Pathology & Oncology Research (2020) 26:327–333
https://doi.org/10.1007/s12253-018-0473-x

ORIGINAL ARTICLE

Clinical Parameters for Predicting the Survival in Patients with Squamous and Non-squamous-cell NSCLC Receiving PD-1 Inhibitor Therapy

Minehiko Inomata[1] · Takahiro Hirai[1] · Zenta Seto[1] · Kotaro Tokui[1] · Chihiro Taka[1] · Seisuke Okazawa[1] · Kenta Kambara[1] · Tomomi Ichikawa[1] · Shingo Imanishi[1] · Toru Yamada[1] · Toshiro Miwa[1] · Ryuji Hayashi[2] · Kazuyuki Tobe[1]

Received: 25 July 2018 / Accepted: 13 September 2018 / Published online: 19 September 2018

Abstract

We explored the associations between progression-free survival (PFS) after the initiation of PD-1 inhibitor therapy and the clinical parameters in patients with NSCLC. We reviewed the clinical data of patients with NSCLC treated with PD-1 inhibitor. Data of a total of 36 patients, including 16 patients with squamous cell NSCLC and 20 patients with non-squamous cell NSCLC were reviewed. Multivariate analyses identified EGFR status, C-reactive protein (CRP), and PFS following previous therapy as being significantly associated with the PFS after initiation of PD-1 inhibitor therapy in patients with NSCLC. In patients with squamous cell NSCLC, the blood neutrophil/lymphocyte ratio (NLR), serum lactate dehydrogenase (LDH), serum C-reactive protein (CRP), and PFS following previous therapy were identified as being significantly associated with the PFS after initiation of PD-1 inhibitor therapy. However, none of these associations, except for PFS following previous therapy, were found in patients with non-squamous cell NSCLC. NLR, LDH and CRP were associated with the PFS after initiation of PD-1 inhibitor therapy in patients with squamous cell NSCLC, and PFS following previous therapy was the common parameter associated with the PFS after initiation of PD-1 inhibitor therapy in both squamous-cell NSCLC and non-squamous-cell NSCLC patients.

Keywords Non-small cell lung cancer · Programmed death 1 inhibitor · Squamous cell lung cancer

Introduction

In two phase III trials, therapy with programmed death 1 (PD-1) inhibitors was demonstrated to prolong the overall survival (OS) than that with the conventional cytotoxic chemotherapeutic agent docetaxel in patients with previously treated non-small cell lung cancer (NSCLC) [1, 2]. However, identification of predictors of the clinical response to PD-1 inhibitor therapy is an important issue, because progressive disease, as defined according to the Response Evaluation Criteria in Solid Tumors (RECIST), was observed more frequently in the PD-1 therapy arm [1, 2]. Although patients with positive tumor PD-L1 expression showed higher survival rates, the correlation between the tumor PD-L1 expression level and efficacy of PD-1 inhibitor therapy was not straightforward [2]. Furthermore, no association between the tumor PD-L1 expression level and survival rate was found in patients with squamous cell NSCLC [1].

Several clinical parameters have been identified as prognostic factors or predictors of survival in patients with NSCLC treated with PD-1 inhibitors, including the serum level of lactate dehydrogenase (LDH) [3–5], blood neutrophil/lymphocyte ratio (NLR) [6], serum level of C-reactive protein (CRP) [4], and tumor response to previous chemotherapy [7]. These previous studies addressed patients with NSCLC as a whole and did not analyze patients with squamous-cell NSCLC and non-squamous-cell NSCLC separately. It is possible that the nature of responses to PD-1 inhibitor therapy differs between patients with squamous-cell NSCLC and those with non-squamous-cell NSCLC, because a direct relationship between tumor PD-L1 expression and efficacy of PD-

✉ Minehiko Inomata
minomata@med.u-toyama.ac.jp

[1] First Department of Internal Medicine, Toyama University Hospital, Sugitani 2630, Toyama City 930-0194, Japan

[2] Department of Medical Oncology, Toyama University Hospital, Toyama City, Japan

1 inhibitor therapy was shown only in patients with non-squamous-cell NSCLC [1, 2]. Therefore, we conducted a retrospective analysis to compare the association between clinical variables and the PFS after initiation of PD-1 inhibitor therapy separately in squamous-cell NSCLC and non-squamous-cell NSCLC patients.

