

Comprehensive prognostic prediction of metastatic breast cancer treated with eribulin using blood-based parameters and ratio

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Abstract. Eribulin is widely used to treat metastatic breast cancer (BC). Higher neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are associated with higher mortality in several cancer types. However, the association between BC prognosis and peripheral immune status remains controversial. In the present study, the relative effects of NLR and PLR on survival in patients with metastatic BC were quantified and their clinical prognostic value was evaluated. This retrospective study included 156 patients with metastatic BC who received eribulin monotherapy at Saitama Medical University International Medical Center. Clinicopathological features were examined (peripheral blood findings and biochemical liver and kidney function test results) and univariate and multivariate analyses were conducted of the overall survival (OS). The 156 patients treated with eribulin had a median follow-up duration of 18.3 months. Before eribulin treatment, patients with absolute lymphocyte counts (ALC) $>1,500/\mu\text{l}$, NLR <3.0 , and PLR <150 had significantly longer OS than those with lower ALC, and higher NLR and PLR (median OS, 25.5 vs. 15.5 months; $P<0.01$; 20.3 vs. 13.6 months, $P<0.01$; and 29.2 vs. 14.8 months; $P<0.001$, respectively). Patients with anemia [hemoglobin (Hb) $<10\text{ g/dl}$] or liver dysfunction [albumin-bilirubin (ALBI) grade 2/3]

had significantly shorter OS than those without ($P<0.001$, respectively). Multivariate analysis revealed low ALBI grade ($P<0.001$), high Hb ($P<0.01$) and low PLR ($P<0.05$) as independent factors of longer OS after eribulin administration. Low PLR, anemia and liver dysfunction might be factors associated with prolonged OS in patients with metastatic BC on eribulin therapy, which could be clinically useful, as their evaluation requires neither new equipment nor invasive testing.

Introduction

Eribulin, a synthetic analog of halichondrin B and non-taxane microtubule dynamics inhibitor (1), is a U.S. Food and Drug Administration-approved drug with proven clinical efficacy and acceptable adverse events in patients with metastatic breast cancer (MBC) (2-4).

MBC has numerous treatment options, but treatment selection can be challenging because patient response can vary for the same treatment. In the treatment of MBC, for prolonging the overall response and progression-free survival (PFS), patient groups showing efficacy can be identified; however, clear indicators to identify patient groups with prolonged overall survival (OS) among those with MBC undergoing eribulin therapy are lacking. Various studies have been conducted to identify predictors of eribulin efficacy in patients with MBC. Higher neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been reported to be associated with higher mortality in several cancer types (5-8). High absolute lymphocyte count (ALC), PLR and low NLR are predictors of survival in patients with BC treated with eribulin (9-12). However, the global phase 3 EMBRACE trial suggested that NLR is a general prognostic factor for improved OS, and ALC is an independent predictor of OS, in eribulin-treated patients (10). However, the association between peripheral immune status and MBC prognosis is controversial.

Liver function is assessed according to the Child-Pugh (C-P) system. This system was originally developed to predict the prognosis of patients being treated for portal hypertension and variceal bleeding associated with cirrhosis (13,14). However, the C-P classification is not statistically constructed owing to concerns regarding subjective and confounding

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Abbreviations: ALC, absolute lymphocyte count; Alb, albumin; ALBI, albumin-bilirubin; BC, breast cancer; C-P, Child-Pugh; ER, estrogen receptor; Hb, hemoglobin; HER2, human epidermal growth factor type 2; MBC, metastatic breast cancer; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PR, progesterone receptor; OS, overall survival; TBil, total bilirubin; TN, triple negative

Key words: BC, ALC, NLR, PLR, ALBI score, eribulin

factors, such as hepatic coma, ascites and albumin (Alb). Previously, a new liver function assessment tool, Alb-bilirubin (ALBI) grading, consisting only of Alb and total bilirubin (TBil), has been proposed (15,16). Compared with the C-P score, the ALBI score is a more appropriate assessment as it only uses objective parameters (Alb and TBil).

