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Changes in Neutrophil-to-lymphocyte Ratio Predict Efficacy of Trabectedin for Soft-tissue Sarcoma

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Abstract. *Background/Aim: Trabectedin and eribulin are widely used for the treatment of soft-tissue sarcoma (STS). Previously it was shown that the baseline neutrophil-to-lymphocyte ratio (NLR) predicts the efficacy of eribulin for STS. However, prognostic factors for trabectedin on STS have not been identified to date. Patients and Methods: We conducted a retrospective study of data collected prospectively from 39 patients treated with trabectedin for recurrent or metastatic STS between October 2012 and December 2019. To determine the predictive factors of overall survival (OS) and progression-free survival (PFS), univariate and multivariate analyses were performed. Results: Age ≥40 (HR=0.33, 95% CI=0.15-0.71; p=0.0050) and changes in NLR (ΔNLR) <0.5 (HR=2.40, 95% CI-1.01-5.72; p=0.048) were independent factors predictive of longer OS. In addition, age ≥40 (HR=0.23, 95% CI=0.10-0.52; p<0.001) was an independent predictor of longer PFS. Conclusion: Changes in NLR and age ≥40 years were able to predict the efficacy of trabectedin for STS.*

Trabectedin, a semisynthetic DNA-binding protein that was initially isolated from the marine ascidian Ecteinascidia turbinata, exerts an antineoplastic effect by binding to the minor groove of DNA and bending the DNA towards the main groove (1).

Trabectedin was first approved for treatment of soft-tissue sarcoma (STS) in Europe (2), based on successful single-arm phase II trials (3-5). Data from subsequent clinical use in Europe suggested that two subsets of STS patients, with leiomyosarcoma/liposarcoma (hereafter referred to as L-sarcoma) or chromosome translocation-related sarcoma, would benefit most from trabectedin treatment (6, 7). A randomised phase III trial in patients with advanced L-sarcoma who had received prior therapy with an anthracycline and at least one additional systemic regimen demonstrated that trabectedin gave longer progression-free survival (PFS) of 4.2 months compared to dacarbazine (1.5 months) (8). These results supported the approval of trabectedin for clinical use in the U.S. (9). In a Japanese randomised phase II study in STS patients that had chromosomal translocations, trabectedin reduced the risk of disease progression compared to best supportive care (BSC) after chemotherapy, achieving a median PFS of 5.6 months for patients treated with trabectedin compared to 0.9 months for BSC (10). Based on these results, trabectedin was approved for the treatment of all types of STS in Japan.

Despite these advances, prognostic predictors for trabectedin in patients with STS have not been identified. Like trabectedin, eribulin mesylate, a microtubule-targeting agent, is also used as a second- or later-treatment option for STS. We recently reported that a low baseline neutrophil-to-lymphocyte ratio (NLR) predicts the efficacy of eribulin treatment in patients with STS (11). Several previous reports have suggested that the baseline NLR may reflect the antitumour immunity status and associated prognosis of cancer patients (12-14). Changes in NLR were also found to

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be prognostic in several retrospective studies in patients with non-small cell lung cancer, renal cell carcinoma, and gastric cancer treated by immune checkpoint inhibitors (15-17). Herein, we explored factors that predict the efficacy of trabectedin, including NLR and changes in NLR, for patients with STS, particularly non-round cell sarcoma.

Patients and Methods

Patients. We retrospectively analysed prospectively collected data from 39 consecutive patients with recurrent or metastatic non-round cell sarcoma who began treatment with trabectedin at the Cancer Institute Hospital of Japanese Foundation for Cancer Research between October 2012 and December 2019. The database comprised the following patient characteristics: age, sex, histological diagnosis, location of the primary tumour, gene translocation, Eastern Cooperative Oncology Group performance status (ECOG PS), number of previous systemic chemotherapies, and the absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) of blood samples collected within a week before (pre-) and after (post-) the first infusion. These factors were categorised as follows. Age: <40 years and ≥40 years, or age <65 years and ≥65 years; histology: L-sarcoma (leiomyosarcoma and liposarcoma) and non-L-sarcoma; location of the primary tumour: extremities and non-extremities; chromosomal translocation: positive and negative; ECOG PS: 0 and ≥1; number of previous systemic chemotherapies: 0-1 and ≥2; ALC: <1,500 cells/μl and ≥1,500 cells/μl; NLR (calculated as ANC divided by ALC): <3.0 and ≥3.0; and changes in NLR (ΔNLR; calculated as post-NLR divided by pre-NLR): <0.5 and ≥0.5.

