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Effect of tumor burden and growth rate on treatment outcomes of nivolumab in head and neck cancer

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Abstract

Background: Nivolumab improves overall survival (OS) in patients with platinum-refractory recurrent and metastatic head and neck squamous cell carcinoma (R/M HNSCC). In one study, however, Kaplan-Meier OS and progression-free survival (PFS) curves for the nivolumab and cytotoxic agent arms crossed at 3–6 months, suggesting that patients with initial resistance to immunotherapy might have better outcomes with cytotoxic treatment. Here, we explored conditions and candidates which are predictive of nivolumab outcomes in R/M HNSCC.

Methods: We retrospectively reviewed the clinical records of 27 consecutive R/M HNSCC patients treated with nivolumab from 2014–2018. Tumor size was evaluated by RECIST ver.1.1. Tumor growth rate (Gr) was defined as $3\text{Log}(D_0/D_{pre})/t$, where D_0 and D_{pre} are the sum of the diameters of the target lesions (SumTLs) at baseline and pre-baseline, and t is time, with $1t$ defined as 4 weeks.

Results: Twenty-five patients were enrolled. Survival was significantly worse in patients with disease progression within 3 months. Outcomes appeared poorer in patients with higher pre-treatment Gr and bigger SumTLs at baseline. We therefore explored the association between prognosis, Gr and SumTLs. Recursive partitioning analysis showed that the characteristics of patients with disease progression after 3 months were $\text{Gr} < 0.76$ and $\text{SumTLs} < 31.0$ mm. Further, $\text{Gr} < 0.76$ and $\text{SumTLs} < 31.0$ mm was associated with significantly longer PFS ($p = 0.01$) and OS ($p < 0.01$).

Conclusions: These results suggest that Gr and SumTLs at baseline are significantly associated with OS and PFS in R/M HNSCC patients treated with nivolumab.

47 **Key words:** nivolumab, head and neck cancer, tumor growth rate, tumor burden,
48 predictive factor, prognostic factor.

49

50 ***Abbreviations:***

51 AICc: Akaike information criterion

52 CI: confidence interval

53 CR: complete response

54 ECOG: Eastern Cooperative Oncology Group

55 Gr: Tumor growth rate

56 HNSCC: head and neck squamous cell carcinoma

57 HR: hazard ratio

58 ICPI: immune checkpoint inhibitors

59 ORR: objective response rate

60 OS: overall survival

61 PD: progressive disease

62 PD-1: programmed cell death-1

63 PD-L1: programmed cell death ligand

64 PFS: progression-free survival

65 PR: partial or complete response

66 RECIST: Response Evaluation Criteria in Solid Tumors

67 R/M: recurrent and metastatic

68 SD: stable disease

69 SumTLs: sum of the diameters of target lesions

70

71

Introduction

A standard treatment option for recurrent and metastatic head and neck squamous cell carcinoma (R/M HNSCC) is platinum-based chemotherapy. However, patients who progress within 6 months after the last administration of platinum-based chemotherapy - so-called platinum-refractory R/M HNSCC - generally have a poor prognosis, with median survival of 5–6 months [1–3]. In one phase III study, CheckMate141, nivolumab, an anti-programmed cell death-1(PD-1) antibody, improved overall survival (OS) compared with investigator's choice of single agent chemotherapy (cetuximab, methotrexate, or docetaxel) for patients with platinum-refractory R/M HNSCC (hazard ratio [HR] = 0.70 [97.73% CI 0.51–0.96]; $p = 0.01$) [4], while in a second, KEYNOTE-040, another PD-1 antibody, pembrolizumab, showed reproducible results for patients with platinum-refractory R/M HNSCC [5].

Programmed cell death-ligand 1 (PD-L1) is a promising biomarker which can be used to select patients with non-small cell lung cancer who may benefit from immune checkpoint inhibitors (ICPi) [6]. In CheckMate141, however, nivolumab was effective against platinum-refractory R/M HNSCC regardless of PD-L1 expression [4,7]. Nevertheless, Kaplan–Meier OS and progression-free survival (PFS) curves for the nivolumab and investigator's choice arms crossed at 3–6 months [4], suggesting that patients with initial resistance to ICPi may be better suited for cytotoxic chemotherapy.