Patients and Method

Patients

Clinical data were collected from the patient medical charts. The inclusion criteria were as follows; 1) patients with histologically or cytologically confirmed NSCLC at Toyama University Hospital; 2) patients treated with nivolumab or pembrolizumab between 2016 and 2018 depending on the attending doctor's discretion; 3) patients who had received more than one regimen of cytotoxic agents prior to the start of PD-1 inhibitor therapy. NLR was calculated by dividing peripheral blood neutrophil count by the peripheral blood lymphocyte count. PFS was calculated from the date of initiation of treatment to the date of documentation of disease progression or death, and censored by the last visit until which no disease progression was observed. Disease progression was determined based on physician's clinical judgment and/or RECIST version 1.1. The present study was conducted with the approval of the Ethics committee, University of Toyama, disclosing the information about study plan for participants, in accordance with Ethical Guidelines for Medical and Health Research Involving Human Subjects (Ministry of Health, Labor and Welfare of Japan).

Statistical Analysis

JMP version 11. 2. 0 was used for the statistical analysis. The primary endpoint was the PFS after initiation of PD-1 inhibitor therapy. The cutoff values for LDH, NLR, CRP, and PFS following prior therapy were determined based on previous reports [4, 8]. The PFS after the start of PD-1 inhibitor therapy assessed according to the clinical parameters was compared using the log rank test in patients with NSCLC, and clinical parameters with P value of <0.2 were entered into Cox proportional hazard model as independent variables. Then, the PFS after the start of PD-1 inhibitor therapy in each patient group assessed according to the clinical parameters was compared using the log rank test in patients with squamous cell and non-squamous cell NSCLC. Differences with p-values of less than 0.05 were considered as being significant.

Results

Patient Characteristics

Table 1 shows the patient characteristics. Data of a total of 36 patients, including 16 patients with squamous cell NSCLC and 20 patients with non-squamous cell NSCLC, were analyzed. In the non-squamous cell NSCLC group, there were 3 (15.0%) patients with *EGFR* gene mutation in the tumors, including exon 19 deletion, insertion, or exon 21 L858R.

Progression-Free Survival

Disease progression was observed in 13 (81.3%) patients of the squamous cell NSCLC group and 18 (90.0%) patients of the non-squamous cell NSCLC group. Table 2 shows the results of the analysis carried out using the Log rank test and Cox proportional hazards model to assess the association between clinical parameters and the PFS after the PD-1 inhibitor therapy started in patients with NSCLC. The P values for EGFR mutation status ($P = 0.121$), CRP ($P = 0.114$), PFS following previous therapy ($P < 0.001$), and histology ($P = 0.038$) were determined to be <0.2 by the log-rank test. These variables were entered into the Cox proportional hazards model as independent variables, and the analysis identified the EGFR status ($P = 0.043$), CRP ($P = 0.019$), and PFS following previous therapy ($P < 0.001$) as being associated with the PFS.

Table 3 shows the PFS times after the initiation of PD-1 inhibitor therapy in the patient group with squamous cell NSCLC. NLR ($P = 0.034$), LDH ($P = 0.049$), CRP ($P = 0.012$), and PFS following previous therapy ($P < 0.001$) were identified as being significantly associated with the PFS after initiation of PD-1 inhibitor therapy.

Table 4 shows the PFS times after the initiation of PD-1 inhibitor therapy in the patient group with non-squamous cell NSCLC. None of the above clinical parameters were significantly associated with the PFS after the initiation of PD-1 inhibitor therapy in this group, with the exception of PFS following previous therapy ($P = 0.028$).

Figure 1 shows Kaplan-Meier curve for PFS after initiation of PD-1 inhibitor therapy in each group divided by PFS following previous therapy in patient with NSCLC, squamous cell NSCLC, and non-squamous cell NSCLC.

