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Comparative study of YKL-40, S-100B and LDH as monitoring tools for Stage IV melanoma ☆

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ABSTRACT

Background: Serum markers can be important tools for the prognostic classification and the treatment monitoring in cancer patients. Recently, the potential new serum marker YKL-40 has been introduced for patients with malignant melanoma. The purpose of this study was to assess the prognostic value of YKL-40 in stage IV melanoma patients regarding treatment outcome and survival compared to the established markers LDH and serum S-100B and to evaluate their ability to discriminate between different stages of the disease.
Methods: YKL-40, LDH and S-100B were measured in serum samples of 50 patients with stage I/II melanoma and 61 patients with metastatic melanoma before and after treatment. Univariate and multivariate analyses were performed to determine prognostic factors.
Results: YKL-40, S-100B and LDH correlated significantly with the stage of disease. In stage IV melanoma patients, only the baseline serum levels of S-100B were significantly associated with treatment response ($p = 0.031$), but not those of LDH ($p = 0.193$) or YKL-40 ($p = 0.186$). We found a strong correlation between treatment response and unchanged or declining S-100B levels over time ($p = 0.003$, OR: 9.52, 95%-CI: 1.87–47.62), but no significant correlation between treatment response and serum changes for LDH ($p = 0.534$) and YKL-40 ($p = 0.306$), respectively. In the Cox Regression analysis, only the serum levels of S-100B proved to have a significant prognostic impact on survival ($p < 0.0001$).
Conclusion: In melanoma patients, serum levels of YKL-40, S-100B and LDH correlate significantly with the stage of disease. In stage IV melanoma, S100-B significantly correlates with treatment response and survival and is superior to LDH and YKL-40.

1. Introduction

In advanced metastatic melanoma (American Joint Committee on Cancer (AJCC) stage IV) the prognosis is still poor and the median overall survival time is 6–12 months only.[1] In addition to an improvement in the available therapeutic regimens, it is essential to identify patients who will more likely respond to systemic treatment with better long-term outcomes. Identifying prognostic factors for predicting the clinical course of the disease is, therefore, crucial.

Routine imaging methods and laboratory tests are part of the regular follow up protocol for detecting and treating metastases as early as possible. Lactate dehydrogenase (LDH) is not specific to melanoma metastases, but it has been

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shown that serum concentrations correlate with prognosis and the tumour load.[2–4] Thus, due to its prognostic impact as well as its easy, cost-efficient and widely distributed detection methodology, LDH has been implemented in the AJCC melanoma staging system in 2001.[5]

Melanoma-associated molecules are also potential candidates for serum markers. Amongst those markers, protein S-100B has been shown to correlate with clinical stage, course of the disease and survival of melanoma patients by several investigators.[6–8] Recently, two large-sized studies on high-risk melanoma patients receiving adjuvant treatment with IFNα revealed that serial determinations of S-100B serum levels are a strong independent prognostic factor for survival.[9,10] Furthermore, several authors reported that the prognostic impact of S-100B is superior to LDH serum concentration in advanced metastatic melanoma.[11–17] Thus, Swiss and German guidelines recommend determination of S-100B in serum of patients with Breslow > 1 mm lesions every 3–6 months.[18,19] However, both markers failed to be of prognostic relevance in early stage tumour-free patients.[20,21] Thus, there is further need for identifying appropriate biomarkers.