In the present study, the relative effect of NLR and PLR on survival was quantified in patients with recurrent/stage IV BC and the clinical significance of NLR, PLR and other clinicopathologic factors (including liver and kidney function tests) on the prognostic value was evaluated.

Materials and methods

Patients. In the present study, 156 patients with recurrent/stage IV BC disease who received eribulin monotherapy as any treatment line at Saitama Medical University International Medical Center, from April 2011 to March 2021, were enrolled. In all patients, metastases were confirmed through diagnostic radiography using computed tomography, whole-body bone scintigraphy, or 2-[(18)F]-fluoro-2-deoxy-D-glucose positron emission tomography. Patients with any type of simultaneous metastatic cancer were excluded. Clinicopathological factors and clinical outcome data were retrospectively extracted from the medical records. Patients received eribulin at a dose of 1.4 mg/m² on days one and eight of a 21-day cycle. The dose was reduced, or the treatment postponed when toxicity developed, and treatment cessation was decided based on confirmed disease progression or intolerable toxicity.

Histological assessment. For the pathological examination of the tumors, the surgically resected specimens were fixed in 10% formalin. The tissues were embedded on paraffin wax blocks. The paraffin blocks were cut to 3–4 μ m sections for hematoxylin-eosin (H&E) and immunohistochemical staining at room temperature. To determine the histologic tumor type, H&E staining of sections of the tumor specimens was performed. The expression statuses of estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor type 2 (HER2), and Ki67 labeling Index were assessed by immunohistochemical staining. The following monoclonal antibodies were used for immunohistochemistry: ER (SP1; cat. no. 790-4324, prediluted); PR (1E2; cat. no. 790-2223, prediluted), HER2 (4B5; cat. no. 790-2991, prediluted, all from Roche Tissue Diagnostics; Roche Diagnostics, Ltd.) and Ki-67 (MIB-1; cat. no. M7240, ready-to-use; Dako; Agilent Technologies, Inc.). Images were captured using a light microscope (Olympus Corporation). According to ASCO/CAP guideline (17), ER and PgR positivity was determined when $\geq 1\%$ of the nuclei in the tumor were stained using immunohistochemistry. According to ASCO/CAP guideline (18–20), HER2 positivity was defined as an immunohistochemical score of 3+ or a positive result on fluorescence in situ hybridization. According to the expression of ER, PR, HER2 and Ki67, patients were divided into the triple-negative (TN) or non-TN groups, including Luminal A or B, Luminal HER2 and HER2 types.

Blood sampling and evaluation of predictive factors. On the same day or just before the start of the first cycle of eribulin

administration, whole blood samples and baseline data for blood-based parameters were obtained. The cutoff values for the baseline ALC, NLR, and PLR were set at 1,500/ μ l (10,11), 3.0 (9,10,21) and 150 (22,23), respectively.

ALBI grading was used to assess the liver function, with ALBI scores and ALBI grades defined as follows: $[\log_{10} \text{bilirubin } (\mu\text{mol/l}) \times 0.66] + [\text{Alb } (\text{g/l}) \times (-)0.085]$ (grades 1, 2, 3= ≤ -2.60 , > -2.60 to -1.39 , and > -1.39 , respectively) (14).

Statistical analysis. Unless otherwise noted, data are presented as percentage (%) or the mean. The relationship between OS and all clinical factors was evaluated using univariate Cox proportional hazards regression models. Candidate predictors with $P < 0.05$ in the univariate analysis were included in the multivariate analysis.

OS for each group was calculated from the date of the start of the first cycle of eribulin administration to the date of death from any cause or the date of the last follow-up. OS was calculated using the Kaplan-Meier method, and patient subgroups were compared using the log-rank test. All statistical analyses were performed using EZR version 1.52 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (24), which is a graphical user interface for R version 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.

