(Suppl 8):viii96, Abstract #2750.
- Blum JL, Twelves CJ, Akerele C, Seegobin S, Wanders J, Cortes J. Impact of the number of prior chemotherapy regimens on overall survival (OS) among subjects with locally recurrent or metastatic breast cancer treated with eribulin mesylate: results from the phase III EMBRACE study. *Cancer Res* 2010;70(24 Suppl):Abstract #P6-13-01.
- Simons W, Rodriguez-Villanueva J, Sheffield RE, Rege J, HE YP, Lin S. Does the prior chemotherapy treatment sequence affect the overall survival (OS) benefit associated with eribulin? *Eur J Cancer* 2013;49(Suppl 2):Abstract #1891.
- Awada A, Kaufman PA, Yelle L, Cortes J, Wanders J, O'Shaughnessy J, et al. A phase III, open-label, randomized study of eribulin versus capecitabine in patients (pts) with metastatic breast cancer (MBC): effect of post-progression anti-cancer treatments (PPT) and metastatic progression events on overall survival. *Cancer Res* 2013;73(24 Suppl): Abstract #P3-13-03.
- Kaufman PA, Cortes J, Awada A, Yelle L, Perez EA, Wanders J, et al. A Phase III, open-label, randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer (MBC) previously treated with anthracyclines and taxanes: subgroup analyses. *J Clin Oncol* 2013;31(Suppl 15):Abstract #1049.

29. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Version 3. Fort Washington: National Comprehensive Cancer Network; 2014.
30. Partridge AH, Rumble RB, Carey LA, Come SE, Davidson NE, Di Leo A, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2014;32:3307-29.
31. Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Ann Oncol* 2014;25:1871-88.
32. Ellis LM, Bernstein DS, Voest EE, Berlin JD, Sargent D, Cortazar P, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol* 2014;32:1277-80.
33. Wilks S, Puhalla S, O'Shaughnessy J, Schwartzberg L, Berrak E, Song J, et al. Phase 2, multicenter, single-arm study of eribulin mesylate with trastuzumab as first-line therapy for locally recurrent or metastatic HER2-positive breast cancer. *Clin Breast Cancer* 2014;14:405-12.
34. Twelves C, Nasim MY, Anthoney A, Savulsky CI, Yin S, Evans TR. Efficacy and safety of eribulin in combination with capecitabine in patients with metastatic breast cancer: an open-label, phase II dose-confirmation study. *Cancer Res* 2015;75(9 Suppl):Abstract #P3-13-04.
35. Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapy-induced neutropenia. *Oncologist* 2005;10:427-37.
36. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JB, Kearney N, et al. 2010 Update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer* 2011;47:8-32.
37. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Myeloid Growth Factors Version 2.2014. Fort Washington: National Comprehensive Cancer Network; 2014.
38. Crawford J, Caserta C, Roila F; ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. *Ann Oncol* 2010;21 Suppl 5:v248-51.
39. Lee JJ, Swain SM. Peripheral neuropathy induced by microtubule-stabilizing agents. *J Clin Oncol* 2006;24:1633-42.
40. Carlson K, Ocean AJ. Peripheral neuropathy with microtubule-targeting agents: occurrence and management approach. *Clin Breast Cancer* 2011;11:73-81.
41. Kaufman P, Olivo M, He Y, McCutcheon S, Vahdat L. Peripheral neuropathy (PN) in patients (pts) with metastatic breast cancer treated with eribulin: resolution and association with efficacy. *J Clin Oncol* 2014; 32(Suppl 26):Abstract #147.
42. Donoghue M, Lemery SJ, Yuan W, He K, Sridhara R, Shord S, et al. Eribulin mesylate for the treatment of patients with refractory metastatic breast cancer: use of a "physician's choice" control arm in a randomized approval trial. *Clin Cancer Res* 2012;18:1496-505.
43. Polomano RC, Bennett GJ. Chemotherapy-evoked painful peripheral neuropathy. *Pain Med* 2001;2:8-14.
44. Armstrong T, Almadrone L, Gilbert MR. Chemotherapy-induced peripheral neuropathy. *Oncol Nurs Forum* 2005;32:305-11.
45. Hausheer FH, Schilsky RL, Bain S, Berghorn EJ, Lieberman F. Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy. *Semin Oncol* 2006;33:15-49.
46. Wilkes G. Peripheral neuropathy related to chemotherapy. *Semin Oncol Nurs* 2007;23:162-73.
47. Argyriou AA, Polychronopoulos P, Iconomou G, Chroni E, Kalofonos HP. A review on oxaliplatin-induced peripheral nerve damage. *Cancer Treat Rev* 2008;34:368-77.
48. Visovsky C. Chemotherapy-induced peripheral neuropathy. *Cancer Invest* 2003;21:439-51.
49. Repetto L. Greater risks of chemotherapy toxicity in elderly patients with cancer. *J Support Oncol* 2003;1(4 Suppl 2):18-24.
50. Dropcho EJ. Neurotoxicity of cancer chemotherapy. *Semin Neurol* 2004;24:419-26.
51. Kannarkat G, Lasher EE, Schiff D. Neurologic complications of chemotherapy agents. *Curr Opin Neurol* 2007;20:719-25.
52. McWhinney SR, Goldberg RM, McLeod HL. Platinum neurotoxicity pharmacogenetics. *Mol Cancer Ther* 2009;8:10-6.
53. Nurgalieva Z, Xia R, Liu CC, Burau K, Hardy D, Du XL. Risk of chemotherapy-induced peripheral neuropathy in large population-based cohorts of elderly patients with breast, ovarian, and lung cancer. *Am J Ther* 2010;17:148-58.
54. Cavaletti G, Cornblath DR, Merkies IS, Postma TJ, Rossi E, Frigeni B, et al. The chemotherapy-induced peripheral neuropathy outcome measures standardization study: from consensus to the first validity and reliability findings. *Ann Oncol* 2013;24:454-62.
55. Stubblefield MD, Burstein HJ, Burton AW, Custodio CM, Deng GE, Ho M, et al. NCCN task force report: management of neuropathy in cancer. *J Natl Compr Canc Netw* 2009;7 Suppl 5:S1-26.
56. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014;32:1941-67.
57. Trüeb RM. Chemotherapy-induced alopecia. *Semin Cutan Med Surg* 2009;28:11-4.
58. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Antiemesis Version 2.2014. Fort Washington: National Comprehensive Cancer Network; 2014.
59. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol* 2010;21 Suppl 5:v232-43.
60. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2011;29:4189-98.
61. Devriese LA, Witteveen PO, Marchetti S, Mergui-Roelvink M, Reyderman L, Wanders J, et al. Pharmacokinetics of eribulin mesylate in patients with solid tumors and hepatic impairment. *Cancer Chemother Pharmacol* 2012;70:823-32.
62. Kaufman PA, Yelle L, Cortes J, Perez EA, Awada A, Wanders J, et al. Effect of age on tolerability and efficacy of eribulin and capecitabine in patients with metastatic breast cancer treated in study 301. *Cancer Res* 2013;73(24 Suppl):Abstract #P3-13-04.