Discussion

In the present study, we demonstrated associations between the PFS after the initiation of PD-1 inhibitor therapy and clinical parameters, including EGFR mutation status, CRP, and PFS following previous therapy in patients with NSCLC. However, differing associations between clinical variables

Table 1 Patient characteristics

Number		NSCLC 36	Squamous cell NSCLC 16	Non-squamous cell NSCLC 20
Gender	Male	27 (75%)	13 (81.3%)	14 (70.0%)
	Female	9 (25%)	3 (18.8%)	6 (30.0%)
Age (y)	<70	16 (44.4%)	6 (37.5%)	10 (50%)
	≥70	20 (55.6%)	10 (62.5%)	10 (50%)
PS	0–1	23 (63.9%)	9 (56.3%)	14 (70.0%)
	≥2	13 (36.1%)	7 (43.8%)	6 (30.0%)
Smoking history	Yes	31 (86.1%)	16 (100%)	15 (75.0%)
	No	5 (13.9%)	0 (0%)	5 (25.0%)
EGFR	Mutant	3 (8.3%)	0 (0%)	3 (15.0%)
	Wild-type/unknown	33 (91.7%)	16 (100%)	17 (85.0%)
ALK	Mutant	0 (0%)	0 (0%)	0 (0%)
	Wild-type/unknown	36 (100%)	16 (100%)	20 (100%)
PD-L1	<1%	12 (33.3%)	2 (12.5%%)	10 (50%)
	≥1%	14 (38.9%)	5 (31.3%)	9 (45.0%)
	Unknown	10 (27.8%)	9 (56.3%)	1 (5%)
NLR	<5	20 (55.6%)	9 (56.3%)	11 (55.0%)
	≥5	16 (44.4%)	7 (43.8%)	9 (45.0%)
LDH	<245 IU/L	23 (63.9%)	13 (81.3%)	10 (50.0%)
	≥245 IU/L	13 (36.1%)	3 (18.8%)	10 (50.0%)
CRP	<1.0 mg/dl	12 (33.3%)	3 (18.8%)	9 (45.0%)
	≥1.0 mg/dl	24 (66.7%)	13 (81.3%)	11 (55.0%)
Prior regimen	Doublet therapy	17 (47.2%)	8 (50%)	9 (45.0%)
	Monotherapy	13 (36.1%)	5 (31.3%)	8 (40.0%)
	Chemoradiation	6 (16.7%)	3 (18.8%)	3 (15.0%)
PFS (prior treatment)	<3 months	13 (36.1%)	4 (25%)	9(45.0%)
	≥3 months	23 (63.9%)	12 (75%)	11 (55.0%)

ALK anaplastic lymphoma kinase, *CRP* serum C-reactive protein, *EGFR* epidermal growth factor receptor, *LDH* serum lactate dehydrogenase, *NLR* neutrophil/lymphocyte ratio, *PD-L1* programmed death ligand 1, *PFS* progression-free survival, *PS* performance status

and the PFS after the start of PD-1 therapy between patients with squamous cell NSCLC and those with non-squamous cell NSCLC were observed.

Existence of an association between the PFS following previous therapy and the PFS following the trial treatment has been reported in studies on cytotoxic agents [8]. PFS following previous therapy may serve as a prognostic factor, because a short PFS following previous therapy could reflect a more aggressive nature of the tumor. On the other hand, it has been proposed that the immunogenic cell death following previous therapy could explain the association between the response to the most recent treatment before the initiation of PD-1 inhibitor therapy and the response to PD-1 inhibitor therapy [7].

CRP is measured as a systemic inflammatory marker in clinical practice. A possible explanation for the association of CRP with survival in cancer patients is its linkage to tumor progression and IL-6 [4]. In cancer patients, an association has been demonstrated between the CRP and tumor progression; patients with inoperable tumors often have significantly higher serum CRP levels than those with operable tumors [9]. Serum IL-6 levels have been shown to be associated with the survival in cancer patients [10], and IL-6 has also been shown to prevent chemotherapy-induced apoptosis of human umbilical vein endothelial cells [11] and to induce DNA methylation, which enhances tumor growth, in cholangiocarcinoma [12].