Results

Characteristics of patients and tumors. The clinicopathological characteristics of the 156 patients included in the present study are Listed in Table I. Tumors were mainly ductal (87.8%) or lobular (5.7%) invasive carcinomas, while 41 (26.3%) were those of TN disease. At the time of eribulin administration, 127 patients (81.4%) had visceral metastases, of which 98 (62.8%) had liver metastases. The mean time from confirmation of metastasis to start of eribulin administration, mean time to treatment failure of eribulin, and median follow-up duration for the 156 patients were 24.0, 6.0 and 18.3 months, respectively (Table II). Of the patients treated with eribulin, 44.23% ultimately received a reduced dose (Table II). Tumor subtypes were classified as TN (ER, PR, HER2-negative) and non-TN, including luminal (ER-positive, PR-positive, HER2-negative); luminal HER2 (ER-positive, PR-PR-positive or negative, HER2-positive), and HER2 (ER-negative, PR-negative, HER2-positive) types, with proportions of 26.3 and 73.7%, respectively (Table I).

Prognostic factors. As demonstrated in Table III, before eribulin administration, OS was not affected by age, subtype, or renal function decline, but patients with anemia (hemoglobin (Hb) < 10 g/dl or liver dysfunction (ALBI grade 2 or 3) had significantly shorter OS than those without it ($P < 0.001$, respectively).

As revealed in Fig. 1A, before eribulin administration, patients with ALC $> 1,500/\mu$ l had significantly longer OS than those with lower ALC (median OS, 25.5 vs. 15.5 months; $P < 0.01$). Patients with NLR < 3.0 and PLR < 150 had significantly longer OS than those with higher NLR and PLR [median OS, 20.3 vs. 13.6 months ($P < 0.01$); 29.2 vs. 14.8 months ($P < 0.001$); respectively] (Fig. 1B and C).

Table I. Patient characteristics.

Variable	Total number (n=156)	Percentage, %
Median age, years (range)	57.1 (29-84)	
<70	132	84.6
>70	24	15.4
Histology		
^a IDC	137	87.8
^b ILC	9	5.7
Others	10	6.4
Visceral metastases	127	81.4
Liver metastases	98	62.8
^c HER2 status		
Negative	128	82.1
Positive	26	16.7
Unknown	2	1.3
^d ER status		
Negative	55	35.3
Positive	101	64.7
^e PR status		
Negative	97	62.2
Positive	59	37.8
Triple (HER2/ER/PR) negative	41	26.3
Mean of baseline ^f WBC, μ l (range)	5,770 (2,550-13,100)	
Mean of baseline ^g ANC, μ l (range)	3,776 (1,238-10,461)	
Mean of baseline ^h Hb, g/dl (range)	12.1 (7.4-16.0)	
<10	15	9.6
>10	141	90.4
Mean of baseline platelet, μ l (range)	255,000 (82,000-653,000)	
Mean of baseline ⁱ ALC, μ l (range)	1434 (439-6,255)	
<1,500	94	60.3
>1,500	62	39.7
^j NLRs	3.0	
<3.0	102	65.4
>3.0	54	34.6
^k PLRs	204.4	
<150	59	37.8
>150	97	62.2
^l ALBI grade		
1	49	31.4
2, 3	40	25.6
N/A	67	42.9
^m eGFR		
<60	13	8.3
>60	135	86.5
ⁿ CRP		
<0.3	49	31.4
>0.3	40	25.6
^m N/A	67	42.9

^aIDC, invasive ductal carcinoma; ^bILC, invasive lobular carcinoma; ^cHER2, Human epidermal growth factor receptor-2; ^dER, Estrogen receptor; ^ePR, Progesterone receptor; ^fWBC, white blood cell count; ^gANC, absolute neutrophil count; ^hHb, hemoglobin; ⁱALC, Absolute lymphocyte count; ^jNLRs, neutrophil-to-lymphocyte ratios; ^kPLRs, platelet-to-lymphocyte ratios; ^lALBI, albumin-bilirubin; ^meGFR, estimated Glomerular Filtration; ⁿCRP, C-reactive protein; ^mN/A, not applicable.

Table II. Eribulin administration.