Recently, a new, promising serum marker has been introduced in malignant melanoma: YKL-40, a 40 kDA heparin binding glycoprotein, is physiologically expressed by different kinds of cells including activated macrophages and neutrophils and has been reported to act as an antiapoptotic protein by initiating the Mitogen-activated protein (MAP) kinase-pathway.[22] It has been found in peritumoural macrophages, which implies a role in tumour surrounding vascular formation and matrix degradation.[23,24] Besides this, elevated serum levels of YKL-40 were reported to be a prognostic factor for poor clinical outcome in various kinds of solid cancers.[25–28]

YKL-40 was reported as a prognostic factor for relapse-free survival and overall survival in AJCC stage I and stage II melanoma patients.[29] In patients with advanced metastatic melanoma, YKL-40 has been described to correlate with the site of metastases and poor performance status as well as with overall survival.[30] However, these reports were performed by one single centre and, to date, there are limited data of confirmatory studies addressing the prognostic value of YKL-40 for treatment monitoring purposes. Moreover, there do not exist comparative investigations with other serum markers like LDH and S-100B.

The aim of our study was to assess the prognostic impact of YKL-40 compared to the established markers LDH and serum S-100B: First, our goal was to determine a possible correlation between the serum marker levels and early and advanced stages of the disease. Furthermore, in stage IV melanoma, we evaluated their usefulness in treatment monitoring and assessed their prognostic impact regarding progression-free and overall survival.

2. Patients and methods

2.1. Patients and treatment

Basic clinical data and tumour specific data from 111 patients, who were treated with melanoma at the Department of Dermatology, University Hospital of Schleswig-Holstein, Campus Kiel, from 2007 until 2009, were analysed. Staging of the patients was performed according to the American Joint Committee on Cancer (AJCC) classification of 2002.[5] The study population consisted of two groups: Group I ($n = 61$): patients with advanced metastatic melanoma (AJCC stage IV: M1a–M1c) receiving surgical, radiotherapeutic or systemic treatment; Group II ($n = 50$): melanoma patients with primary cutaneous melanoma without metastatic disease of the lymph nodes (AJCC stage Ia–IIc: pT1a–pT4b, N0, M0). Patients with severe concomitant conditions or secondary malignancies were not included.

Patients provided written informed consent. This study was approved by the local Ethics Committee.

2.2. Tumour marker assays

Blood samples were collected in Group I prior to treatment (visit 1: start of treatment ± 7 days) and after the first treatment course (visit 2: assessment examination/end of treatment ± 7 days), in Group II after surgical resection of the primary tumour. Serum samples were investigated immediately for LDH- and S-100B-concentrations. For YKL-40 measurement, the blood samples were collected, serum was separated and frozen immediately after blood extraction. Samples were stored at −80 °C until the final analysis was done.

Total LDH activity was measured with an automated controlled system (reagent and analyser: Roche/Hitachi 747, Roche Diagnostics, Mannheim, Germany). The assay was performed according to the manufacturer's instructions. For interpretation of LDH levels in serum the upper institutional limit of 240 units per litre was chosen.

For protein S-100B measurement, we used the Elecsys® S100 assay (Roche Diagnostics, Mannheim, Germany), which forms a sandwich complex with both the biotinylated MoAb S23 and MoAb S53 conjugated with a ruthenium complex. In a second step, the complex binds to a solid phase by biotin/streptavidin interaction. We used a serum concentration of 0.11 μg/l for S-100B as the upper institutional limit (reference range) according to the manufacturer's instructions.

For measurement of YKL-40 serum levels, a commercial two-site, sandwich-type enzyme-linked immunosorbent assay (ELISA; TECOmedical GmbH, Bünde, Germany) was chosen, using a microassay plate coated with streptavidin, a biotinylated murine monoclonal antibody to human YKL-40, an alkaline phosphatase-conjugated rabbit polyclonal detection antibody to YKL-40 and a chromogenic substrate. The lower limit of detection was 10 ng/ml. We used a serum concentration of 125 ng/ml in men and 93 ng/ml in women as the upper institutional limit (reference range) according to the manufacturer's instructions.