Here, we explored candidate predictive factors for nivolumab in R/M HNSCC previously treated with platinum by analyzing clinical characteristics in patients with early disease progression.

Patients and Methods

Patients

This retrospective study was approved by the ethics committee of the Graduate School of Medicine, Kobe University. We reviewed the medical charts of 27 consecutive patients who started treatment with nivolumab at our institution between November 2014 and March 2018. Cut-off date for data analysis was 31 December, 2018. Eligibility criteria were R/M HNSCC previously treated with platinum, with radiologically measurable target lesions per RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 and monotherapy with at least 1 cycle of nivolumab (3 mg/kg intravenously every 2 weeks) as second- or later-line treatment. We excluded two patients without target lesions. All patients were followed regularly at our outpatient clinic. Dose interruption or discontinuation was made by the attending physician according to the type and grade of adverse events. In cases with first progression during nivolumab, nivolumab was continued if the patient maintained a good general condition and tolerated nivolumab.

We categorized patients into two groups according to best overall response and the time from date of diagnosis to documented disease progression. Patients were categorized into responders and non-responders according to best overall response, with responders identified by partial or complete response (PR/CR) and non-responders by stable or progressive disease (SD/PD). Patients were also categorized into two groups according to time from the date of diagnosis to documented disease progression, namely those with disease progression within 3 months ($PD \leq 3M$) and those with disease progression after 3 months ($PD > 3M$).

Evaluation of tumor parameters

Patient treatment responses were evaluated according to the Response Evaluation Criteria in Solid Tumors using whole-body computed tomography. We analyzed the following tumor parameters: sum of the diameters (longest diameters for non-nodal lesions with a longer axis of ≥ 10 mm and nodes with a short axis of ≥ 15 mm as per RECIST 1.1.) of the target lesions (SumTLs), and tumor growth rate (Gr) [8], calculated where t was the time expressed in months at tumor evaluation. We assumed that tumor growth behaves exponentially and that tumors have a spherical shape. Under these hypotheses, we can calculate the volume at baseline (V_0) from the following formula using Gr, $V_0 = V_{pre} \times e^{Gr \times t}$. V_{pre} stands for the volume pre-baseline. Baseline imaging was performed just before the start of nivolumab. Pre-baseline imaging was done just before baseline. The radius of a sphere is equal to half of the tumor diameter (D). Accordingly, we can calculate tumor volume by the following formula, $V_0 = 4/3 \times \pi \times (D_0/2)^3$, $V_{pre} = 4/3 \times \pi \times (D_{pre}/2)^3$. Consequently, Gr is equal to $3\text{Log}(D_0/D_{pre})/t$, where t is time, defined as the corrected value per tumor evaluation interval, defined as 4 weeks.

Statistical Analyses

PFS was calculated as time from the date of diagnosis to documented disease progression, or death from any cause. OS was calculated as time from the date of diagnosis until death from any cause. Patients were censored at the time they were last known to be alive. PFS and OS were evaluated using the Kaplan–Meier method and differences between covariates were evaluated using the log-rank test. Differences in characteristics between outcomes in PFS and response were analyzed for significance

using the chi-squared test for categorical values, t-tests and Mann-Whitney U test for continuous variables. A stepwise Cox proportional hazards model was used to assess the impact of pretreatment markers of each variable with $p < 0.20$ in univariate analysis. We selected covariates by the backward selection of stepwise methods using the second-order Akaike information criterion (AICc). Univariate linear regression was used to assess the association between continuous variables. Recursive partitioning analysis was applied to identify the optimal SumTLs and Gr cutoff point for discriminating disease progression within 3 months.

All data were analyzed with a statistical software program (JMP14, SAS Institute, Inc., Cary, NC, USA). Statistical significance was determined by a p -value less than 0.05.

Results

Characteristics of the Study Population

The study cohort consisted of 25 patients. Median follow-up period for survivors was 12.2 (range, 8.8–46.0) months. The median evaluation period between the time of baseline and pre-baseline is 10 (interquartile range, 7.0–13.9) weeks. Patients received a median of 6 (range, 1–61) cycles of nivolumab treatment. Baseline characteristics of all patients are shown in Table 1.