Trabectedin was administered at a dose of 1.2 mg/m^2 as the standard approved dose in Japan, and subsequent administration was continued at the same dose every 3 weeks. Dose reductions to 1.0 and 0.8 mg/m^2 or prolonged administration intervals were permitted until improvement of adverse events at the physician's discretion. Dosing was adjusted or discontinued depending on the condition of each individual patient. All treatment was continued until the occurrence of unacceptable adverse effects or disease progression. The requirement for informed consent was waived because the data were reported anonymously. This study was approved by the Institutional Review Board of the Cancer Institute Hospital of Japanese Foundation for Cancer Research.

Statistical analysis. PFS and overall survival (OS) were estimated using the Kaplan–Meier method and the log-rank test. Data were censored on January 31, 2021. Patients who were lost to follow-up were censored at the date of last contact or follow-up. PFS was calculated from the date of trabectedin initiation to the date of disease progression or death from any cause. OS was calculated from the date of trabectedin initiation to the date of death from any cause. Patients who were alive on January 31, 2021 were censored for OS analysis. Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumours, version 1.1 (8), based on computed tomographic findings. The best overall response was assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The overall response corresponded to the sum of the CR and PR, and disease control corresponded to the sum of the CR, PR, and SD. We performed univariate and multivariate analyses to estimate factors potentially prognostic of PFS and OS; we calculated hazard ratios (HRs) using a Cox proportional hazards model for PFS and OS. The level of significance was set to $p<0.1$ for the univariate analysis and $p<0.05$ for the multivariate analysis and was two-sided. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (www.r-project.org). More precisely, it is a modified version of R Commander designed to add statistical functions that are frequently used in biostatistics (18).

Table I. *Baseline characteristics of the study patients (n=39).*

Characteristic		n (%)
Age	≥40 years	27 (69)
	≥65 years	7 (18)
Gender	Male	19 (49)
Histology	L-sarcoma	19 (49)
Location of primary lesion	Extremity	18 (46)
Gene translocation	Positive	23 (59)
ECOG PS	0	28 (72)
	1	10 (26)
	2	1 (3)
No. of previous chemotherapies	1	11 (28)
	≥2	28 (72)
Pre-ALC	≥1,500 cells/μl	13 (33)
	<1,500 cells/μl	26 (67)
Pre-NLR	≥3.0	24 (62)
	<3.0	15 (38)
Post-ALC	≥1,500 cells/μl	30 (77)
	<1,500 cells/μl	9 (23)
Post-NLR	≥3.0	27 (69)
	<3.0	12 (31)

ECOG PS: Eastern Cooperative Oncology Group performance status; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; L-sarcoma: leiomyosarcoma and liposarcoma.

Table II. *Efficacy of trabectedin monotherapy in the study patients (n=39).*

		n (%)
Best overall response	CR	0 (0)
	PR	5 (12)
	SD	18 (46)
	PD	12 (31)
	Not evaluable	4 (10)
Objective response		5 (12)
Disease control		23 (59)

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Results

Patient characteristics. A total of 39 patients with non-round cell sarcoma were treated with trabectedin between October