2.3. Follow-up and further treatment

Patients with advanced metastatic melanoma (AJCC stage IV = Group I) underwent an extensive assessment programme prior to the initiation of treatment and were referred to computed tomography (CT) of the chest and abdominal tract, magnetic resonance imaging (MRI) of the brain and bone scan to exclude distant metastasis. Objective responses (OR) were re-assessed by subsequent MRI/CT scans four weeks later. If progressive disease (PD) was detected, surgical excisions

were performed wherever indicated. Otherwise, chemotherapy or combined systemic treatment within clinical trials was administered.

Group II patients (AJCC stage I/II) were seen at the outpatient department according to a defined follow-up schedule. Regular visits including physical examinations and blood evaluations (i.e. LDH and S-100B) were performed every 3 months for the first 3 years and every 6 months afterwards. Chest x-rays and ultrasounds of the abdomen were repeated once a year.

2.4. Statistical methods

The data were analysed using SPSS for Windows (Version 13.0, Chicago, Illinois, USA). Baseline descriptive statistics included proportions and mean or median values, as appropriate by data distribution. Normality distribution was checked by Kolmogorov–Smirnov test. Differences between groups with non-parametric data distribution were assessed using the Mann–Whitney-U test and the Kruskal–Wallis test, respectively. The Spearman correlation test was used to test for correlations. Clinical response was dichotomised as disease control (DC) = complete response (CR) + partial response (PR) + stable disease (SD) versus progressive disease (PD).

A univariate analysis of the clinical variables was performed using logistic regression analysis. Estimated survival curves were constructed by the Kaplan–Meier method. Differences between the curves were evaluated using the log-rank test. Melanoma-related deaths were considered as events in overall survival. Progression-free survival (PFS) and overall survival (OS) were calculated from the day of treatment start until progression of the disease (locoregional/distant) or death, respectively. A multivariate analysis using the Cox proportional hazards model was performed to identify independent prognostic factors. Probabilities of less than 0.05 were considered to be statistically significant.

3. Results

3.1. Patientś characteristics

Between January and December 2008, 61 melanoma patients were classified as having AJCC stage IV disease. Eight patients (13.1%) received local surgery or radiotherapy of metastases, 5 patients (8.2%) did not receive any specific therapy during the observation period and the remaining 48 patients (78.7%) received chemo-(immuno)-therapy within randomised clinical trials with almost identical major eligibility criteria for a median duration of 56 days (range: 14–183 days): Paclitaxel ($n = 20$), paclitaxel plus carboplatin ($n = 8$), dacarbazine ($n = 6$), paclitaxel plus elesclomol ($n = 5$), fotemustine ($n = 3$), sorafenib plus pegylated interferon α2b ($n = 3$), others ($n = 3$).

Fifty patients with AJCC stage I/II disease and without any signs of metastatic disease served as a control population. The clinical characteristics of the entire study population are summarised in Table 1; stage IV disease characteristics are shown in Table 2.

Table 1 – Patientś characteristics.

	Stage I/II ($n = 50$)	Stage IV ($n = 61$)	Total ($n = 111$)
Age, years			
Mean ± SD	52.8 1 ± 7.9	55.02 ± 16.6	54.02 1 ± 7.2
Median (range)	55.0 (14–85)	58.0 (20–84)	57.0 (14–85)
Gender			
Male	21 (42.0%)	30 (49.2%)	51 (45.9%)
Female	29 (58.0%)	31 (50.8%)	60 (54.1%)
Primary site			
Head/neck	9 (18.0%)	8 (13.1%)	17 (15.3%)
Trunk	10 (20.0%)	16 (26.2%)	26 (23.4%)
Extremities	30 (60.0%)	26 (42.7%)	56 (50.5%)
Other	1 (2.0%)	11 (18.0%)	12 (10.8%)
Histology			
Superficial spreading	19 (38.0%)	10 (16.4%)	29 (26.2%)
Nodular	20 (40.0%)	35 (57.4%)	55 (49.5%)
Other	11 (22.0%)	16 (26.2%)	27 (24.3%)
Breslowś thickness			
Mean, mm ± SD	1.70 ± 0.75	4.56 ± 5.2	–
Median, mm (range)	1.65 (0.3–3.5)	2.7 (0.4–27.00)	
Type of primary melanoma			
Cutaneous	50 (100.0%)	48 (78.7%)	98 (88.3%)
Mucosal	–	5 (8.2%)	5 (4.5%)
Ocular	–	2 (3.3%)	2 (1.8%)
Other	–	6 (9.8%)	6 (5.4%)
Ulceration			
Present	2 (4.0%)	20 (32.8%)	22 (19.8%)
Absent	48 (96.0%)	30 (49.2%)	78 (70.3%)
Unknown	–	11 (18.0%)	11 (9.9%)

