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ORIGINAL RESEARCH

Economic evaluation of eribulin as second-line treatment for metastatic breast cancer in South Korea

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Background: Metastatic breast cancer (MBC) is associated with poor prognosis, particularly for those patients with human epidermal growth factor receptor (HER2)-negative tumor. Similar to the rest of the world, treatment options are limited in South Korea following first-line chemotherapy with anthracyclines and/or taxanes. This study examined the cost-effectiveness and cost-utility of eribulin in South Korean patients with HER2-negative MBC who have progressed after usage of at least one chemotherapeutic regimen for advanced disease (second-line therapy).

Methods: A partition survival model was developed from the perspective of the South Korean health care system. The economic impact of introducing eribulin as second-line therapy for HER2-negative MBC was compared to that of capecitabine and vinorelbine. The analysis estimated incremental cost per life-year (LY), that is, cost-effectiveness, and cost per quality-adjusted life-year (QALY), that is, cost-utility, of eribulin for management of HER2-negative MBC in South Korea. The model accounted for overall survival, progression-free survival, drug costs, grade 3/4 adverse events, and health care utilization. Deterministic and probabilistic sensitivity analyses were performed to identify uncertainty in the results of the economic evaluation.

Results: Second-line eribulin was associated with greater benefits in terms of LY and QALY, compared to capecitabine and vinorelbine. The incremental cost-effectiveness ratio was ₩10.5M (approximately USD 9,200) per LY, and the incremental cost-utility ratio was ₩17M (approximately USD 14,800) per QALY in the basecase analysis. The incremental cost-utility ratio ranged from ₩12M (USD 10,461) to ₩27M (USD 23,538) per QALY in the deterministic sensitivity analysis. In the probabilistic sensitivity analysis, >99% of the simulations were below ₩50M (USD 42,300), and the lower and upper 95% confidence intervals were ₩3M (USD 2,600) and ₩24M (USD 20,900) per QALY, respectively.

Conclusion: There currently exist a limited number of treatment choices for women with HER2-negative MBC. Eribulin is a cost-effective option for second-line therapy in South Korea and should be added to the current indications for reimbursement.

Keywords: eribulin, metastatic breast cancer, cost-utility, economic analysis

Introduction

Women presenting with locally advanced or metastatic breast cancer (LABC/MBC) have a poor prognosis, with <25% surviving beyond 5 years.[1,2] Though therapeutic options for patients with human epidermal growth factor receptor (HER2)-positive MBC generally consist of several lines of single-agent or combination chemotherapy, options are particularly limited for women with HER2-negative tumor, which is associated with a poor prognosis. Recent data from the Korean Breast Cancer Registry show that ~75% of women who received surgery for breast cancer had the HER2-negative subtype.[3]

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Eribulin is a chemotherapy drug belonging to the halichondrin class of drugs that has a different mode of action compared to the existing chemotherapies. Eribulin is licensed as a third-line MBC drug and its label is recently expanded to include second line HER-2 negative MBC as well.[4,5]

Study 301 established the safety and efficacy of eribulin as second-line chemotherapy for patients with MBC who previously received treatment with an anthracycline and a taxane.[6] This was a multicenter, Phase III, open-label, randomized, two-arm study conducted in 1,102 patients (554 eribulin, 548 capecitabine) with LABC/MBC. Patients were prestratified according to their geographical region and HER2 status and then randomized in a 1:1 ratio to receive either eribulin or capecitabine. Eribulin was administered as an intravenous infusion of 1.23 mg/m^2 over 2–5 minutes on days 1 and 8 of a 21-day cycle. Exactly 1,250 mg/m^2 of capecitabine was administered orally twice daily in two equal doses on days 1–14, every 21 days. In a prespecified subgroup analysis, HER2-negative patients (~70% of randomized patients) treated with eribulin had significantly longer overall survival (OS) (15.9 months) than those who received capecitabine (13.5 months) (P=0.030).[7]

Halaven is currently reimbursed for patients with LABC/MBC who have previously received at least two chemotherapies in Korea. In line with the new approval label, this study examines the cost-utility of introducing eribulin following one prior chemotherapy (FOPC) for HER2-negative MBC in Korea, focusing on the patient population where eribulin was observed to provide the greatest clinical benefit. The primary economic endpoints were incremental cost per quality-adjusted life-year (QALY) supported by incremental cost per life-year (LY).