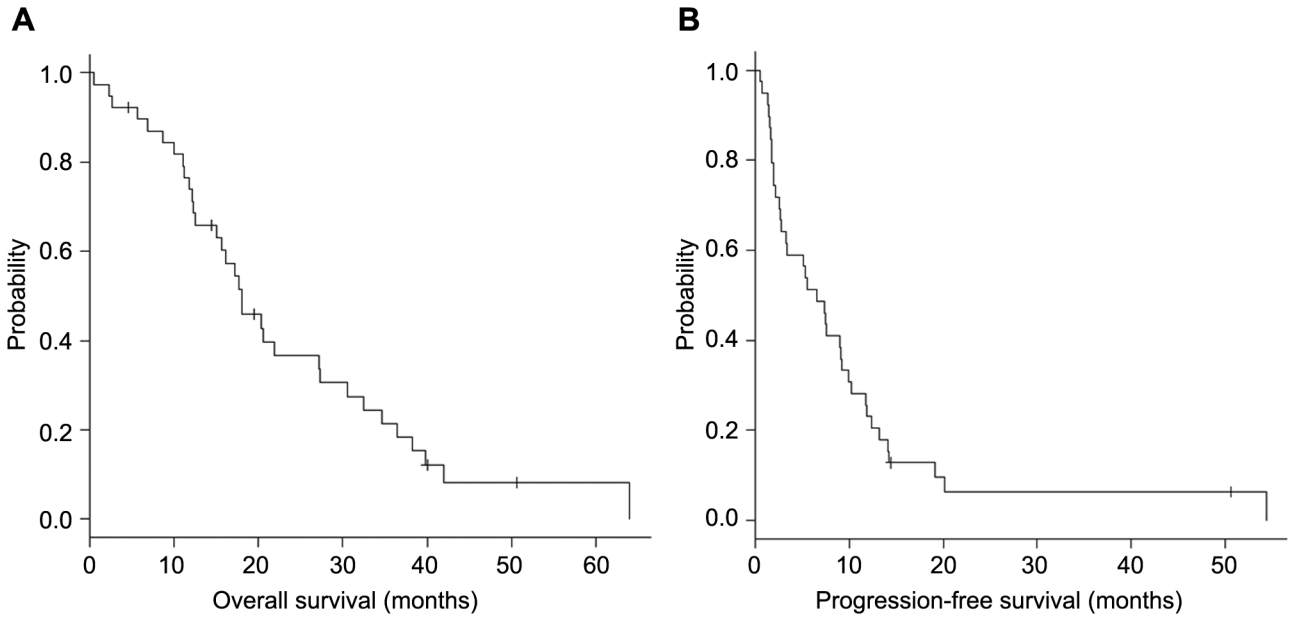

Figure 1. *Kaplan–Meier curves for overall survival (A) and progression-free survival (B) of patients treated with trabectedin for soft-tissue sarcoma (n=39).*

2012 and December 2019. The 39-patient cohort included 19 men, and the median age was 49 years (range=21-74 years). The median duration of observation was 17.2 months (range=0.5-64.0 months). The patient characteristics are shown in Table I. The median pre-treatment and post-treatment ANCs were 3,070 cells/μl (range=1,930-28,830 cells/μl) and 2,010 cells/μl (range=570-34,770 cells/μl), respectively, and the median pre-treatment and post-treatment ALCs were 1,230 cells/μl (range=410-3,590 cells/μl) and 950 cells/μl (range=400-3,030 cells/μl), respectively. The median pre-treatment and post-treatment NLRs were 2.71 (range=0.89-20.59) and 2.04 (range=0.66-31.63), respectively.

Clinical efficacy of trabectedin. The objective response rate was 12% (n=5) and the disease control rate was 59% (n=23) (Table II). Trabectedin was withdrawn in four patients without evaluation of best objective response because of deterioration of their general conditions. The median PFS and OS were 6.5 months [95% confidence interval (CI)=2.6-5.2] and 18.0 months (95% CI=12.5-27.2), respectively (Figure 1).

Predictive factors for OS and PFS. As shown in Table III, multivariate analysis indicated that age ≥40 years (HR=0.33, 95% CI=0.15-0.71; p=0.0050) and ΔNLR <0.5 (HR=2.40, 95% CI=1.01-5.72; p=0.048) were independent predictors of OS. Gender, histology, location of primary lesion, gene translocation, ECOG PS, number of previous chemotherapies, pre-ALC and pre-NLR, and post-ALC and post-NLR were not associated with OS. Moreover, as shown in Table IV, multivariate analysis indicated that age ≥40 (HR=0.23, 95% CI=0.10-0.52; p<0.001) was an independent predictor of longer PFS. Gender, histology, location of primary lesion, gene translocation, ECOG PS, number of previous chemotherapies, pre-ALC and pre-NLR, post-ALC and post-NLR, and ΔNLR were not associated with PFS.