Table 2 – AJCC stage IV characteristics.

Number of patients	61	(100%)
M stage		
M1a	5	(8.2%)
M1b	12	(19.7%)
M1c	44	(72.1%)
LDH elevated		
Yes	20	(33.9%)
No	39	(66.1%)
ECOG		
0	59	(96.7%)
1	2	(3.3%)
2	0	(0.0%)
Baseline metastatic sites[*]		
Skin	11	(18.0%)
Regional lymph nodes	21	(34.4%)
Lung	22	(36.1%)
Liver	22	(36.1%)
Brain	12	(19.7%)
Bone	8	(13.1%)
Others	14	(23.0%)
First line Therapy	33	(54.1%)
Second-line Therapy	28	(45.9%)
After previous		
Surgery	7	(11.5%)
Radiotherapy	4	(6.6%)
Chemotherapy	9	(14.8%)
Other	8	(13.1%)
Response to treatment[**]		
CR	2	(3.6%)
PR	1	(1.8%)
SD	10	(17.9%)
DC (CR + PR + SD)	18	(32.1%)
PD	38	(67.9%)
NED	5	(8.9%)
Death[***]		
Yes	42	(68.9%)
No	19	(31.1%)

Abbreviations: CR: complete remission, PR: partial remission, SD: stable disease, DC: disease control, PD: progressive disease, NED: no evidence of disease.

[*] Multiple selections possible.

[**] Objective responses were confirmed by subsequent MRI/CT scans four weeks later.

[***] All deaths were melanoma-related.

3.2. Discrimination of stage I/II versus stage IV melanoma with serum markers

YKL-40, S-100B as well as LDH correlated significantly with the stage of disease: the median baseline levels of all three serum markers in patients with stage IV melanoma were significantly higher compared to the control group of stage I/II melanoma patients after correction for age (YKL-40: $p = 0.002$; S-100B: $p = 0.03$; LDH: $p = 0.001$; Table 3). However, there was no significant difference between the median serum concentrations in stage I melanoma patients compared to stage II melanoma patients (YKL-40: $p = 0.534$; S-100B: $p = 0.844$; LDH: $p = 0.926$) and between the different M-stages in stage IV (M1a versus M1b versus M1c). These effects may be due to the relatively small sample size in the different subgroups.

3.3. Treatment monitoring in stage IV melanoma with serum markers

Out of 61 AJCC stage IV melanoma patients, 56 were evaluable for efficacy parameters. Assessment of tumour response using RECIST criteria was performed after treatment (median: 105 days, mean: 135 days) and is shown in Table 2. Response to treatment was dichotomised into disease control (DC = CR: complete response + PR: partial response + SD: stable disease) and progressive disease (PD).

The predictive impact of the baseline serum marker levels on the treatment response is illustrated in Table 4. Only the baseline serum levels of S-100B were significantly associated with the type of response ($p = 0.031$), whereas neither the serum levels of LDH ($p = 0.193$) nor of YKL-40 ($p = 0.186$) did reach statistical significance (Mann–Whitney-U-test).