Efficacy

One-year PFS and OS were 23.3% and 42.6%, respectively. Survival curves of PFS and OS are shown in supplemental Fig. 1. The swimmer plots of duration of treatment, subsequent treatment and follow-up period are shown in Fig 1. The spider

plots of changes in SumTLs over time for all patients are shown in supplemental Fig. 2. One patient was excluded from this spider plot because of death due to rupture of the carotid artery from clinical disease progression and was not evaluated by computed tomography. Best overall response rate (ORR) was 32.0% [95% CI: 48.4–82.8].

The question of whether nivolumab will show a durable response is usually answered during the first 3 months. At 3 months, 52% of our patients (13/25) had disease progression after nivolumab. Patients who progressed within 3 months under treatment with nivolumab had a poorer prognosis than those who did not (HR = 4.42 [95% CI: 1.57–14.3], $p < 0.01$, supplemental Fig. 3).

Factors for Disease Progression within 3 Months

Clinical characteristics between $PD \leq 3M$ and $PD > 3M$ were compared. In univariate analysis, SumTLs was not associated with $PD \leq 3M$. (Fig 2a). However, higher Gr was significantly associated with $PD \leq 3M$ in a one-sided test (one-sided; $p = 0.03$) (Fig 2b).

Factors Related to Response

Clinical characteristics between the responders and non-responders were compared. SumTLs was the only factor related to response in univariate analysis: patients with a bigger SumTLs did not respond significantly in a one-sided test (one-sided; $p = 0.05$) (Fig. 2c). The pretreatment median value of SumTLs of responders and non-responders was 37.9 (11.2–68.4) mm and 44.1 (14.7–135.3) mm. Gr at baseline did not significantly differ between non-responders and responders (Fig. 2d).

Relationship between SumTLs, Gr and Response

We evaluated the relationship between SumTLs, Gr and response to nivolumab. A scatter plot (Fig. 3a) showed the relationship between SumTLs and Gr, and a 95% confidence ellipse for response (blue: PR/CR, red: SD/PD). Based on this, we created a 3D scatter plot with PFS as the vertical axis to visualize the patient group with a poor outcome (Fig. 3b). From the data, patients with a bigger tumor burden or higher tumor growth rate appeared to have worse PFS.

Evaluation of prognosis and SumTLs and Gr

Recursive partitioning analysis showed that the characteristics of $PD > 3M$ were $Gr < 0.76$ and $SumTLs < 31.0$ mm (Fig. 4a). $Gr < 0.76$ and $SumTLs < 31.0$ mm was a significant positive prognostic factor for PFS (HR = 0.20 [0.03–0.72], $p = 0.01$) and OS (HR = 0.13 [95% CI: 0.01–0.65], $p < 0.01$) (Fig. 4b, c).

Supplemental Table 1 shows the results of univariate analysis. Table 2 summarizes the results of univariate and multivariate analysis of clinical parameters of all patients. Multivariate analyses revealed that the condition $Gr < 0.76$ and $SumTLs < 31.0$ mm was an independent positive prognostic factor for OS and PFS in patients with R/M HNSCC who were treated with nivolumab.

Discussion

This study explored candidate predictive factors for treatment outcomes in previously treated R/M HNSCC patients who were treated with nivolumab. Patients with

PD $\leq$ 3M under treatment with nivolumab showed a significantly worse prognosis and higher tumor growth rate. Patients who did not respond to nivolumab had a significantly greater tumor burden. The 3D scatter plot showed that patients with a smaller tumor burden and lower tumor growth rate achieved longer PFS. Pre-treatment Gr and SumTLs (Gr $<$ 0.76 and SumTLs $<$ 31.0 mm) may predict better prognosis for R/M HNSCC patients treated with nivolumab. To our knowledge, this is the first report to investigate the association between tumor burden, tumor growth rate and prognosis for R/M HNSCC patients who were previously treated with nivolumab as monotherapy.