Existence of an association between the serum LDH level and survival has been reported in patients with various malignant tumors [13]. LDH is a glycolytic enzyme involved in the anaerobic production of adenosine triphosphate. The proposed mechanisms underlying the association include production of lactic acid and intratumoral hypoxia, with activation of the hypoxia inducible factor-1 alfa-molecular cascade [14, 15]. LDH activity results in the production of lactic acid and acidification, which could facilitate the metastatic and invasive ability of cancer cells [14, 15]. Furthermore, it has been shown that accumulation of lactic acid suppresses cytokine

Table 2 Log rank test and Cox proportional hazard model of the progression-free survival (PFS) after initiation of PD-1 inhibitor therapy in patients with NSCLC ($n = 36$)

		Log rank test		Cox proportional hazard model	
		PFS	P	HR (95%CI)	P
Age (y)	<70	3.2 (1.3–4.2)	0.342		
	≥70	4.0 (1.4–8.8)			
PS	0–1	4.0 (1.4–8.1)	0.564		
	≥2	2.6 (1.1–7.8)			
Smoking history	Yes	4.0 (2.1–7.8)	0.215		
	No	1.7 (1.0–4.2)			
EGFR	Mutant	1.1 (1.0–4.2)	0.121	5.6 (1.1–25.9)	0.043
	Wild-type/unknown	3.7 (2.1–6.8)		1.0	
PD-L1	<1%	3.3 (0.8–4.2)	0.642		
	≥1%	4.1 (1.7–8.8)			
	Unknown	3.3 (0.7–8.3)			
NLR	<5	3.4 (1.3 (8.8)	0.201		
	≥5	3.7 (1.7–4.2)			
LDH	<245 IU/L	3.7 (1.4–8.1)	0.433		
	≥245 IU/L	3.6 (1.6–4.3)			
CRP	<1.0 mg/dl	4.2 (1.1–18.7)	0.114	0.3 (0.1–0.8)	0.019
	≥1.0 mg/dl	3.6 (1.4–4.1)		1.0	
Prior regimen	Doublet therapy	4.2 (1.6–8.8)	0.741		
	Monotherapy	3.7 (0.8–8.1)			
	Chemoradiation	3.4 (1.0-NE)			
PFS (prior treatment)	<3 months	1.6 (0.7–2.8)	<0.001	5.4 (2.1–14.8)	<0.001
	≥3 months	4.3 (3.6–8.3)		1.0	
Histology	Squamous	4.2 (2.1–8.8)	0.038	0.5 (0.2–1.1)	0.087
	Non-squamous	2.6 (1.1–4.2)		1.0	

CRP serum C-reactive protein, *EGFR* epidermal growth factor receptor, *HR* hazard ratio, *PFS* progression-free survival

Table 3 Analysis of the progression-free survival (PFS) after initiation of PD-1 inhibitor therapy in patients with squamous cell NSCLC ($n = 16$)

		PFS (month, 95% CI)	P
Age (y)	<70	4.1 (2.1-NE)	0.656
	≥70	5.6 (0.7–18.7)	
PS	0–1	6.8 (1.4–18.7)	0.320
	≥2	4.1 (0.7–8.3)	
NLR	<5	8.8 (1.4–18.7)	0.034
	≥5	3.7 (0.7–6.8)	
LDH	<245 IU/L	6.8 (2.8–18.7)	0.049
	≥245 IU/L	2.1 (0.7–4.3)	
CRP	<1.0 mg/dl	18.7 (NE)	0.012
	≥1.0 mg/dl	4.1 (2.1–6.8)	
Prior regimen	Doublet therapy	5.6 (0.7–18.7)	0.841
	Monotherapy	3.7 (1.4-NE)	
	Chemoradiation	4.1 (4.1-NE)	
PFS (previous treatment)	<3 months	2.1 (0.7–2.8)	<0.001
	≥3 months	7.6 (3.7–18.7)	