Also, the impact of serum level changes over time (visit 1 versus visit 2) on the response rate was assessed (DC versus PD). The absolute amounts of serum level changes from visit 1 to visit 2 were significantly associated with the type of response only for S-100B ($p = 0.011$), but not for LDH and YKL-40 (LDH: $p = 0.053$; YKL-40: $p = 0.424$; Mann–Whitney-U-test, data not shown). Moreover, the correlation between unchanged or declining S-100B levels over time and response to treatment (DC) was strong (Pearson Chi-square test, $p = 0.003$, Odds Ratio: 9.52, 95%-CI: 1.87–47.62), whereas we did not find statistically significant correlations between treatment response and serum changes of LDH (Pearson Chi-square test,

Table 3 – AJCC stage IV patients characteristics: Baseline serum markers according to M-stage (univariate analysis).

AJCC stage		I/II $n = 50$	IV $n = 61$ (100%)	M1a $n = 5$ (8.2%)	M1b $n = 12$ (19.7%)	M1c $n = 44$ (72.1%)	p-Value[**]
LDH (U/l)[*]	Median (range)	164 (123–263)	202 (105–859)	164.0 (130–257)	170.0 (131–332)	213.0 (105–859)	0.001
	Mean ± SD	170.5 ± 30.1	226.0 ± 114.9	178.0 ± 51.5	197.0 ± 63.3	239.9 ± 128.9	
S-100B (μg/dl)[*]	Median (range)	0.06 (0.03–0.21)	0.11 (0.03–10.5)	0.08 (0.04–1.42)	0.21 (0.03–1.51)	0.11 (0.03–10.5)	0.03
	Mean ± SD	0.07 ± 0.04	0.59 ± 1.84	0.36 ± 0.60	0.38 ± 0.44	0.68 ± 2.16	
YKL-40 (μg/l)[*]	Median (range)	78.6 (33.7–197.1)	102 (28.3–404.1)	101 (80–404.1)	84.65 (28.3–203.1)	106.5 (29.8–389)	0.002
	Mean ± SD	84.4 ± 38.0	123.6 ± 80.3	156.08 ± 139.4	109.55 ± 62.7	123.76 ± 77.3	

[*] Start of treatment.

[**] Univariate analysis: p-values refer to AJCC Stage I/II ($n = 50$) versus AJCC Stage IV ($n = 61$).

Table 4 – Predictive impact of baseline serum concentrations on treatment response (DC versus PD) in AJCC stage IV melanoma patients* (Mann–Whitney-U test).

	Baseline (visit 1)		*p*-Value
	PD	DC	
LDH			
Mean (SD	244.1 ± 140.1	198.0 ± 50.5	0.193
Median (range)	219.5 (105–859)	190.5 (130–322)	
S-100B			
Mean ± SD	0.84 ± 2.32	0.18 ± 0.25	0.031
Median (range)	0.12 (0.3–10.5)	0.07 (0.03–0.90)	
YKL-40			
Mean ± SD	123.6 ± 68.6	105.2 ± 84.8	0.186
Median (range)	109.1 (28.3–280.2)	80.4 (29.8–404.1)	

Abbreviations: PD: progressive disease; DC: disease control (complete remission + partial remission + stable disease)
* Fifty six patients evaluable for efficacy parameters after different kinds of therapeutic regimens.

$p = 0.534$) and YKL-40 (Pearson Chi-square test, $p = 0.306$) (Table 5).

Table 5 – Serum level changes of tumour markers (visit 1 versus visit 2) and treatment response.

