in vivo *36*: 1854-1859 (2022)
doi:10.21873/invivo.12903

The Modified Glasgow Prognostic Score and Prognostic Nutritional Index as Prognostic Markers in Patients With Metastatic Breast Cancer Treated With Eribulin

SHINYA YAMAMOTO[1], SHOKO ADACHI[1], TOMOKO WADA[1], KAZUTAKA NARUI[1], AKI KIMURA[2], MASANORI OSHI[2], AKIMITSU YAMADA[2], TOSHIHIRO MISUMI[3] and ITARU ENDO[2]

[1]*Department of Breast and Thyroid Surgery, Yokohama City University Medical Center, Yokohama, Japan;*
[2]*Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Yokohama, Japan;*
3Department of Biostatistics, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Abstract. *Aim: To examine the role of the Modified Glasgow Prognostic Score (mGPS) and Prognostic Nutritional Index (PNI) as prognostic markers for patients with metastatic breast cancer (MBC). Patients and Methods: We investigated the associations of clinico-pathological factors with time-to-treatment failure (TTF) and overall survival (OS) in 110 patients with MBC treated with eribulin. Results: C-Reactive protein >1 mg/dl, albumin <3.5 g/dl, mGPS=2, and PNI <40 were significant predictors of shorter TTF in univariate analyses. PNI <40 remained a significant and independent predictor of shorter TTF in multivariate analyses. De novo tumor, visceral metastases, C-reactive protein >1 mg/dl, albumin <3.5 g/dl, mGPS=2, and PNI <40 were significant predictors of poor OS at the univariate level. A PNI <40 was a significant and independent predictor of poor OS in multivariate analyses. Conclusion: PNI is a reliable predictor of TTF and OS in patients with MBC treated with eribulin.*

Breast cancer is the most common form of cancer worldwide (1). Although drug treatment has advanced, metastatic breast cancer (MBC) is still difficult to cure. Various drugs have been developed to treat MBC. Many studies have examined predictors of outcome and poor prognosis in patients with MBC.

Eribulin mesylate (eribulin) is an inhibitor of microtubule dynamics. It is distinct from other tubulin-targeting agents, since it inhibits the microtubule growth phase without affecting the shortening phase (2). The EMBRACE study showed that eribulin significantly prolongs overall survival (OS) compared to standard treatment in women with human epidermal growth factor receptor 2 (HER2)-negative MBC (2). Several prognostic markers for MBC have been identified, including the absolute lymphocyte count (ALC), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) (3-5). In a *post-hoc* analysis of the EMBRACE study, Miyoshi *et al*. (3) identified an ALC of ≥1500/μl as a significant predictor of better OS in patients with MBC treated with eribulin. Miyagawa *et al*. (4) reported that the progression-free survival (PFS) of patients with an NLR <3 was significantly longer than that of patients with an NLR≥3. Koyama *et al*. (5) reported that ALC and PLR were significantly associated with OS.

On the other hand, other multi-marker prognostic models for different cancer types have been developed. These include the Glasgow Prognostic Score (GPS) calculated from C-reactive protein (CRP) and serum albumin levels, and the Prognostic Nutritional Index (PNI) calculated from albumin and ALC, which have been reported for other carcinomas. The GPS was originally reported for non-small-cell lung cancer (6), and then the modified GPS (mGPS) was developed for colorectal cancer (7) and validated in other carcinoma types (8). The PNI was developed for gastrointestinal cancer (9) and reported for other carcinomas (10). There are few studies on these markers as predictors of prognosis in patients with MBC treated with eribulin. The present study thus investigated the utility of mGPS and PNI compared to existing laboratory-based prognostic markers

Correspondence to: Shinya Yamamoto, Department of Breast and Thyroid Surgery, Yokohama City University Medical Center, 4-57 Urafune-cho, Naka-ku, Yokohama city, Kanagawa 232-0024, Japan. Tel: +81 452615656, Fax: +81 452311846, e-mail: shinya@rf.catv.ne.jp

Key Words: Breast cancer, eribulin, modified Glasgow Prognostic Score, prognostic nutritional index, prognostic marker.