Discussion

In this study, we investigated predictive factors of trabectedin monotherapy in patients with non-round cell sarcoma, including NLR and changes in NLR. Notably, we identified ΔNLR <0.5 and age ≥40 as independent predictors of OS. Age ≥40 was also identified as an independent predictor of prolonged PFS.

To the best of our knowledge, no other study has evaluated NLR in trabectedin-treated patients with sarcoma. In the present study, change in NLR was identified as an independent predictive marker of OS. Pre-treatment NLR was not a predictive factor of trabectedin efficacy in patients with non-round cell sarcoma, unlike eribulin for STS patients. This disparity between the two drugs may be due to differences in their mechanisms of cytotoxicity and in their influences on antitumour immunity status. The inhibition of trans-activated transcription and DNA repair proteins are hallmarks of trabectedin cytotoxicity. Inhibition

Table III. *Univariate and multivariate analyses of factors associated with overall survival.*

Characteristic		Univariate		Multivariate	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	≥40 *vs.* <40 years	0.44 (0.21-0.92)	**0.028**	0.33 (0.15-0.71)	**0.005**
	≥65 *vs.* <65 years	3.16 (1.11-8.95)	**0.030**		
Gender	Male *vs.* female	0.70 (0.35-1.43)	0.33	0.58 (0.27-1.24)	0.16
Histology	L-Sarcoma *vs.* other	1.20 (0.59-2.45)	0.62		
Location of primary lesion	Extremity *vs.* other	0.84 (0.42-1.69)	0.62		
Chromosomal translocation	Positive *vs.* negative	0.64 (0.31-1.33)	0.23		
ECOG PS	≥1 *vs.* 0	1.62 (0.75-3.48)	0.22		
No. of previous chemotherapies	≥2 *vs.* 0-1	0.83 (0.38-1.81)	0.65		
Pre-ALC	<1,500 *vs.* ≥1,500 cells/µl	1.13 (0.54-2.38)	0.74		
Pre-NLR	<3.0 *vs.* ≥3.0	0.59 (0.29-1.23)	0.16		
Post-ALC	<1,500 *vs.* ≥1,500 cells/µl	1.37 (0.59-3.20)	0.46		
Post-NLR	<3.0 *vs.* ≥3.0	0.78 (0.36-1.67)	0.52		
ΔNLR	<0.5 *vs.* ≥0.5	2.09 (0.91-4.77)	**0.080**	2.40 (1.01-5.72)	**0.048**

ECOG PS: Eastern Cooperative Oncology Group performance status; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; L-sarcoma: leiomyosarcoma and liposarcoma. Statistically significant *p*-values are shown in bold.

Table IV. *Univariate and multivariate analyses of factors associated with progression-free survival.*

Characteristic		Univariate		Multivariate	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	≥40 *vs.* <40 years	0.24 (0.11-0.53)	**<0.001**	0.23 (0.10-0.52)	**<0.001**
	≥65 *vs.* <65 years	2.17 (0.93-5.09)	**0.074**		
Gender	Male *vs.* female	0.97 (0.50-1.87)	0.92	0.84 (0.43-1.65)	0.62
Histology	L-Sarcoma *vs.* other	0.57 (0.30-1.11)	0.10		
Location of primary lesion	Extremity *vs.* other	1.00 (0.52-1.92)	1.00		
Chromosomal translocation	Positive *vs.* negative	0.84 (0.43-1.63)	0.60		
ECOG PS	≥1 *vs.* 0	0.73 (0.35-1.52)	0.40		
No. of previous chemotherapies	≥2 *vs.* 0-1	0.87 (0.42-1.80)	0.71		
Pre-ALC	<1,500 *vs.* ≥1,500 cells/µl	1.03 (0.52-2.05)	0.93		
Pre-NLR	<3.0 *vs.* ≥3.0	0.76 (0.39-1.50)	0.43		
Post-ALC	<1,500 *vs.* ≥1,500 cells/µl	1.27 (0.59-2.73)	0.53		
Post-NLR	<3.0 *vs.* ≥3.0	0.66 (0.32-1.35)	0.25		
ΔNLR	<0.5 *vs.* ≥0.5	0.90 (0.41-2.00)	0.79		

ECOG PS: Eastern Cooperative Oncology Group performance status; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; L-sarcoma: leiomyosarcoma and liposarcoma. Statistically significant *p*-values are shown in bold.