Methods

Economic perspective and patient population

A partition survival model was constructed from the perspective of the South Korean health care system to examine the cost-utility of introducing eribulin as second-line chemotherapy for HER2-negative LABC/MBC.

In the economic model, the eribulin comparator mix consisted of capecitabine and vinorelbine (cape/vin), with 50% of patients assumed to be treated with each agent. In comparison to the Study 301 design, vinorelbine was added to the treatment mix in order to reflect as accurately as possible the current clinical practice, since capecitabine and vinorelbine are the most widely used monotherapies in South Korea based on the expert opinion (Nielsen Korea, unpublished data, 2014). A 50%/50% split in the utilization between treatments was assumed, since no local market share data were available. In the absence of comparative clinical data for vinorelbine versus eribulin or capecitabine in the specific patient population, vinorelbine was assumed to have equal efficacy to capecitabine based on Study 301. The hazard ratios for eribulin relative to capecitabine in Study 301 (HER2-negative patients, second-line treatment only) were 0.75 for OS (95% confidence interval [CI]: 0.60, 0.92) and 0.86 for progression-free survival (PFS) (0.69, 1.08). The hazard ratios for eribulin versus vinorelbine were assumed to be the same.

The economic endpoints were incremental cost per LY and incremental cost per QALY. Ethical approval for this study was not sought as this was an economic evaluation. It was however, previously obtained for the clinical trial which has been published separately.

Health states and treatments

The partition survival model included three health states: stable disease, progressive disease, and death. Patients entered the model in stable disease and switched to progressive disease or death. Primary therapy was assumed to be administered until tumor progression and secondary therapy after progression for a total treatment duration of maximum up to 8 months. This average duration of chemotherapy (7.35 months in Western Europe, rounded to 8 months – Western European data used as a proxy for South Korea, since no local data were available) was based on CancerMpact MBC data from Kantar Health,[8] and included second-line treatment and beyond. The transition of patients between health states was based on data from Study 301. The partition in the current model was directly based on the Kaplan–Meier survivor function from patient-level data for the subgroup of HER2-negative patients in Study 301 who received second-line therapy.

Drug dose calculations were based on individual drug summary product characteristics. Wastage based on body surface area distribution was included in the analysis, and 10% dose rounding was employed for the smallest dose. Treatment cycles of 21 days[9] were converted to 30.42-day (1-month) cycles for the ease of calculations (hereafter referred to as months).

Efficacy measures and survival extrapolation

The model considered OS and PFS data from Study 301. In the HER2-negative subgroup of patients in Study 301 who received eribulin or capecitabine as second-line therapies, survival was ~12% for eribulin and 7% for

capecitabine at the end of the 5-year follow-up period. A 5-year model horizon was, therefore, chosen to avoid the uncertainty created by long-term extrapolation of OS and PFS, while it was sufficient duration to capture most LY benefits. The Kaplan–Meier survivor function, which was based on patient-level data, was found to be sufficient for estimating the survival benefits of the two arms. Since the area under the curve was used in the calculations, the mean differences of efficacy endpoints between treatment groups were examined.

Costs

Total costs in this economic analysis comprised drug costs, administration costs, direct medical costs, and adverse event costs. The costs of the chemotherapeutic agents (drug and administration) are listed in Table 1. Direct medical costs or health care utilization costs were split into preprogression, postprogression, and end-of-life costs. Postprogression costs were applied after progression, and end-of-life costs were applied in the last 0.5 months of life. These costs are presented in Table 2. A micro-costing analysis of resource utilization for AE treatments and disease management pre- and postprogression was performed, which was based on a previously published methodology.[10]

All direct medical costs and administration costs, including the drug costs, were obtained from the National Health Insurance (NHI) lists 2014 and 2015.[11] Costs were not inflated. A discounting rate of 5% per year was applied according to South Korean guidelines.[12] Other model assumptions were further tested in sensitivity analyses (SA).