CI confidence interval, *CRP* serum C-reactive protein, *EGFR* epidermal growth factor receptor, *LDH* serum lactate dehydrogenase, *NE* not estimated, *NLR* neutrophil/lymphocyte ratio, *PFS* progression-free survival, *PS* performance status

Table 4 Analysis of the progression-free survival (PFS) after initiation of PD-1 inhibitor therapy in patients with non-squamous cell NSCLC ($n = 20$)

		PFS (month, 95% CI)	P
Age (y)	<70	2.1 (0.8–4.2)	0.811
	≥70	2.7 (0.5–8.1)	
PS	0–1	2.7 (1.0–4.2)	0.581
	≥2	2.1 (0.8–7.8)	
Smoking history	Yes	2.7 (0.8–7.8)	0.634
	No	1.7 (1.0–4.2)	
EGFR	Mutant	1.1 (1.0–4.2)	0.349
	Wild type/unknown	2.7 (1.3–7.8)	
PD-L1	<1%	2.1 (0.5–4.2)	0.272
	≥1%	3.6 (0.7–10.8)	
NLR	<5	1.4 (0.8–8.1)	0.697
	≥5	4.0 (0.5–7.8)	
LDH	<245 IU/L	1.4 (0.5–2.7)	0.159
	≥245 IU/L	4 (0.8–7.8)	
CRP	<1.0 mg/dl	2.7 (1.0–7.8)	0.443
	≥1.0 mg/dl	2.6 (0.7–4.0)	
Prior regimen	Doublet therapy	3.6 (1.1–10.8)	0.328
	Monotherapy	1.4 (0.5–8.1)	
	Chemoradiation	1.7 (1.0–2.7)	
PFS (previous treatment)	<3 months	1.3 (0.5–4.0)	0.028
	≥3 months	3.6 (1.4–8.1)	

CI confidence interval, *CRP* serum C-reactive protein, *LDH* serum lactate dehydrogenase, *NLR* neutrophil/lymphocyte ratio, *PFS* progression-free survival, *PS* performance status

production from T cells and influences dendritic cell activation [16, 17].

NLR has been reported to be associated with the prognosis in patients with various solid tumors [18]. Several clinical studies and meta-analyses have pointed out the importance of CD3- or CD8-positive tumor-infiltrating lymphocytes for survival in cancer patients, and the presence of tumor-infiltrating lymphocytes has been reported as a favorable factor for the outcome in cancer patients [19]. However, in vitro experimental research has demonstrated that neutrophils inhibit cytotoxic T lymphocyte cell lytic activity [20, 21]. Furthermore, the presence of tumor-infiltrating CD15-positive neutrophils has been reported to be associated with tumor progression and poorer survival in patients with gastric cancer [22]. Although the precise mechanisms remain to be clarified, these could explain the association between NLR and the prognosis in cancer patients.

Because these parameters mentioned above were reported to be associated with the survival in various clinical settings not limited to patients receiving PD-1 inhibitors, these are