With regard to the association between tumor burden and the efficacy of ICPi, several studies reported that a smaller tumor burden resulted in better response. In the KEYNOTE 012 study, patients with a smaller tumor burden responded better to pembrolizumab than those with a greater tumor burden among patients with R/M HNSCC [9]. Similarly, tumor burden is reported to be a prognostic factor for patients with melanoma and lung cancer treated with ICPi [10–12]. In the present study, although tumor burden was associated with OS, tumor burden itself was not an independent prognostic factor in our study. With regard to translational research, Huang et al. used immune profiling of peripheral blood in melanoma patients treated with pembrolizumab to show that clinical failure in these patients was associated with an imbalance between reinvigoration of exhausted T-cells and tumor burden [13]. Among findings, they showed that reinvigorated Ki67+ CD8 T cells before treatment may reflect a higher tumor burden, and that this finding itself was a poor prognostic indicator. They also showed that patients with longer PFS had a smaller tumor burden [13]. These results suggested that ICPi may be more effective if the initial tumor burden is smaller.

With regard to the association between tumor growth rate and the efficacy of ICPi, data on this issue is scarce. Our results suggest that patients with exacerbations within 3 months under treatment with nivolumab have a significantly worse prognosis and higher tumor growth rate. This may reflect initial resistance in the treatment of nivolumab which appeared within the first 3 months. Our results suggest that initial resistance was associated with growth rate. We consider that tumors with higher growth are uncontrollable by ICPi alone, because the speed of immune detection may not catch up with the speed of tumor growth. In their immune-mathematical model, DeBoer et al. showed tumor regression with a highly antigenic tumor and uncontrolled tumor growth with a low antigenic tumor [14]. Accordingly, progression within 3 months might reflect immune escape and result in a poor response to ICPi due to low antigenic tumors. Our results also suggest that patients with a greater tumor burden and higher tumor growth rate did not benefit from nivolumab. This might support the hypothesis that T cell activity to eliminate tumor cells cannot compete with tumors with a bigger tumor burden and higher tumor growth rate. Therefore, inhibiting tumor growth rate is the most effective way to control tumors, and combination therapy with chemotherapy and ICPi has in fact shown promise in non-small cell lung cancer and R/M HNSCC [15, 16].

Theories aimed at providing the best strategy for ICPi use should be optimized in terms of not only their basic but also clinical aspects. Here, we focused on clinical aspects in the association between growth rate, tumor size and prognosis. Our results revealed that patients with a smaller tumor burden or lower tumor growth rate had a better prognosis. Although several biomarkers have been explored to predict the efficacy of ICPi, including PD-L1 expression, tumor mutation burden [17], microbiome [18] and

neutrophil/lymphocyte ratio [19], few reliable biomarkers are yet available in clinical practice. With regard to PD-L1 expression, nivolumab provided a survival benefit regardless of PD-L1 expression in 2-year follow-up data for platinum-refractory R/M HNSCC [7]. On the other hand, pembrolizumab monotherapy significantly improved survival as compared with standard first-line chemotherapy in cases with high PD-L1 expression (combined positive score: CPS $\geq$ 20%) [16]. Therefore, PD-L1 expression as a predictive biomarker in R/M HNSCC remains controversial, and exploration for a reliable predictive biomarker for ICPi should therefore continue.

Several limitations of this study warrant mention, namely its small sample size and lack of evaluation of PD-L1 expression. In the CheckMate141 study, the effect of nivolumab was not related to PD-L1 expression for platinum-refractory R/M HNSCC [4], and we accordingly did not check this variable in the clinic during the period of this study. We calculated Gr from images taken only two times. For a more accurate estimation, Gr would ideally be estimated from the fixed tumor evaluation intervals and from 3 or more time points. However, regular evaluation is difficult, and it is not realistic to estimate Gr from 3 or more time points in routine practice. Moreover, the formula for Gr becomes more complex with repeated timings. Accordingly, we used only two timings. Although we designed the eligibility process to minimize selection bias, a degree of residual selection bias was inevitable. In addition, the retrospective, single-arm design restricted the results to candidate predictive factors only, and our findings therefore require validation in prospective randomized trials with a larger number of patients. Allowing for these factors, we found that previously treated R/M HNSCC patients with a smaller tumor burden and lower tumor growth rate may respond to nivolumab and

279 achieve longer survival. Our results may aid in clinical decision making concerning the
280 suitability of treatment with ICPI for R/M HNSCC.