Adverse events

The model considered grade 3/4 AEs that were observed in at least 5% of patients in Study 301. These AEs were used for the disutility analysis. For the costs associated with AEs, a clinician-based validation was performed to ensure that all important AEs were considered; febrile neutropenia was, therefore, included, even though it had <5% prevalence in Study 301.[13]

Consistent with other economic evaluation models and without evidence to suggest the contrary, the incidence of AEs was assumed to be constant. The AE data collected in Study 301 were based on the entire duration of the treatment in the clinical trial. Hence, a formula for cycle transformation was applied to the cost component only in order to generate the monthly prevalence of AEs. The incidences of hospitalization and treatment per AE were collected from Study 301 and used to calculate the costs associated with management

Table 1 Monthly treatment costs (₩) of patients on MBC treatments FOPC

Drug name	Dosage and scheduling					Market share in treatment arms		Drug utilization based on BSA distribution			
	Dosage form	Dose (mg/m^2)	Number of doses per cycle	Cycle length (days)	Number per cycle	Cape + vin arm (%)	TPC arm* (after FOPC) (%)	Total dose per treatment (mg)	Drug cost per treatment cycle (21–28 days)	Drug costs per cycle (1 month)	Administration costs
Eribulin arm											
Eribulin	IV	1.23	2	21	1.45			1.68	761,559	1,103,807	13,152
Capecitabine + vinorelbine arm											
Capecitabine	Oral	2,500	14	21	1.45	50.0	23.6	3,409.40	190,857	267,628	11,708
Vinorelbine	IV	30	3	21	1.45	50.0	32.6	41.41	341,005	494,254	19,728
TPC arm (FOPC)											
Gemcitabine	IV	1,250	2	21	1.45	0.0	24.6	1,705.18	497,366	720,885	26,928
Taxanes											
Docetaxel	IV	100	1	21	1.45	0.0	5.3	136.87	653,836	947,674	6,640
Paclitaxel	IV	90	3	28	1.09	0.0	13.9	123.23	726,363	789,596	4,980
Average cost of comparator arm										385,441	15,718
Average cost of chemotherapy mix FOPC										563,729	16,863

Note: *Source: Based on clinical trial distribution in the TPC arm (EMBRACE trial).[1]
Abbreviations: FOPC, following one prior chemotherapy; IV, intravenous; MBC, metastatic breast cancer; BSA, body surface area; TPC, treatment of physician's choice.

Table 2 Health care resource utilization in MBC patients FOPC (costs in ₩)

Preprogression costs			Postprogression costs			End-of-life costs	
Type of cost	**Monthly utilization**	**Cost per month**	**Type of cost**	**Monthly utilization**	**Cost per month**	**Type of cost**	**Cost for 2 weeks**
Medical oncologist – first appointment	1.00	17,910	Medical oncologist-follow-up	1.96	27,205	Hospital/ medical institution	4,213,038
Medical oncologist – follow-up	1.62	22,486	GP home visit	1.00	44,560	Total	4,213,038
Community nurse home visit	1.00	44,560	Psychotherapist	1.00	14,092		
Complete blood count	1.85	10,606	Community nurse home visit	1.00	44,560		
Blood chemistry panel, liver function test, CT scan	1.71	51,018	Complete blood count	1.83	10,491		
Urea and electrolytes	0.53	49,303	Blood chemistry panel, liver function test, CT scan, urea and electrolytes	1.78	53,106		
Total		195,883	Total		194,014		

Note: Data from National Health Insurance Services: South Korea.[11]
Abbreviations: CT, computed tomography; FOPC, following one prior chemotherapy; GP, general practitioner; MBC, metastatic breast cancer.

of AEs. Health care utilization for the treatment of AEs was based on physician input. The costs associated with these treatments were obtained from the NHI cost database, 2014. Hospitalization costs were applied for AEs using a length of stay of 7.15 days and cost per hospitalization of ₩253,163 (USD 221), based on the World Health Organization CHOosing Interventions that are Cost-Effective (CHOICE) database (2008 data),[14] resulting in a unit cost of ₩300,931 (USD 262) after applying inflation at 2.5% for 7 years.[15]

Utilities and quality of life

Health-related quality of life (HRQOL) data were collected in Study 301 and have been presented in Cortes et al.[13] HRQOL data obtained using Quality of Life Questionnaire Cancer 30 in Study 301 were mapped to EuroQoL 5 Dimension Questionnaire (EQ-5D)-derived utility scores using a previously published and validated regression algorithm.[16] The elicited utilities are presented in Hudgens et al.[17] The resulting EQ-5D scores were used to infer utilities for the following states: baseline, tumor response, and progression.