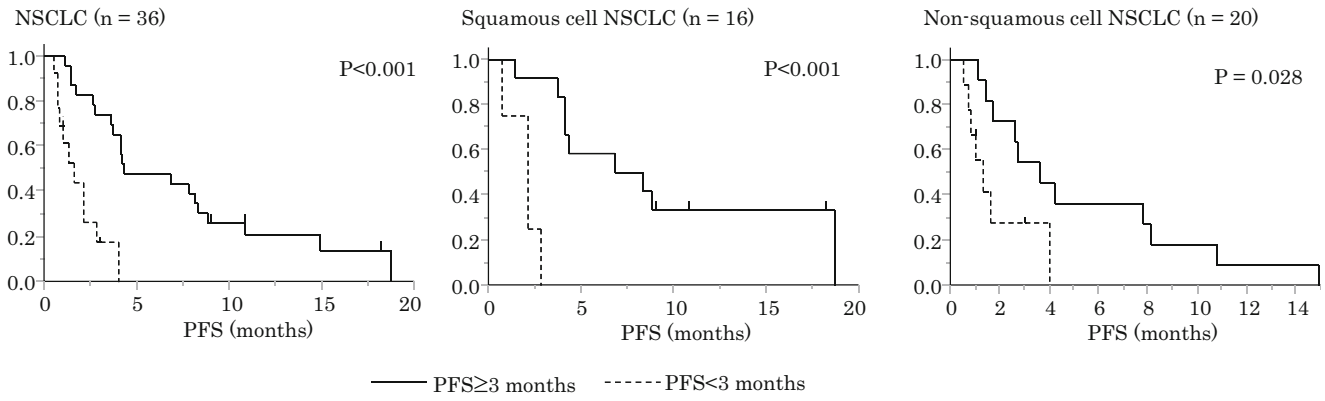

Fig. 1 Kaplan-Meier curve for PFS in each group divided according to the PFS following previous therapy (solid line; PFS ≥ 3 months, dashed line; PFS < 3 months) in patient with NSCLC, squamous cell NSCLC, and non-squamous cell NSCLC

likely to be prognostic factors. However, it remains unclear whether these can serve as predictors of the response to PD-1 inhibitor therapy.

We are unable to explain, from the present data, the reasons for the differing associations between clinical variables and the PFS after the start of PD-1 therapy between patients with squamous cell NSCLC and those with non-squamous cell NSCLC. The immunological characteristics of the tumor environment may differ between non-squamous cell NSCLC and squamous cell NSCLC, given that an association between tumor PD-L1 expression and the efficacy of PD-1 inhibitor therapy was shown only in patients with non-squamous cell NSCLC, and not in squamous cell NSCLC patients.

One of the important limitations of the present study was the small sample size, which could have led to a lower statistical power and difficulty in adjustment for the relevant patient characteristics in the multivariate analysis in a subset analysis of patients with squamous cell and non-squamous cell NSCLC.

In conclusion, the present study showed an association between PFS following previous therapy and PFS after the initiation of PD-1 inhibitor therapy in both patients with non-squamous cell NSCLC and those with squamous cell NSCLC. On the other hand, LDH, NLR and CRP were associated with the PFS after initiation of PD-1 inhibitor therapy only in patients with squamous cell NSCLC. These findings may indicate the different nature of responses to PD-1 inhibitor therapy between squamous-cell NSCLC and non-squamous cell NSCLC.

Compliance with Ethical Standards

Conflict of Interest None.

Financial Support None.