(ALC, NLR, PLR) for HER2-negative cancer in order to predict outcome in patients treated with eribulin.

Patients and Methods

Patients. A total of 110 consecutively enrolled patients treated with eribulin for HER2-negative MBC at our institutions between January 2012 and September 2021 were included in present study. Clinical data were collected retrospectively. The present study was approved by the Yokohama City University Medical Center Ethics Committee (B200900015) and Yokohama City University Hospital Ethics Committee (B200700008). Informed consent was obtained using an opt-out system.

Treatment and outcome. Eribulin was administered intravenously at 1.4 mg/m^2 on days 1 and 8 of each 21-day cycle. When patients were unable to tolerate this dose due to adverse events, the dose was reduced to 1.1 or 0.7 mg/m^2, or the treatment schedule was changed to bi-weekly. Treatment was continued until disease progression or intolerable toxicity developed. Disease progression was determined by comprehensive judgment based on radiological findings, clinical symptoms, laboratory data, and other findings. Time to treatment failure (TTF) and OS were calculated. TTF was defined as the duration of administration of eribulin. OS was defined from the date of eribulin initiation to the date of death from any cause.

Evaluation of predictors. We collected baseline data before the first eribulin administration including neutrophil, lymphocyte, and platelet counts, as well as CRP, albumin, carbohydrate antigen 15-3, and carcinoembryonic antigen levels. These data were used to calculate the NLR and PLR. The mGPS score was derived as follows: Score 0: CRP ≤1.0 mg/dl; score 1: CRP >1.0 mg/dl and albumin ≥3.5 g/dl, Score 2: CRP >1.0 mg/dl and albumin <3.5 g/dl. The PNI was calculated as follows: 10×albumin in g/dl+0.005×lymphocytes/μl. The cut-off value was determined based on literature (3, 4, 8, 10, 11): NLR: 3, ALC: 1,500/μl, PLR: 200, mGPS: 1, and PNI: 40. ER or PgR positivity was defined as a positive cell rate of >1% (12). The cut-off values for carbohydrate antigen 15-3 and carcinoembryonic antigen were 25 U/ml and 5.0 ng/ml, respectively (13).

Statistical analysis. Baseline characteristics were summarized by descriptive statistics. Univariate and multivariate analyses for TTF and OS were calculated using a Cox proportional hazards model to obtain the hazard ratio (HR) and 95% confidence interval (CI). TTF and OS were estimated using the Kaplan-Meier method and groups were compared using log-rank tests. A two-sided value of $p<0.05$ was considered statistically significant. All statistical analyses were performed using Bell Curve version 3.20 for Excel (Social Survey Research Information, Tokyo, Japan).

Results

Patient characteristics. The characteristics of patients included in present study are shown in Table I. There was one male patient in the present study. Most patients had ER-positive disease (68.2%). The majority of patients had an ALC of <1500/μl (70.9%), mGPS of 0-1T (82.7%) and PNI≥40 (74.5%). The median follow-up was 12.1 months (range=0.2-85.8 months).

Table I. *Patient characteristics*.

		Number of patients (%)
Sex	Male	1 (0.9)
	Female	109 (99.1)
Age	≥50 Years	85 (77.3)
	<50 Years	25 (22.7)
ER	Positive	75 (68.2)
	Negative	35 (31.8)
PgR	Positive	52 (47.3)
	Negative	49 (44.5)
	Unknown	9 (8.2)
Tumor status	Recurrent	86 (78.2)
	De novo	24 (21.8)
Visceral metastases	Present	73 (66.4)
	Absent	37 (33.6)
Prior CTx for MBC,	≥2	77 (70)
	0.1	33 (30)
Prior ET for MBC	Present	53 (48.2)
	Absent	57 (51.8)
ALC	≥1,500/μl	31 (28.2)
	<1,500/μl	78 (70.9)
	Unknown	1 (0.9)
NLR	≥3	44 (40)
	<3	65 (59.1)
	Unknown	1 (0.9)
PLR	≥200	57 (51.8)
	<200	52 (47.3)
	Unknown	1 (0.9)
CRP	>1 mg/dl	35 (31.8)
	≤1 mg/dl	74 (67.3)
	Unknown	1 (0.9)
Albumin	≥3.5 g/dl	84 (76.4)
	<3.5 g/dl	23 (20.9)
	Unknown	3 (2.7)
mGPS	2	17 (15.5)
	0 or 1	91 (82.7)
	Unknown	2 (1.8)
PNI	≥40	82 (74.5)
	<40	25 (22.7)
	Unknown	3 (2.7)
CA15-3	≥25 U/ml	74 (67.3)
	<25 U/ml	35 (31.8)
	Unknown	1 (0.9)
CEA	≥5 ng/ml	65 (59.1)
	<5 ng/ml	44 (40)
	Unknown	1 (0.9)