Since the health states of the HRQOL analysis did not reflect the states considered in the economic evaluation, further post hoc calculations needed to be made. To determine the utility for the stable disease state, the incremental utility of tumor response was multiplied by the objective response rate obtained in Study 301. To determine the utility of the progression state, the EQ-5D utilities of the total study population were used to avoid a potential selection bias, since the observed Quality of Life Questionnaire Cancer 30 scores in Study 301 were only for eribulin and capecitabine arms (Table 3). Furthermore, the annual disutility of AEs, estimated using independent linear mixed-effects models, was subtracted from the product of tumor response and objective response rate. The utility levels thus calculated and used in the model are presented in Table 4.[17,18]

Table 3 EQ-5D utilities

Health states	Eribulin utility scores (SD)	Capecitabine utility scores (SD)	Total study population scores (SD)
Baseline	0.704 (0.228)	0.691 (0.238)	0.697 (0.233)
Tumor response	0.780 (0.194)	0.783 (0.185)	0.782 (0.189)
Progression (per treatment arm)	0.705 (0.211)	0.651 (0.250)	0.679 (0.232)

Note: Data from Hudgens et al.[17,18]
Abbreviation: SD, standard deviation.

Table 4 Health state utilities used in the model

Health states	Eribulin	Capecitabine/ vinorelbine arm
PFS	0.717	0.715
Progression	0.695	0.695

Abbreviation: PFS, progression-free survival.

Sensitivity analyses

Deterministic SA and probabilistic SA (PSA) were conducted to identify uncertainty in the results of the economic analysis. The variables tested in the univariate deterministic SA included discounting rate, dose intensity, administration costs, direct health care costs for stable and progressive disease, secondary treatment costs, and utility level (Table 5). As the price of eribulin is a key variable, it was not incorporated into the SA but instead evaluated using a price acceptability curve.

A PSA was also developed using Monte Carlo simulations to create an incremental cost-effectiveness plane and a cost-effectiveness acceptability curve, in addition to determining the probability of cost-effectiveness, given a range of incremental cost-effectiveness ratio per QALY threshold. The PSA assessed first-order stochastic uncertainty related to the following variables: utility for each health state, costs (primary and secondary drug costs, administration costs), preprogression survival, and OS (generating postprogression survival) for both arms (Table 6).

Table 5 Deterministic sensitivity analysis: scenario presentation

Scenario presentation	Low	Basecase	High
Scenario 1: Benefits discounting rate	0.0%	5.0%	7.0%
Scenario 2: Costs discounting rate	7.0%	5.0%	0.0%
Scenario 3: Costs and benefits discounting rates	0.0%	5.0%	7.0%
Scenario 4: Dose intensity	70.0%	85.4%	100.0%
Scenario 5: Administration costs	20.0%	0.0%	–20.0%
Scenario 6: Direct health care costs of stable state	–20.0%	0.0%	20.0%
Scenario 7: Direct health care costs of progression state	–20.0%	0.0%	20.0%
Scenario 8: New line of treatment costs after progression	–20.0%	0.0%	20.0%
Scenario 9: Utility of stable state of eribulin	0.788	0.717	0.645
Scenario 10: Utility of progression state of eribulin	0.765	0.695	0.626
Scenario 11: Utility of stable state of capecitabine	0.643	0.715	0.786
Scenario 12: Utility of progression state of capecitabine	0.626	0.695	0.765

Results

Efficacy

The monthly partition is presented in Figure 1. The mean OS benefit over the 5-year horizon was of 21.75 months for eribulin and 17.13 months for cape/vin, with a mean difference of 4.61 months. The mean PFS benefit over the 5-year horizon was of 4.56 months for eribulin and 3.99 months for capecitabine, with a difference of mean 0.57 months.

Drug costs

Drug costs were ₩7,092,981 (USD 6,183) for eribulin versus ₩3,622,884 (USD 3,158) for cape/vin, with a difference of ₩3,470,098 (USD 3,025); 98% of this difference was due to primary drug costs. Other medical costs totaled ₩7,377,117 (USD 6,431) for eribulin and ₩6,823,025 (USD 5,948) for cape/vin, with a difference of ₩554,091 that was mainly due to improved survival in the eribulin arm. Overall, the analyses found a difference of ₩4,062,052 (USD 6,541) between eribulin and the cape/vin comparator. The total treatment costs are presented in Table 7.