References

1. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR (2015) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373:123–135
2. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhäufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crinò L, Blumenschein GR Jr, Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR (2015) Nivolumab versus docetaxel in advanced non-squamous non-small-cell lung cancer. N Engl J Med 373:1627–1639
3. Taniguchi Y, Tamiya A, Isa SI, Nakahama K, Okishio K, Shiroyama T, Suzuki H, Inoue T, Tamiya M, Hirashima T, Imamura F, Atagi S (2017) Predictive factors for poor progression-free survival in patients with non-small cell lung cancer treated with nivolumab. Anticancer Res 37:5857–5862
4. Oya Y, Yoshida T, Kuroda H, Mikubo M, Kondo C, Shimizu J, Horio Y, Sakao Y, Hida T, Yatabe Y (2017) Predictive clinical parameters for the response of nivolumab in pretreated advanced non-small-cell lung cancer. Oncotarget 8:103117–103128
5. Mezquita L, Auclin E, Ferrara R, Charrier M, Remon J, Planchard D, Ponce S, Ares LP, Leroy L, Audigier-Valette C, Felip E, Zerón-Medina J, Garrido P, Brosseau S, Zalcman G, Mazieres J, Caramela C, Lahmar J, Adam J, Chaput N, Soria JC, Besse B (2018) Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. JAMA Oncol 4:351–357
6. Bagley SJ, Kothari S, Aggarwal C, Bauml JM, Alley EW, Evans TL, Kosteva JA, Ciunci CA, Gabriel PE, Thompson JC, Stonehouse-Lee S, Sherry VE, Gilbert E, Eaby-Sandy B, Mutale F, DiLullo G, Cohen RB, Vachani A, Langer CJ (2017) Pretreatment neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with advanced non-small-cell lung cancer. Lung Cancer 106:1–7
7. Kobayashi H, Omori S, Nakashima K, Wakuda K, Ono A, Kenmotsu H, Naito T, Murakami H, Endo M, Takahashi T (2017) Response to the treatment immediately before nivolumab monotherapy may predict clinical response to nivolumab in patients with non-small cell lung cancer. Int J Clin Oncol 22(4):690–697
8. Inomata M, Hayashi R, Tokui K, Taka C, Okazawa S, Kambara K, Imanishi S, Suzuki K, Yamada T, Miwa T, Kashii T, Matsui S, Tobe K (2014) Outcome and prognostic factors in patients with small cell lung cancer who receive third-line chemotherapy. Tumori 100:507–511
9. Koukourakis MI, Kambouromiti G, Pitsiava D, Tsousou P, Tsiarkatsi M, Kartalis G (2009) Serum C-reactive protein (CRP) levels in cancer patients are linked with tumor burden and are reduced by anti-hypertensive medication. Inflammation 32:169–175
10. Lippitz BE, Harris RA (2016) Cytokine patterns in cancer patients: a review of the correlation between interleukin 6 and prognosis. Oncoimmunology 5:e1093722
11. Lo CW, Chen MW, Hsiao M, Wang S, Chen CA, Hsiao SM, Chang JS, Lai TC, Rose-John S, Kuo ML, Wei LH (2011) IL-6 trans-signaling in formation and progression of malignant ascites in ovarian cancer. Cancer Res 71:424–434
12. Wehbe H, Henson R, Meng F, Mize-Berge J, Patel T (2006) Interleukin-6 contributes to growth in cholangiocarcinoma cells by aberrant promoter methylation and gene expression. Cancer Res 66:10517–10524
13. Ulas A, Turkoz FP, Silay K, Tokluoglu S, Avci N, Oksuzoglu B, Alkis N (2014) A laboratory prognostic index model for patients with advanced non-small cell lung cancer. PLoS One 9:e114471
14. Koukourakis MI, Giatromanolaki A, Sivridis E, Bougioukas G, Didilis V et al (2003) Lactate dehydrogenase-5 (LDH-5) overexpression in non-small-cell lung cancer tissues is linked to tumour hypoxia, angiogenic factor production and poor prognosis. Br J Cancer 89:877–885
15. Danner BC, Didilis VN, Wiemeyer S, Stojanovic T, Kitz J, Emmert A, Füzesi L, Schöndube FA (2010) Long-term survival is linked to serum LDH and partly to tumour LDH-5 in NSCLC. Anticancer Res 30:1347–1351
16. Gottfried E, Kunz-Schughart LA, Ebner S, Mueller-Klieser W, Hoves S, Andreesen R, Mackensen A, Kreutz M (2006) Tumor-derived lactic acid modulates dendritic cell activation and antigen expression. Blood 107:2013–2021
17. Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, Gottfried E, Schwarz S, Rothe G, Hoves S, Renner K, Timischl B, Mackensen A, Kunz-Schughart L, Andreesen

R, Krause SW, Kreutz M (2007) Inhibitory effect of tumor cell-derived lactic acid on human T cells. Blood 109:3812–3819

18. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF, Amir E (2014) Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 106:dju124
19. Gooden MJ, de Bock GH, Leffers N, Daemen T, Nijman HW (2011) The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. Br J Cancer 105:93–103
20. Petrie HT, Klassen LW, Kay HD (1985) Inhibition of human cytotoxic T lymphocyte activity in vitro by autologous peripheral blood granulocytes. J Immunol 134:230–234
21. el-Hag A, Clark RA (1987) Immunosuppression by activated human neutrophils. Dependence on the myeloperoxidase system. J Immunol 139:2406–2413
22. Hiramatsu S, Tanaka H, Nishimura J, Sakimura C, Tamura T, Toyokawa T, Muguruma K, Yashiro M, Hirakawa K, Ohira M (2018) Neutrophils in primary gastric tumors are correlated with neutrophil infiltration in tumor-draining lymph nodes and the systemic inflammatory response. BMC Immunol 19(13):16