ALC: Absolute lymphocyte count; CA15-3: carbohydrate antigen 15-3; CEA: carcinoembryonic antigen; CRP: C-reactive protein; CTx: chemotherapy; ER: estrogen receptor; ET: endocrine therapy; MBC: metastatic breast cancer; mGPS: modified Glasgow Prognostic Score; NLR: neutrophil-to-lymphocyte ratio; PgR: progesterone receptor; PLR: platelet-to-lymphocyte ratio; PNI: Prognostic Nutritional Index.

Predictors of TTF. The results of univariate Cox regression analysis for factors associated with TTF are shown in Table II. CRP >1 mg/dl, albumin <3.5 g/dl, mGPS of 2, and PNI <40 were significantly associated with shorter TTF. Factors which were significant ($p<0.05$) at the univariate analysis

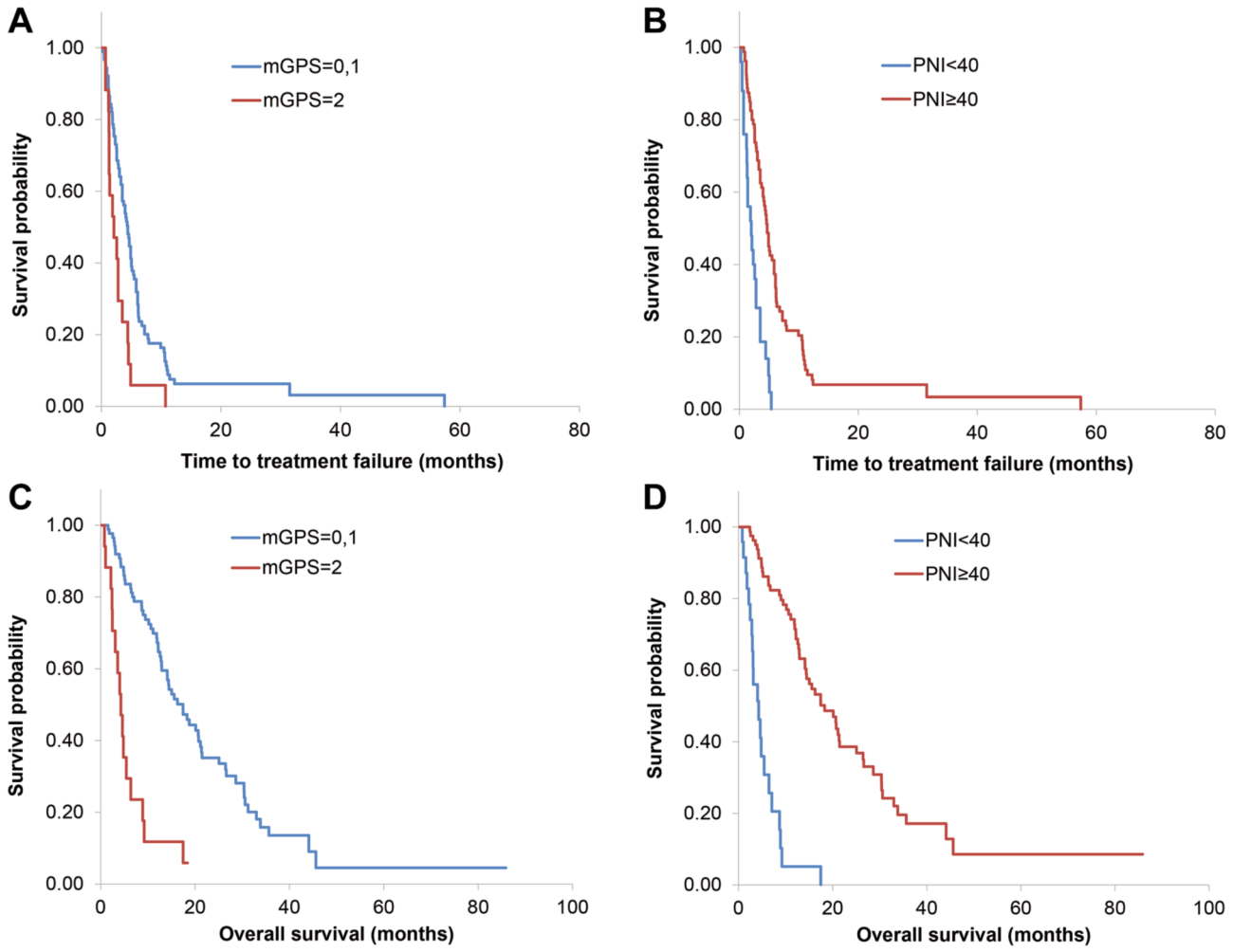

Figure 1. *Output summaries of Kaplan-Meier survival curve analysis according to Modified Glasgow Prognostic Score (mGPS) and Prognostic Nutritional Index (PNI). A: A mGPS of 0-1 was associated with a significantly longer time to treatment failure compared to a mGPS of 2 (4.4 vs. 2.1 months, p=0.002). B: The median time to treatment failure of patients with a PNI ≥40 was significant longer than that of patients with a PNI <40 (4.6 vs. 2.0 months, p<0.001). C: A mGPS of 0-1 was associated with significantly longer overall survival compared to a mGPS of 2 (17.4 vs. 4.2 months, p<0.001). D: A PNI ≥40 was associated with significantly longer overall survival compared to a PNI <40 (18.3 vs. 4.2 months, p<0.001).*