Cost-effectiveness results

The benefits associated with eribulin compared to the cape/vin comparator were 1.81 LY versus 1.43 LY, with a

Table 6 Parameters evaluated in probabilistic sensitivity analysis

Parameters	Variables	Point estimate	Standard error	Distribution	Source
Utility	Baseline – eribulin	0.713	0.23	Beta	Trial QOL data
	Tumor response – eribulin	0.801	0.19	Beta	Trial QOL data
	Progression – eribulin	0.695	0.21	Beta	Trial QOL data
	Baseline – TPC	0.713	0.24	Beta	Trial QOL data
	Tumor response – TPC	0.808	0.19	Beta	Trial QOL data
	Progression – TPC	0.695	0.25	Beta	Trial QOL data
Costs	Primary, secondary therapy and administration drug cost		SD = ±20%	Normal	Assumption
Survival	Preprogression – eribulin	4.56	0.42	Normal	Mean based on the clinical trial Kaplan–Meier and SD based on clinical trial (based on restricted OS mean)
	Postprogression – eribulin	17.19	1.05	Normal	Mean based on the clinical trial Kaplan–Meier and SD based on clinical trial (based on restricted OS mean)
	Preprogression – TPC	3.99	0.45	Normal	Mean based on the clinical trial Kaplan–Meier and SD based on clinical trial (based on restricted PFS mean)
	Postprogression – TPC	13.15	0.95	Normal	Mean based on the clinical trial Kaplan–Meier and SD based on clinical trial (based on restricted OS mean)
Dose intensity		0.854	70%–100%	Beta	Assumption

Abbreviations: OS, overall survival; PFS, progression-free survival; QOL, quality of life; SD, standard deviation; TPC, treatment of physician's choice.