of active transcription is achieved by interaction of trabectedin with RNA polymerase II, which subsequently alters the production of cytokines and chemokines by tumour-associated macrophages (1). Eribulin, a synthetic analogue of halichondrin B that was originally isolated from the marine sponge Halichondria okadai, selectively binds to the polymerisation site of microtubules with high affinity and inhibits microtubule growth. Its potent microtubule-depolymerising properties and its profound effects on the tumour microenvironment differ from those of other microtubule-targeting agents such as paclitaxel (19). Further research into the cytotoxic mechanisms of eribulin and trabectedin is warranted in order to understand their disparate effects in sarcoma patients.

In the present study, age ≥40 years was also an independent predictor of longer OS and PFS. As shown in Table V, histological features between the two groups were not significantly different (p=0.99). A previous study of trabectedin in children with STS, including 22% with non-round cell sarcoma, did not demonstrate sufficient antitumour

Table V. *Histology of patients stratified by age (<40 years and ≥40 years).*

Histology	n (%)	
	AYA (<40 years) (n=12)	Older (≥40 years) (n=27)
Myxoid liposarcoma	4 (33)	7 (26)
Dedifferentiated liposarcoma	0 (0)	3 (11)
Leiomyosarcoma	1 (8)	4 (15)
Synovial sarcoma	4 (22)	5 (19)
Mesenchymal chondrosarcoma	0 (0)	1 (4)
Alveolar soft part sarcoma	0 (0)	2 (7)
Clear cell sarcoma	1 (8)	0 (0)
Undifferentiated endometrial sarcoma	0 (0)	2 (7)
Endometrial stromal sarcoma	0 (0)	1 (4)
Undifferentiated pleomorphic sarcoma	1 (8)	1 (4)
Others	1 (8)	1 (4)

AYA: Adolescent/young adult.

activity (20). Our data are consistent with this previous result. Patients aged <40 years are defined as adolescent and young adult (AYA) patients, and there are several differences between AYA and older patients with STS in regard to presentation, treatment, and survival (21). Moreover, the same pathologically diagnosed sarcoma has a different profile of genetic mutations in young patients compared to adults (22). Further investigation of the potential biological mechanisms underlying STS in these two age groups is warranted.

Our study shows that histology features and chromosomal translocation were not associated with efficacy of trabectedin. These data were consistent with our previous retrospective report that evaluated differences in the efficacy and safety of trabectedin for patients with STS separated by histological subtype or chromosomal translocation (23).

Several limitations of this study should be acknowledged. First, this was a retrospective study with a small number of patients, and a selection bias may have resulted from physician subjectivity when determining which patients should receive trabectedin at which time. Second, the NLR value is variable, not only because of tumour factors but also owing to infection, corticosteroids, radiotherapy, or other physiological stressors. Although we used a cut-off value of 3.0 for NLR and 0.5 for ΔNLR according to the findings of previous studies (11, 17), the appropriate cut-off value is still under debate. We plan to continue accumulating data from a greater number of patients to inform future studies.

In conclusion, this retrospective study evaluated predictive factors of trabectedin monotherapy in non-round cell sarcoma patients. Notably, we found that changes in NLR (ΔNLR ≥0.5) and age ≥40 years were independent predictors of prolonged OS.

Conflicts of Interest

YS reports personal fees from ONO Pharmaceutical Co., Ltd., Bristol Myers Squibb Company, MSD KK, and Taiho Pharmaceutical Co., Ltd., outside the submitted work. NF and JT report personal fees from Eisai Co., Ltd. ST reports grants and personal fees from Bristol Myers Squibb Company, grants and personal fees from ONO Pharmaceutical Co., Ltd., grants and personal fees from MSD KK, grants and personal fees from AstraZeneca plc, grants and personal fees from Chugai Pharmaceutical Co., Ltd., and grants and personal fees from Bayer AG, outside the submitted work. The other Authors report no competing interests to disclose.

Authors' Contributions

YS designed the study and wrote the manuscript. KN designed the study and revised the manuscript. KK, NF, XW, TU, AO, NH, MY, MO, TJ, KH, YF, TT, KA, SM, and TT contributed critical revisions of the manuscript. All Authors read and approved the final version of the manuscript.