Variable	Total number (n=156)	Percentage, %
Median follow-up time	18.3 (1.6-76.1)	
Time to eribulin administration for ^a MBC	24.0 (0-114)	
Time to treatment failure	6.0 (1-68)	
Eribulin dose reduction level		
0	87	55.77
-1	53	33.97
-2	16	10.26

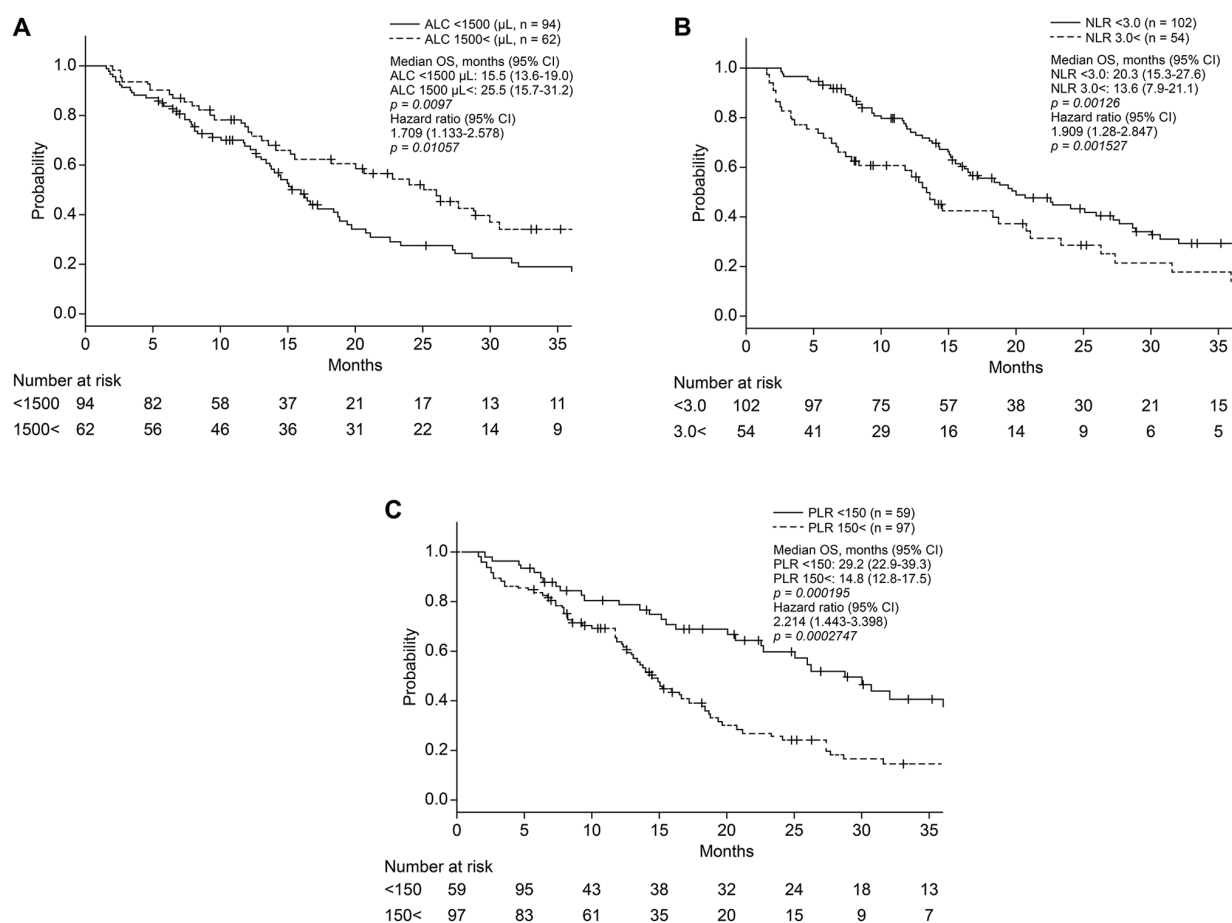
^aMBC, metastatic breast cancer.