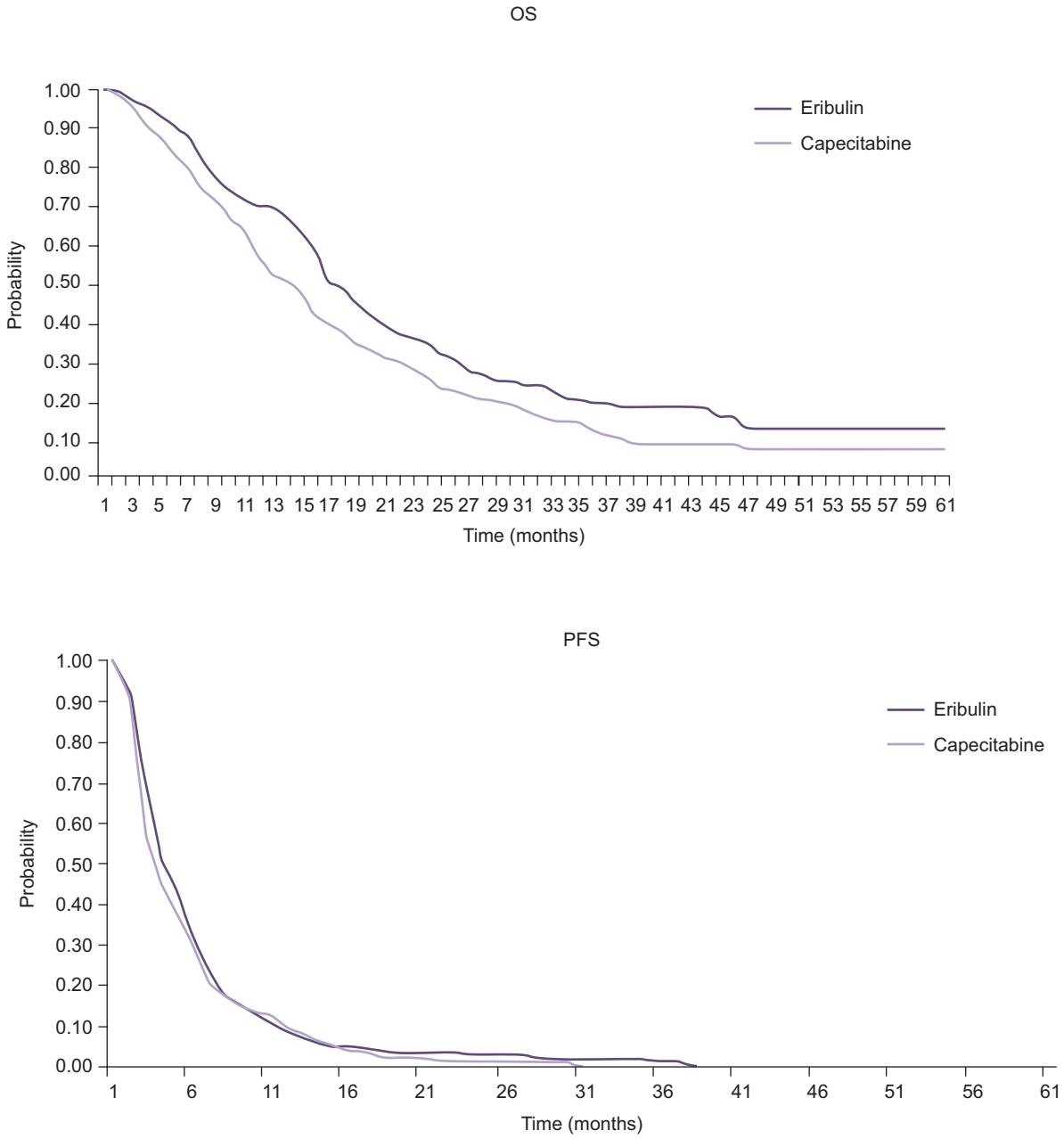

Figure 1 Monthly partition analysis.
Abbreviations: OS, overall survival; PFS, progression-free survival.

difference of 0.38 LY. The incremental cost-effectiveness ratio was calculated as ₩10,564,275 (USD 9,200) for eribulin versus cape/vin.

Cost-utility results

The benefits associated with eribulin compared to the cape/vin comparator were 1.18 QALY versus 0.94 QALY, with a difference of 0.24 QALY. The incremental cost-utility ratio was calculated and found to be ₩16,898,483 (approximately USD 14,800) for eribulin versus cape/vin.

Since eribulin is indicated for life-threatening MBC, at a threshold of ₩50,000,000 (USD 42,300) per QALY,[17] eribulin is likely to be a cost-effective treatment FOPC for HER2-negative MBC patients. The price acceptability curve is presented in Figure 2 and shows that the treatment is still cost-effective at different price levels.

Sensitivity analyses

Results of the deterministic SA are presented with a tornado graph in Figure 3. The univariate scenario analyses

demonstrated that the cost-utility of eribulin is sensitive to the utility level per health state and the dose intensity, but less sensitive to other variables.

The PSA found that the cost per LY ranged from ₩9M (USD 7,800) to ₩10M (USD 8,700), with an average of ₩9.1M (USD 7,900). The cost per QALY ranged from ₩13M (USD 11,300) to ₩14M (USD 12,200), with an average at ₩13.5M (USD 11,700). When looking at the probability of being under a certain threshold, 50% of the cost per QALY estimates were below ₩12.6M (USD 11,000), 75% were below ₩16.9M (USD 14,700), 90% were below ₩21.2M (USD 18,500), and 99% were below ₩35M (USD 30,500).

Table 7 Total treatment costs

Treatment	Eribulin	Capecitabine/ vinorelbine arm	Difference
Main therapy costs	4,897,727	1,502,572	3,395,155
Main therapy administration costs	58,357	48,695	9,662
Post-therapy – TPC costs	2,074,833	2,011,448	63,385
Post-therapy administration costs	62,065	60,169	1,896
Total drug costs	**7,092,981**	**3,622,884**	**3,470,098**
Direct medical costs			
Stable state costs	869,156	763,613	105,543
Progression state costs	3,060,246	2,364,651	695,595
End-of-life costs	3,447,715	3,694,761	–247,046
Total direct medical costs	**7,377,117**	**6,823,025**	**554,091**
Adverse events costs	57,626	19,764	37,863
Total costs	**14,527,724**	**10,465,673**	**4,062,052**

Abbreviation: TPC, treatment of physician's choice.

One per 1,000 (0.1%) was above ₩50M (USD 42,300), the threshold used for this model. The lower and upper 95% CIs were ₩3M (USD 2,600) and ₩24M (USD 20,900) per QALY, respectively. The cost-effectiveness plane is shown in Figure 4.

Discussion

MBC remains a devastating disease with poor prognosis and limited treatment options. Eribulin has emerged as a safe and effective treatment for women with the disease, particularly those with the HER2-negative subtype.

The clinical data for the economic evaluation was obtained from the Phase III clinical trial data of eribulin against capecitabine. Given the maturity of the clinical data, no survival extrapolation was necessary. Hence, the partition in the current model was based on the Kaplan–Meier survivor function from patient-level data for the subgroup of HER2-negative patients in Study 301 who received eribulin or capecitabine FOPC.

Most of the costs used in the model (ie, drug acquisition costs, administration costs, AE management costs) were obtained from local data sources like the NHI Service and World Health Organization databases. The analysis excluded patients' out-of-pocket expenses, carers' costs, and lost productivity derived costs, since the analysis was conducted from the South Korean payer perspective.