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References

1 Larsen AK, Galmarini CM and D'Incalci M: Unique features of trabectedin mechanism of action. Cancer Chemother Pharmacol *77(4)*: 663-671, 2016. PMID: 26666647. DOI: 10.1007/s00280-015-2918-1

2 Carter NJ and Keam SJ: Trabectedin: a review of its use in the management of soft tissue sarcoma and ovarian cancer. Drugs *67(15)*: 2257-2276, 2007. PMID: 17927287. DOI: 10.2165/00003495-200767150-00009

3 Yovine A, Riofrio M, Blay JY, Brain E, Alexandre J, Kahatt C, Taamma A, Jimeno J, Martin C, Salhi Y, Cvitkovic E and Misset JL: Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol *22(5)*: 890-899, 2004. PMID: 14990645. DOI: 10.1200/JCO.2004.05.210

4 Garcia-Carbonero R, Supko JG, Manola J, Seiden MV, Harmon D, Ryan DP, Quigley MT, Merriam P, Canniff J, Goss G, Matulonis U, Maki RG, Lopez T, Puchalski TA, Sancho MA, Gomez J, Guzman C, Jimeno J and Demetri GD: Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. J Clin Oncol *22(8)*: 1480-1490, 2004. PMID: 15084621. DOI: 10.1200/JCO.2004.02.098

5 Le Cesne A, Blay JY, Judson I, Van Oosterom A, Verweij J, Radford J, Lorigan P, Rodenhuis S, Ray-Coquard I, Bonvalot S, Collin F, Jimeno J, Di Paola E, Van Glabbeke M and Nielsen OS: Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. J Clin

Oncol *23(3)*: 576-584, 2005. PMID: 15659504. DOI: 10.1200/JCO.2005.01.180

6 Samuels BL, Chawla S, Patel S, von Mehren M, Hamm J, Kaiser PE, Schuetze S, Li J, Aymes A and Demetri GD: Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study. Ann Oncol *24(6)*: 1703-1709, 2013. PMID: 23385197. DOI: 10.1093/annonc/mds659

7 Le Cesne A, Cresta S, Maki RG, Blay JY, Verweij J, Poveda A, Casali PG, Balaña C, Schöffski P, Grosso F, Lardelli P, Nieto A, Alfaro V and Demetri GD: A retrospective analysis of antitumour activity with trabectedin in translocation-related sarcomas. Eur J Cancer *48(16)*: 3036-3044, 2012. PMID: 22749255. DOI: 10.1016/j.ejca.2012.05.012

8 Demetri G, Von mehren M, Jones R, Hensley M, Schuetze S, Staddon A, Milhem M, Elias A, Ganjoo K, Tawbi H, Van tine B, Spira A, Dean A, Khokhar N, Park Y, Knoblauch R, Parekh T, Maki R and Patel S: Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. Journal of Clinical Oncology *34(8)*: 786-793, 2020. DOI: 10.1200/JCO.2015.62.4734

9 Barone A, Chi DC, Theoret MR, Chen H, He K, Kufrin D, Helms WS, Subramaniam S, Zhao H, Patel A, Goldberg KB, Keegan P and Pazdur R: FDA approval summary: Trabectedin for unresectable or metastatic liposarcoma or leiomyosarcoma following an anthracycline-containing regimen. Clin Cancer Res *23(24)*: 7448-7453, 2017. PMID: 28774898. DOI: 10.1158/1078-0432.CCR-17-0898

10 Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, Morioka H, Hiraga H, Hiruma T, Kunisada T, Matsumine A, Tanase T, Hasegawa T and Takahashi S: Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. Lancet Oncol *16(4)*: 406-416, 2015. PMID: 25795406. DOI: 10.1016/S1470-2045(15)70098-7

11 Sato Y, Nakano K, Fukuda N, Wang X, Urasaki T, Ohmoto A, Yunokawa M, Ono M, Tomomatsu J, Hayakawa K, Funauchi Y, Tanizawa T, Ae K, Matsumoto S and Takahashi S: Pre-treatment neutrophil-to-lymphocyte ratio predicts efficacy of eribulin for soft-tissue sarcoma. Anticancer Res *41(1)*: 527-532, 2021. PMID: 33419852. DOI: 10.21873/anticanres.14804