Figure 1. (A) OS based on absolute lymphocyte count. Patients with a higher ALC had a significantly longer OS compared with those with lower ALC (median OS, 25.5 vs. 15.5 months, respectively; $P=0.0097$). (B) OS based on the NLR. Patients with a lower NLR had a significantly longer OS compared with those with a higher NLR (median OS, 20.3 vs. 13.6 months, respectively; $P=0.00126$). (C) OS based on PLR. Patients with a lower PLR had a significantly longer OS compared with those with higher PLR (median OS, 29.2 vs. 14.8 months, respectively; $P=0.000195$). OS, overall survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

As shown in Table III, there were no significant differences in OS based on age and subtypes such as ER/HER2. Multivariate analysis demonstrated that high ALBI grade ($P<0.001$) was an independent predictor of shorter OS after eribulin treatment, regardless of the presence or absence of liver metastases. Furthermore, high Hb ($P<0.01$), and low PLRs ($P<0.05$) were independent factors that predicted longer OS after eribulin administration (Table III).

Discussion

While it has become clear that the tumor microenvironment significantly affects cancer cells and contributes to the formation of cancer-specific properties (25-27), it is interesting to examine its impact on the systemic immune environment. In the present retrospective study, the baseline blood-based clinical parameters were evaluated and PLR as a predictor of

Table III. Univariate and multivariate analyses for the overall survival.

Variable		Univariate analysis		Multivariate analysis	
		^a HR (95% CI)	P-value	HR (95% CI)	P-value
Age	<70	1.144 (0.6474-2.023)	0.6425		
Liver metastases	Positive	1.342 (0.8895-2.026)	0.168		
^b ER status	Negative	1.224 (0.8137-1.841)	0.332		
^c HER2 status	Positive	0.6051 (0.3369-1.087)	0.0927		
Subtype	^d TN	1.202 (0.7716-1.872)	0.416		
^e ALBI grade	2, 3	2.575 (1.589-4.784)	<0.001	2.895 (1.602-5.234)	<0.001
^f eGFR	<60	1.359 (0.7231-2.555)	0.3406		
^g Hb	<10	4.029 (2.186-7.427)	<0.001	2.785 (1.329-5.836)	<0.01
^h CRP	Positive	3.004 (1.971-4.578)	<0.001	1.629 (0.7797-3.403)	0.19430
ⁱ NLRs	>3.0	1.909 (1.28-2.847)	<0.01	1.311 (0.6768-2.538)	0.42250
^j ALC	<1,500	1.709 (1.133-2.578)	<0.05	1.020 (0.5063-2.055)	0.95570
^k PLRs	>150	2.214 (1.443-3.396)	<0.001	2.124 (1.157-3.898)	<0.05

^aHR, Hazard ratio; ^bER, Estrogen receptor; ^cHER2, Human epidermal growth factor receptor-2; ^dTN, triple negative; ^eALBI, albumin-bilirubin; ^feGFR, estimated Glomerular Filtration; ^gHb, hemoglobin; ^hCRP, C-reactive protein; ⁱNLRs, neutrophil-to-lymphocyte ratios; ^jALC, Absolute lymphocyte count; ^kPLRs, platelet-to-lymphocyte ratios; CI, confidence interval.

OS in patients with MBC treated with eribulin was confirmed. Additionally, high degrees of anemia (Hb <10 g/dl) and liver dysfunction (ALBI grade 2 or 3) were significantly associated with impaired OS in patients with MBC treated with eribulin. The present study is the first one, to the best of the authors' knowledge, to have comprehensively analyzed the peripheral blood parameters and ratios in patients with MBC treated with eribulin and revealed relevant predictors of OS. Predictors related to systemic immune response and hepatic reserve in the treatment of BC have not been considered in clinical practice.

Eribulin induces the remodeling of the tumor vasculature and reoxygenation in patients with advanced BC and decreases the levels of transforming growth factor-beta (TGF- β), which is typically associated with hypoxic conditions (28). A retrospective analysis reported decreased expression of programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1), and forkhead box P3 (FoxP3) and increased infiltrating CD8⁺ T cell levels in eribulin responders (29). As PD-L1, FoxP3 and TGF- β have potent immunosuppressive effects, eribulin may have exerted an immunomodulatory effect mediated through vascular remodeling. Therefore, the analysis of the present study focused on peripheral immunological biomarkers and organ reserve associated with the efficacy of eribulin.