were entered into a multivariate analysis model. However, since CRP and albumin, being components of the mGPS, are strongly correlated with mGPS, only the latter of these significant variables was used. The results of the multivariate Cox regression analysis are shown in Table II. A PNI <40 was confirmed as a significant and independent prognostic marker for shorter TTF (HR=3.135, 95% CI=1.704-5.747, p<0.001).

Predictors of OS. The results of univariate Cox regression analysis for factors associated with OS are shown in Table III. *De novo* tumor, present of visceral metastasis, CRP >1 mg/dl, albumin ≤3.5 g/dl, mGPS=2, and PNI <40 were significant factors resulting in poor OS. In multivariate analysis, mGPS was used, and CRP and albumin were excluded, as with TTF. The results of the multivariate Cox regression analysis modelling predictors of OS are shown in Table III. A PNI <40 was confirmed as a significant and independent predictor of poor OS (HR=6.711, 95% CI=2.899-15.625, p<0.001).

Kaplan-Meier survival curve analysis. Kaplan-Meier survival curves for TTF and OS compared between patients stratified according to mGPS and PNI are shown in Figure 1. A mGPS of 0-1 was associated with a significantly longer median TTF than a mGPS of 2 (4.4 *vs*. 2.1 months, p=0.002)

Table II. *Univariate and multivariate analyses of each factor for time-to-treatment failure.*