12 Rosenberg SA: Progress in human tumour immunology and immunotherapy. Nature *411(6835)*: 380-384, 2001. PMID: 11357146. DOI: 10.1038/35077246

13 Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF and Amir E: Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst *106(6)*: dju124, 2014. PMID: 24875653. DOI: 10.1093/jnci/dju124

14 Chen ZY, Raghav K, Lieu CH, Jiang ZQ, Eng C, Vauthey JN, Chang GJ, Qiao W, Morris J, Hong D, Hoff P, Tran H, Menter DG, Heymach J, Overman M and Kopetz S: Cytokine profile and prognostic significance of high neutrophil-lymphocyte ratio in colorectal cancer. Br J Cancer *112(6)*: 1088-1097, 2015. PMID: 25688736. DOI: 10.1038/bjc.2015.61

15 Sacdalan DB, Lucero JA and Sacdalan DL: Prognostic utility of baseline neutrophil-to-lymphocyte ratio in patients receiving immune checkpoint inhibitors: a review and meta-analysis. Onco Targets Ther *11*: 955-965, 2018. PMID: 29503570. DOI: 10.2147/OTT.S153290

16 Lalani AA, Xie W, Martini DJ, Steinharter JA, Norton CK, Krajewski KM, Duquette A, Bossé D, Bellmunt J, Van Allen EM, McGregor BA, Creighton CJ, Harshman LC and Choueiri TK: Change in Neutrophil-to-lymphocyte ratio (NLR) in response to immune checkpoint blockade for metastatic renal cell carcinoma. J Immunother Cancer *6(1)*: 5, 2018. PMID: 29353553. DOI: 10.1186/s40425-018-0315-0

17 Ota Y, Takahari D, Suzuki T, Osumi H, Nakayama I, Oki A, Wakatsuki T, Ichimura T, Ogura M, Shinozaki E, Suenaga M, Chin K and Yamaguchi K: Changes in the neutrophil-to-lymphocyte ratio during nivolumab monotherapy are associated with gastric cancer survival. Cancer Chemother Pharmacol *85(2)*: 265-272, 2020. PMID: 31907646. DOI: 10.1007/s00280-019-04023-w

18 Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant *48(3)*: 452-458, 2013. PMID: 23208313. DOI: 10.1038/bmt.2012.244

19 Dybdal-Hargreaves NF, Risinger AL and Mooberry SL: Eribulin mesylate: mechanism of action of a unique microtubule-targeting agent. Clin Cancer Res *21(11)*: 2445-2452, 2015. PMID: 25838395. DOI: 10.1158/1078-0432.CCR-14-3252

20 Baruchel S, Pappo A, Krailo M, Baker KS, Wu B, Villaluna D, Lee-Scott M, Adamson PC and Blaney SM: A phase 2 trial of trabectedin in children with recurrent rhabdomyosarcoma, Ewing sarcoma and non-rhabdomyosarcoma soft tissue sarcomas: a report from the Children's Oncology Group. Eur J Cancer *48(4)*: 579-585, 2012. PMID: 22088484. DOI: 10.1016/j.ejca.2011.09.027

21 Papworth KE, Arroyo VM, Styring E, Zaikova O, Melin BS and Lupo PJ: Soft-tissue sarcoma in adolescents and young adults compared with older adults: A report among 5000 patients from the Scandinavian Sarcoma Group Central Register. Cancer *125(20)*: 3595-3602, 2019. PMID: 31287163. DOI: 10.1002/cncr.32367

22 van der Graaf WTA, Orbach D, Judson IR and Ferrari A: Soft tissue sarcomas in adolescents and young adults: a comparison with their paediatric and adult counterparts. Lancet Oncol *18(3)*: e166-e175, 2017. PMID: 28271871. DOI: 10.1016/S1470-2045(17)30099-2

23 Kawaguchi K, Nakano K, Urasaki T, Fukuda N, Taira S, Ono M, Tomomatsu J, Nishizawa M, Ae K, Matsumoto S and Takahashi S: Retrospective analysis of trabectedin therapy for soft tissue sarcoma. In Vivo *33(5)*: 1609-1614, 2019. PMID: 31471412. DOI: 10.21873/invivo.11644

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