Serum level changes	Response	
	DC	PD
S-100B ($p = 0.003$)		
Unchanged/declining	15/17 (88.2%)	15/34 (44.1%)
Increasing	2/17 (11.8%)	19/34 (55.9%)
LDH ($p = 0.534$)		
Unchanged/declining	7/17 (41.2%)	11/34 (32.4%)
Increasing	10/17 (58.8%)	23/34 (67.6%)
YKL-40 ($p = 0.306$)		
Unchanged/declining	8/17 (47.1%)	11/34 (32.4%)
Increasing	9/17 (52.9%)	23/34 (67.6%)

3.4. *Prognostic value of serum markers in stage IV melanoma*

Forty-two (68.9%) out of the 61 patients included in the study died during the observation period. The median time to progression after start of treatment was 3.0 months (SD: 0.8; 95% CI: 1.4–8.6; mean: 6.5 months). The median survival time after initiation of treatment was 14.0 months (SD 1.8; 95% CI: 10.4–17.6; mean: 14.3 months). The estimated survival rates of the AJCC stage IV melanoma patients were as following: 1-year progression-free survival (PFS) rate: 21.1%, 1-year overall survival (OS) rate: 51.8%, 2-year OS rate: 24.7%. The univariate analysis regarding clinical characteristics as potential prognostic factors for survival in stage IV is shown in Table 6.

In the Cox Regression analysis, only the baseline serum levels of S-100B proved to have a significant prognostic impact on PFS and OS (PFS: $p = 0.034$; OS: $p < 0.0001$; Table 7). YKL-40 and LDH, however, could not be established as prognostic parameters by Cox Regression analysis, neither for PFS (YKL-40: $p = 0.255$; LDH: $p = 0.299$) nor for OS (YKL-40: $p = 0.448$; LDH: $p = 0.183$).

Table 6 – Univariate analysis of potential prognostic factors for overall survival.

Factor	Mean (median) survival [months]	Events [*n*]	Censored [*n*] (%)	*p*-Value
Gender				
Female	17.3 (17.0)	12	17 (58.6%)	0.015
Male	22.5 (22.0)	7	29 (80.6%)	
Response				
DC	18.2 (18.0)	9	9 (50.0%)	0.271
PD	22.0 (25.0)	7	85 (89.5%)	
ECOG				
0	20.2 (22.0)	57	39 (68.4%)	0.176
1	11.0 (6.0)	2	1 (50.0%)	
M stage				
M1a	18.3 (14.0)	3	2 (40.0%)	0.854
M1b	19.8 (18.0)	3	9 (75.0%)	
M1c	20.2 (20.0)	13	29 (69.0%)	

Abbreviations: PD: progressive disease; DC: disease control (complete remission + partial remission + stable disease).

Table 7 – Cox-Regression analysis of baseline serum markers as predictors for PFS and OS in AJCC stage IV melanoma patients.

Survival	Factor	*p*-Value	Hazard ratio	95% CI
PFS	S-100B	0.034	1.21	1.02–1.44
	LDH	0.299		
	YKL-40	0.255		
OS	S-100B	<0.0001	1.35	1.16–1.57
	LDH	0.183		
	YKL-40	0.448		

Abbreviations: PFS: progression-free survival, OS: overall survival.

4. Discussion

Until now, there are no comparative studies on YKL-40 and the established serum markers LDH and S-100B in terms of correlation with stage of disease, treatment monitoring, and prognostic value for survival outcome in stage IV disease.

4.1. *Correlation between stage of disease and serum marker levels*

Both S-100B and LDH have been shown to fail to identify melanoma patients with micrometastatic disease of the lymph nodes.[20,21] In order to detect clear differences in the serum marker concentrations between stages, we focused on early stage melanoma patients (stage I/II) after excision of the primary tumour and without signs of metastases compared to stage IV melanoma patients with high tumour burden.

In our present study, we were able to show a significant correlation between tumour stage and serum concentrations of YKL-40 as well as of LDH and S-100B: all markers showed significantly rising serum levels with higher tumour stage (stage I/II versus stage IV). The mechanism by which YKL-40 leaks to the blood is not fully understood. YKL-40 expression has been found in melanoma cells but also in peritumoural stromal macrophages.[23,25] Schmidt et al. reported that YKL-40 serum levels are elevated in stage II melanoma patients compared to healthy controls and also significantly correspond to tumour stage (stage I versus stage II).[29] In our study, however, we could not confirm a statistically significant difference in YKL-40 serum concentrations between stage I and stage II melanoma patients. The latter may be due to the relatively small sample size in the different subgroups, so minor differences might have not been detected.