		Univariate analysis			Multivariate analysis		
Factor	Comparator *vs.* reference	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Sex	Male *vs.* female	4.874	0.654-36.324	0.122			
Age	≥50 *vs.* <50 Years	1.064	0.667-1.698	0.794			
ER	Positive *vs.* negative	1.392	0.903-2.145	0.134			
PgR	Positive *vs.* negative	1.193	0.785-1.811	0.409			
Tumor status	Recurrent *vs. de novo*	0.729	0.455-1.169	0.190			
Visceral metastasis	Present *vs.* absent	1.403	0.916-2.149	0.120			
Prior CTx for MBC	≥2 *vs.* 0, 1	1.390	0.912-2.118	0.126			
Prior ET for MBC	Present *vs.* absent	1.081	0.730-1.601	0.697			
ALC	≥1,500 *vs.* <1,500/μl	0.714	0.461-1.106	0.131			
NLR	≥3 *vs.* <3	1.146	0.771-1.705	0.500			
PLR	≥200 *vs.* <200	1.015	0.685-1.505	0.940			
CRP	>1 *vs.* ≤1 mg/dl	1.576	1.041-2.385	0.032			
Albumin	≥3.5 *vs.* <3.5 g/dl	0.369	0.227-0.600	<0.001			
mGPS	2 *vs.* 0, 1	2.264	1.324-3.871	0.003	1.201	0.623-2.314	0.585
PNI	≥40 *vs.* <40	0.287	0.173-0.477	<0.001	0.319	0.174-0.587	<0.001
CA15-3	≥25 *vs.* <25 U/ml	1.302	0.848-1.999	0.227			
CEA	≥5 *vs.* <5 ng/ml	1.362	0.903-2.055	0.141			

ALC: Absolute lymphocyte count; CA15-3: carbohydrate antigen 15-3; CEA: carcinoembryonic antigen; CRP: C-reactive protein; CTx: chemotherapy; ER: estrogen receptor; ET: endocrine therapy; MBC: metastatic breast cancer; mGPS: modified Glasgow Prognostic Score; NLR: neutrophil-to-lymphocyte ratio; PgR: progesterone receptor; PLR: platelet-to-lymphocyte ratio; PNI: Prognostic Nutritional Index.

(Figure 1A). The median TTF was significantly longer in patients with a PNI ≥40 compared to patients with a PNI <40 (4.6 *vs.* 2.0 months, $p<0.001$) (Figure 1B). A mGPS of 0-1 was associated with a significantly longer OS than a mGPS of 2 (17.4 *vs.* 4.2 months, $p<0.001$) (Figure 1C). A PNI ≥40 was associated with a significantly longer OS than a PNI <40 (18.3 months *vs.* 4.2 months, $p<0.001$) (Figure 1D).

Discussion

To the best of our knowledge, this is the first study to evaluate the role of mGPS for the prognostication of patients with HER2-negative MBC treated with eribulin. Both mGPS and PNI were associated with significantly better TTF and OS in univariate analyses; however, only PNI was associated with significantly better TTF and OS in multivariate analyses. ALC, NLR and PLR were not significant markers of TTF and OS in present study.

The mGPS has been widely validated as a marker of systemic inflammation (14). Proctor *et al.* identified mGPS as a powerful prognostic factor in various cancer types including breast cancer (15). However, their study examined the relationship between the mGPS upon diagnosis of a malignant tumor and survival. In keeping with the link between MBC treated with eribulin and inflammation, Sata *et al.* reported that baseline levels of CRP, as well as the NLR and ALC, were significantly associated with OS (11). Inflammation is an important driver of tumor progression. The tumor microenvironment is orchestrated by inflammatory cells, which play an essential role in the proliferation, survival, and migration of cancer cells (16). Thus, it is plausible that mGPS may be prognostic marker; however, it was not found to be a significant marker in our multivariate analysis. Therefore, the PNI was considered to be a more useful factor in patients with MBC treated with eribulin.

The PNI is a marker of nutrition and systemic immune status. In the present study, PNI was a significant predictor of TTF and OS in patients with MBC treated with eribulin. Similar results were reported by Oba *et al.* (17), who found an association between a higher PNI and longer OS (HR=0.27, $p=0.0068$) in a sample of 60 patients. The PNI has also been described as a useful prognostic marker in patients with other malignant tumors (10, 18-20).