MBC treatment aims to maintain quality of life and prolong OS, unlike numerous drugs that only prolong PFS. In a post hoc analysis using the EMBRACE trial data (10), a high ALC ($\geq 1,500/\mu\text{l}$) was a significant and independent predictor of prolonged OS in patients treated with eribulin but not in those receiving a different treatment of physician's choice, suggesting that NLRs may not be a specific predictor of OS for eribulin but a general prognostic factor. The present results suggested that a high PLR (≥ 150) is a stronger prognostic factor for TN and non-TN BC than NLR and ALC, which are charac-

teristic of TNBC. However, this finding does not imply that a high PLR (≥ 150) is a significant and independent predictor of shorter OS during eribulin treatment (data not shown).

Liver metastasis reduces the response rate and worsens the prognosis of patients who receive immune-checkpoint inhibitor therapy (30-32), partly because lactic acid induces PD-1 expression by Treg cells in liver metastatic lesions (33). Liver tumors induce the loss of systemic tumor-specific effector T cells by activation of Treg cells and/or hepatic macrophages (34,35). There is evidence that as a biomarker, ALBI grade can be used to optimize patient selection and treatment planning in hepatocellular carcinoma (HCC) (36). In particular, changes in ALBI grade after hepatic resection are independently associated with decreased OS and recurrence-free survival (37). In the present study, the hepatic reserve capacity due to liver metastasis and drug-induced liver injury from previous line treatment in BC by ALBI grade was evaluated, and it was demonstrated that liver dysfunction (ALBI grade 2 or 3) affects the OS. Liu *et al* (38) revealed that the PALBI grade, which incorporates platelet counts as an indicator of the severity of portal hypertension into the ALBI grade, could be more clinically feasible because of its superior prognostic power in HCC compared with the ALBI grade. In HCC, the effect of reduced platelet counts associated with portal hypertension should be considered but in the present study, a high PLR (≥ 150) may have been an independent prognostic factor that reflected a stronger immune response. However, the interpretation of the present study is limited by the fact that it is retrospective and that there were missing values in the ALBI score data.

In conclusion, blood-based parameters and ratios are easily calculated and are feasible adjunctive tools to predict prognosis, relapse rates and treatment efficacy in various types of cancers (39-42). In the present study, PLR and Hb were closely correlated with prognosis in patients with MBC who received eribulin therapy. Thus, low PLR and anemia may be useful

surrogate markers for OS in patients with MBC. Blood count parameters can be easily measured without the need for new equipment or invasive testing. Further prospective studies are needed to confirm these preliminary results and to investigate the correlations between MBC characteristics or subtypes and PLR.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

HS, AF, KM, SK, AN, YI, AA, MO, HI, AO and TS provided the clinical data included in the text and confirm the authenticity of all the raw data. HS, AF, and KM wrote the manuscript draft. SK and MO contributed to the conception of the work and interpreted and revised the laboratory test results included in the present study. AO, HI, and TS revised the manuscript critically and modified the text. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures performed in the present study were in accordance with the ethical standards of committee of Saitama Medical University International Medical Center (approval no. 19-224; Hidaka, Japan) and/or national research committee and in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The requirement of informed consent was waived given the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

Toshiaki Saeki received research grants from Eisai Co., Ltd.; Taiho Pharmaceutical Co., Ltd.; and Chugai Pharmaceutical Co., Ltd., and received personal fees from Taiho Pharmaceutical Co. and Chugai Pharmaceutical Co. Akihiko Osaki received research grants from AstraZeneca K.K., Eisai Co., Ltd., MSD K.K., Ono Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Daiichi Sankyo Co., Ltd., Taiho Pharmaceutical Co., Ltd., Sawai Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., Novartis Pharma K.K., Hamamatsu Photonics K.K., Parexel International Inc., and Fuji Pharma Co. Akihiko Osaki also received personal fees from AstraZeneca

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