LDH and S-100B are cytoplasmic proteins, and a substantial release to the blood is most probably related to cell damage or death.[31] Thus, in line with our observations, rising serum concentrations in melanoma patients correspond with tumour load, but in turn, both markers are not useful for the distinction between healthy controls and melanoma patients in early stages of the disease.[7,8,20,21,32]

4.2. *Treatment monitoring in stage IV melanoma with serum markers*

For treatment monitoring purposes, neither the baseline serum levels of YKL-40 and LDH nor their serum level changes over time correlated significantly with the treatment response. However, we could clearly demonstrate that not only the baseline value of S-100B *per se* was a strong predictor of response to treatment but also the serum level changes over time correlated significantly with treatment response. The chance of a disease control (CR + PR + SD) was almost 10-fold higher with unchanged or declining S-100B levels compared to increasing ones. These findings support our previous reports, which showed that S-100B serum changes are strongly correlated with treatment outcome in melanoma patients.[11,32,33] Nevertheless, the findings of our present study may have been influenced by the homogenous nature of the therapeutic regimens used.

Interestingly, Schmidt et al. also investigated the serum levels of YKL-40 in their population of stage IV melanoma patients after 3 weeks of treatment and after the first treatment cycle compared to the baseline samples. In line with our observations, the authors observed no significant correlation between objective response during or after treatment and changes in serum concentrations of YKL-40 over time.[30] In conclusion, only S-100B proved to be a suitable serum marker for treatment monitoring in stage IV melanoma patients compared to YKL-40 and LDH.

4.3. *Prognostic value of serum markers in stage IV melanoma*

In our patient population, neither YKL-40 nor LDH were significant independent prognostic parameters with respect to progression-free and overall survival. This stands in contrast to the study by Schmidt et al. on 110 stage IV melanoma patients, in which they showed that elevated serum levels of YKL-40 were an independent prognostic factor for poor survival and comparable to serum LDH.[30]

Instead, the baseline S-100B serum value was the only independent prognostic factor for both progression-free and overall survival upon Cox regression analysis. These findings are in agreement with our previous studies, in which we demonstrated that S-100B serves as an independent prognostic marker in stage IV melanoma patients and is superior to LDH.[11,17]

YKL-40 serum level changes have been reported after treatment with immunotherapy such as Interleukin-2 (Il-2) and Interferon α (IFNα).[30,34] Notably, all stage IV melanoma patients, that were enrolled in the study by Schmidt et al. received Interleukin 2- and/or Interferon α-based systemic therapies. Thus, the results of their study regarding the prognostic impact of YKL-40 levels in stage IV melanoma patients may be not transferable to other treatment settings. This might be one reason, why we could not confirm YKL-40 as a prognostic factor in our patient population.

The quite heterogeneous composition of our study population reflects a broad rather than a specific treatment situation and may have influenced the results of the serum marker analysis. But to our point of view, a useful tumour marker should be independent of the treatment setting. In this context, only S-100B could be established as a valuable serum marker, whereas YKL-40 serum levels seemed to be too inconsistent.

Moreover, taking into account, that elevated serum levels are not only found in various kinds of solid cancers, but also

in patients with non-malignant diseases characterised by inflammation and tissue remodelling, such as inflammatory bowel disease, rheumatoid arthritis or liver fibrosis,[35,36] YKL-40 seems to be a rather unspecific marker.

Our study provides novel evidence, that the S-100B serum level is a significant predictor of treatment response and is also significantly associated with progression-free and overall survival in patients with stage IV melanoma. In this context we were able to show, that S-100B is superior to other laboratory parameters like LDH and also YKL-40.

Conflict of interest statement

None declared.

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