The antitumor effects of eribulin are driven in part by modulation of the immune system (21). Lymphocytes play an important role in antitumor immune responses (5). Therefore, it is reasonable for the PNI to be a prognostic marker, however, the ALC alone was not a significant marker. Thus, albumin, which reflects nutritional status, seemed to play an important role, because albumin was included in the formulas used to calculate the mGPS and PNI. Albumin alone was also significantly associated with a better prognosis in univariate analyses. However, albumin was not a significant independent predictor in the multivariate analysis when albumin and CRP instead of mGPS were input (data not shown). A complex index of

Table III. *Univariate and multivariate analyses of each factor for overall survival.*

		Univariate analysis			Multivariate analysis		
Factor	Comparator *vs*. reference	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Sex	Male *vs*. female	1.433	0.198-10.384	0.722			
Age	≥50 *vs*. <50 Years	1.268	0.752-2.137	0.374			
ER	Positive *vs*. negative	0.822	0.511-1.322	0.418			
PgR	Positive *vs*. negative	0.666	0.421-1.052	0.081			
Tumor status	Recurrent *vs*. *de novo*	0.539	0.315-0.920	0.024	0.753	0.415-1.367	0.351
Visceral metastasis	Present *vs*. absent	1.665	1.008-2.749	0.046	1.595	0.947-2.686	0.079
Prior CTx for MBC	≥2 *vs*. 0, 1	1.264	0.826-1.934	0.281			
Prior ET for MBC	Present *vs*. absent	0.773	0.498-1.201	0.252			
ALC	≥1,500 *vs*. <1,500/μl	0.624	0.380-1.023	0.061			
NLR	≥3 *vs*. <3	1.201	0.764-1.886	0.427			
PLR	≥200 *vs*. <200	1.127	0.725-1.752	0.594			
CRP	>1 *vs*. ≤1 mg/dl	2.632	1.644-4.212	<0.001			
Albumin	≥3.5 *vs*. <3.5 g/dl	0.191	0.113-0.324	<0.001			
mGPS	2 *vs*. 0, 1	4.708	2.606-8.505	<0.001	1.172	0.510-2.690	0.709
PNI	≥40 *vs*. <40	0.130	0.072-0.235	<0.001	0.149	0.064-0.345	<0.001
CA15-3	≥25 *vs*. <25 U/ml	1.248	0.751-2.075	0.392			
CEA	≥5 *vs*. <5 ng/ml	1.031	0.649-1.638	0.896			

ALC: Absolute lymphocyte count; CA15-3: carbohydrate antigen 15-3; CEA: carcinoembryonic antigen; CRP: C-reactive protein; CTx: chemotherapy; ER: estrogen receptor; ET: endocrine therapy; MBC: Metastatic breast cancer; mGPS: modified Glasgow Prognostic Score; NLR: neutrophil-to-lymphocyte ratio; PgR: progesterone receptor; PLR: platelet-to-lymphocyte ratio; PNI: Prognostic Nutritional Index.

nutrition and immunity seems to be important for predicting prognosis in patients with MBC treated with eribulin.

The treatment approach for patients with a poor prognosis who were included in the present study was not investigated, however, it is an urgent issue. Since patients with a low PNI had a poor prognosis, improving nutritional and immune status is important. Oba *et al*. closely monitored the results of an ongoing clinical trial examining whether nutritional intervention could improve treatment outcomes in patients with MBC (NCT03045289). We are also looking for a similar way to maintain the PNI.

The present study has several limitations. Firstly, we did not examine whether the associations of mGPS and PNI with prognosis in patients with MBC are specific to being treated with eribulin, or also extend to other forms of treatment. Secondly, this was a retrospective study with a small sample size. There is a need for more multi-center studies with larger cohorts to validate our results.

In conclusion, we found that the PNI was a strong predictor of prognosis in patients with MBC treated with eribulin. Maintaining nutritional and immunological status might improve survival in patients with MBC. In the future, we would like to validate our results in a larger cohort.

Conflicts of Interest

SY received research honoraria from Esai, Chugai, Novartis. AY received honoraria from AstraZeneca, Chugai, Daiichi Sankyo, Eisai, Eli Lily, Kyowa Kirin, Nihon Medi-Physics, Nippon Kayaku, Pfizer, and Taiho. K.N. received honoraria from EISAI, Nippon Kayaku, Kyowa Kirin, Novartis, AstraZeneca, Eli Lilly, Pfizer. IE received grants from Asahikasei, Ono, Taiho, Chugai, Eisai, Takeda and Eli Lilly; and honoraria from Asahikasei. The other Authors declare that they have no conflicts of interest related this study.