The incremental cost-utility ratio of eribulin compared with capecitabine and vinorelbine was calculated as the ratio of the difference in cost to the difference in QALYs. Consistent with the economic evaluations of eribulin for second- and third-line therapy performed for other payer

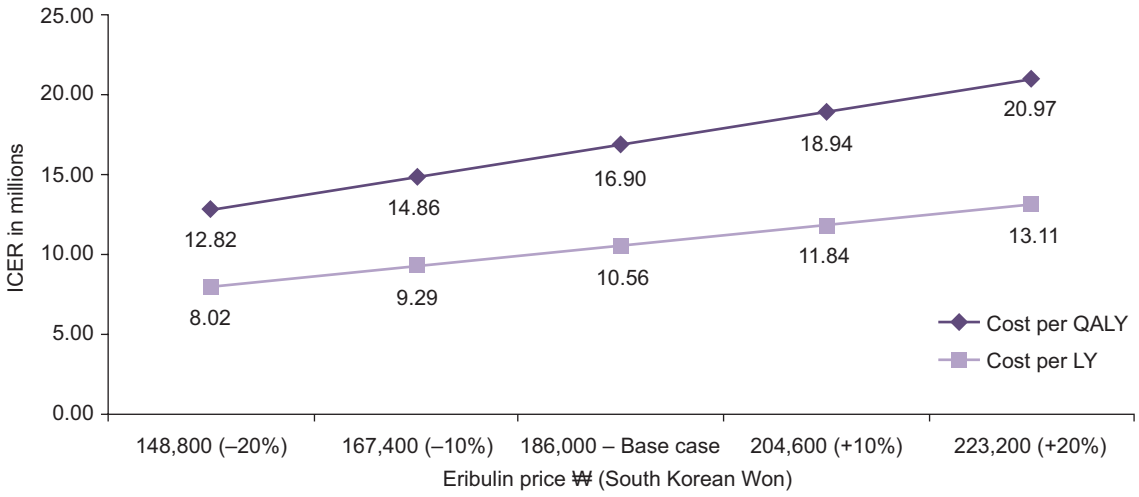

Figure 2 Cost acceptability curve.
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.

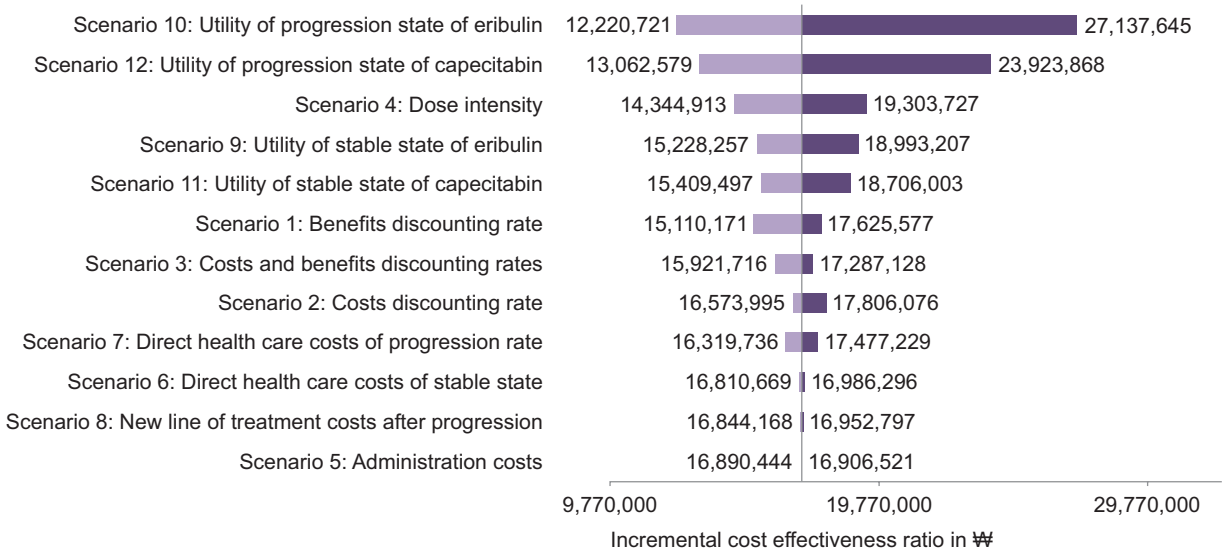

Figure 3 Deterministic sensitivity analysis results: tornado diagram.