Authors' Contributions

SY designed the study, collected the clinical data, analyzed statistics, and wrote the article. SA, TW, AK collected the clinical data. KN, AY collected the clinical data and revised the article. MO designed the study and collected the clinical data. TM analyzed statistics. IE revised the article. All Authors read and approved the article.

Acknowledgements

The Authors would like to thank Editage for English language editing.

References

1 Loibl S, Poortmans P, Morrow M, Denkert C and Curigliano G: Breast cancer. Lancet *397(10286)*: 1750-1769, 2021. PMID: 33812473. DOI: 10.1016/S0140-6736(20)32381-3

2 Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, Chollet P, Manikas A, Diéras V, Delozier T, Vladimirov V, Cardoso F, Koh H, Bougnoux P, Dutcus CE, Seegobin S, Mir D, Meneses N, Wanders J, Twelves C and EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice *Versus* E7389) investigators: Eribulin monotherapy *versus* treatment of physician's choice in patients

with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet *377(9769)*: 914-923, 2011. PMID: 21376385. DOI: 10.1016/S0140-6736(11)60070-6

3 Miyoshi Y, Yoshimura Y, Saito K, Muramoto K, Sugawara M, Alexis K, Nomoto K, Nakamura S, Saeki T, Watanabe J, Perez-Garcia JM and Cortes J: High absolute lymphocyte counts are associated with longer overall survival in patients with metastatic breast cancer treated with eribulin-but not with treatment of physician's choice-in the EMBRACE study. Breast Cancer *27(4)*: 706-715, 2020. PMID: 32133606. DOI: 10.1007/s12282-020-01067-2

4 Miyagawa Y, Araki K, Bun A, Ozawa H, Fujimoto Y, Higuchi T, Nishimukai A, Kira A, Imamura M, Takatsuka Y and Miyoshi Y: Significant association between low baseline neutrophil-to-lymphocyte ratio and improved progression-free survival of patients with locally advanced or metastatic breast cancer treated with eribulin but not with nab-paclitaxel. Clin Breast Cancer *18(5)*: 400-409, 2018. PMID: 29605174. DOI: 10.1016/j.clbc.2018.03.002

5 Koyama Y, Kawai S, Uenaka N, Okazaki M, Asaoka M, Teraoka S, Ueda AI, Miyahara K, Kawate T, Kaise H, Yamada K and Ishikawa T: Absolute lymphocyte count, platelet-to-lymphocyte ratio, and overall survival in eribulin-treated HER2-negative metastatic breast cancer patients. Cancer Diagn Progn *1(5)*: 435-441, 2021. PMID: 35403160. DOI: 10.21873/cdp.10058

6 Forrest LM, McMillan DC, McArdle CS, Angerson WJ and Dunlop DJ: Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer. Br J Cancer *90(9)*: 1704-1706, 2004. PMID: 15150622. DOI: 10.1038/sj.bjc.6601789

7 McMillan DC, Crozier JE, Canna K, Angerson WJ and McArdle CS: Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. Int J Colorectal Dis *22(8)*: 881-886, 2007. PMID: 17245566. DOI: 10.1007/s00384-006-0259-6

8 Watanabe J, Otani S, Sakamoto T, Arai Y, Hanaki T, Amisaki M, Tokuyasu N, Honjo S and Ikeguchi M: Prognostic indicators based on inflammatory and nutritional factors after pancreaticoduodenectomy for pancreatic cancer. Surg Today *46(11)*: 1258-1267, 2016. PMID: 26869184. DOI: 10.1007/s00595-016-1308-6

9 Onodera T, Goseki N and Kosaki G: [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. Nihon Geka Gakkai Zasshi *85(9)*: 1001-1005, 1984. PMID: 6438478.

10 Ishiyama Y, Kondo T, Nemoto Y, Kobari Y, Ishihara H, Tachibana H, Yoshida K, Hashimoto Y, Takagi T, Iizuka J and Tanabe K: Predictive impact of prognostic nutritional index on pembrolizumab for metastatic urothelial carcinoma resistant to platinum-based chemotherapy. Anticancer Res *41(3)*: 1607-1614, 2021. PMID: 33788756. DOI: 10.21873/anticanres.14922

11 Sata A, Fukui R, Miyagawa Y, Bun A, Ozawa H, Fujimoto Y, Higuchi T, Imamura M and Miyoshi Y: C-reactive protein and absolute lymphocyte count can predict overall survival of patients treated with eribulin. Anticancer Res *40(7)*: 4147-4156, 2020. PMID: 32620664. DOI: 10.21873/anticanres.14414

12 Yip CH and Rhodes A: Estrogen and progesterone receptors in breast cancer. Future Oncol *10(14)*: 2293-2301, 2014. PMID: 25471040. DOI: 10.2217/fon.14.110

13 Wu SG, He ZY, Zhou J, Sun JY, Li FY, Lin Q, Guo L and Lin HX: Serum levels of CEA and CA15-3 in different molecular subtypes and prognostic value in Chinese breast cancer. Breast *23(1)*: 88-93, 2014. PMID: 24291374. DOI: 10.1016/j.breast.2013.11.003

14 McMillan DC: The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev *39(5)*: 534-540, 2013. PMID: 22995477. DOI: 10.1016/j.ctrv.2012.08.003

15 Proctor MJ, Morrison DS, Talwar D, Balmer SM, O'Reilly DS, Foulis AK, Horgan PG and McMillan DC: An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. Br J Cancer *104(4)*: 726-734, 2011. PMID: 21266974. DOI: 10.1038/sj.bjc.6606087

16 Coussens LM and Werb Z: Inflammation and cancer. Nature *420(6917)*: 860-867, 2002. PMID: 12490959. DOI: 10.1038/nature01322

17 Oba T, Maeno K, Ono M, Ito T, Kanai T and Ito KI: Prognostic Nutritional Index is superior to neutrophil-to-lymphocyte ratio as a prognostic marker in metastatic breast cancer patients treated with eribulin. Anticancer Res *41(1)*: 445-452, 2021. PMID: 33419842. DOI: 10.21873/anticanres.14794

18 Matsuyama Y, Nakamura T, Yoshida K, Nakamura K, Hagi T, Asanuma K and Sudo A: Role of the Prognostic Nutritional Index in patients with soft-tissue sarcoma. In Vivo *35(4)*: 2349-2355, 2021. PMID: 34182517. DOI: 10.21873/invivo.12511

19 Takao K, Konishi H, Fujiwara H, Shiozaki A, Shoda K, Kosuga T, Kubota T, Arita T, Morimura R, Murayama Y, Kuriu Y, Ikoma H, Nakanishi M, Okamoto K and Otsuji E: Clinical significance of Prognostic Nutritional Index in the treatment of esophageal squamous cell carcinoma. In Vivo *34(6)*: 3451-3457, 2020. PMID: 33144453. DOI: 10.21873/invivo.12184

20 Watanabe H, Yamada T, Komori K, Hara K, Kano K, Takahashi K, Kumazu Y, Fujikawa H, Numata M, Aoyama T, Tamagawa H, Inokuchi Y, Machida N, Shiozawa M, Yukawa N, Morinaga S, Rino Y, Masuda M, Ogata T and Oshima T: Effect of Prognostic Nutrition Index in gastric or gastro-oesophageal junction cancer patients undergoing nivolumab monotherapy. In Vivo *35(1)*: 563-569, 2021. PMID: 33402510. DOI: 10.21873/invivo.12292

21 Goto W, Kashiwagi S, Asano Y, Takada K, Morisaki T, Fujita H, Takashima T, Ohsawa M, Hirakawa K and Ohira M: Eribulin promotes antitumor immune responses in patients with locally advanced or metastatic breast cancer. Anticancer Res *38(5)*: 2929-2938, 2018. PMID: 29715119. DOI: 10.21873/anticanres.12541

Received March 19, 2022
Revised April 21, 2022
Accepted April 29, 2022