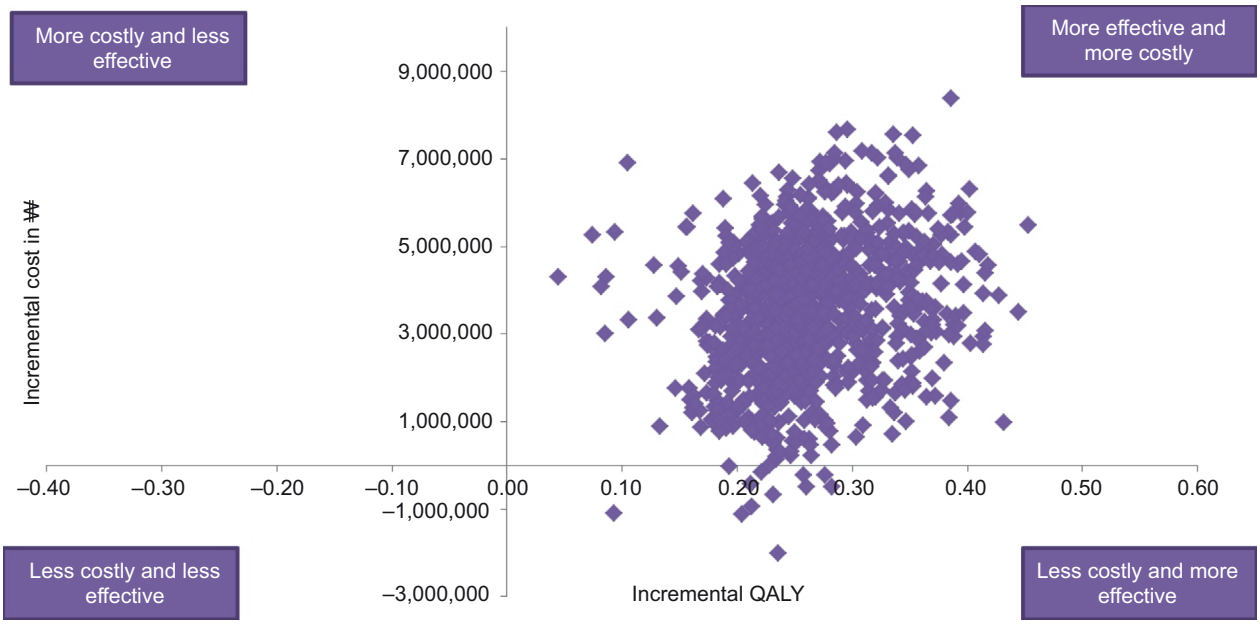

Figure 4 Cost-effectiveness plane.
Abbreviation: QALY, quality-adjusted life-year.

perspectives,[19] this analysis shows that eribulin as second-line therapy would be a cost-effective option in South Korea even against generic and less-expensive treatments such as capecitabine and vinorelbine.

The SA were highly consistent with the basecase analysis. The results of the PSA showed that the risk of introducing eribulin FOPC at the current price is low, as over 99% of the simulations were below ₩50,000,000 (USD 42,300) per QALY.

Limitations

Several limitations of this analysis should be noted. Most estimates used in the model were derived from a subgroup of patients from Study 301. However, stratified analysis of HER2-negative patients was prespecified as part of the trial design and almost 70% of the participants had HER2-negative disease; the CIs associated with the effect estimates in this subgroup, therefore, reflect good precision.[7]

Conclusion

The time horizon in the model was bounded at 5 years, and therefore, the analyses do not reflect the costs associated with survival beyond that period, which may apply to ~10% of the patients in our model. However, we believe the 5-year model horizon appropriately balances the risk of longer extrapolation with greater uncertainty while capturing the majority of survival benefits for most patients.

Most importantly, vinorelbine was not included in Study 301, and thus, estimates for the efficacy of vinorelbine as second-line therapy were not available. However, because this drug is now commonly used as second-line therapy, it was felt important to include it in our analysis, and therefore, a conservative estimate of its efficacy was used based on the 301 trial. By adding vinorelbine to the comparator mix, we were able to make comparisons that reflect the current treatment patterns, which is an important goal of cost-effectiveness analysis.

There currently exist only a limited number of second-line treatment choices for women with HER2-negative MBC. Second-line eribulin is an important and cost-effective addition to the treatment mix in South Korea.

Acknowledgments

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Disclosure

Tremblay G was working for Eisai Inc. at the time of development of analysis. The authors report no other conflicts of interest in this work.

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