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Conflict of Interest

Dr. Kiyota has received grant support from Eisai, Inc.; research funding from Ono Pharmaceutical and Pfizer; and honoraria from Ono Pharmaceutical, Bristol-Meyers Squibb, Astra Zeneca, Eisai, Bayer and Merck Serono.

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Figure legend

Fig. 1: Swimmer plot. Duration of response and time to response in patients receiving nivolumab. PD, progressive disease; DOD, dead of disease; Nivo, nivolumab; Tx, treatment.

Fig. 2: SumTLs (a) and Gr (b) among $PD \leq 3M$ and $PD > 3M$. *SumTLs* was significantly higher in non-responders than responders. Gr was significantly higher in $PD \leq 3M$. One-way ANOVA for SumTLs (c) and Gr (d) among non-responders and responders. SumTLs was significantly higher in non-responders than responders. SumTLs, the sum of the diameters of the target lesions; Gr, tumor growth rate; NR, non-responder; R, responder.

Fig. 3: (a) Scatter plot of the tumor growth rate (Gr) versus the sum of diameters of the target lesions (SumTLs). 95% confidence ellipse for response (blue: PR/CR, red: SD/PD). (b) 3D Scatter plot of tumor growth rate (Gr), and sum of diameters of the target lesions (SumTLs) versus PFS. Patients with a greater tumor burden or higher tumor growth rate appeared to have worse PFS. CR, complete response; PD, progressive disease; PR, partial response.

Fig. 4: (a) Characteristics of $3M > PD$ by recursive partitioning analysis, showing $Gr < 0.76$ and $SumTLs < 31.0$ mm. (b,c) Overall survival and progression-free survival based on the cut-off value of $Gr < 0.76$ and $SumTLs < 31.0$ mm. PD, progressive disease; Gr, tumor growth rate; SumTLs, sum of diameters of the target lesions.

406

407 **Supplemental fig. 1:** Overall survival (OS) and progression-free survival (PFS) in all
408 patients. MST, median survival time.

409

410 **Supplemental Fig. 2:** Spider plot. Time-dependent change rate for the sum of diameters
411 of target lesions.

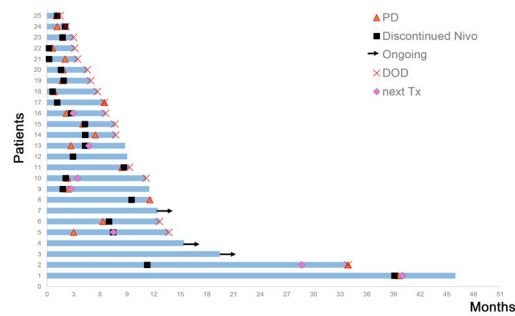
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413 **Supplemental fig. 3:** Overall survival curves of patients with $PD \leq 3M$ (blue line),
414 versus $PD > 3M$ (red line). PD, progressive disease.

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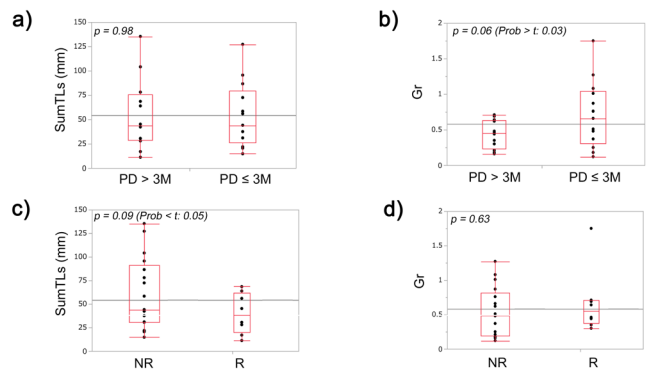
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Fig. 1



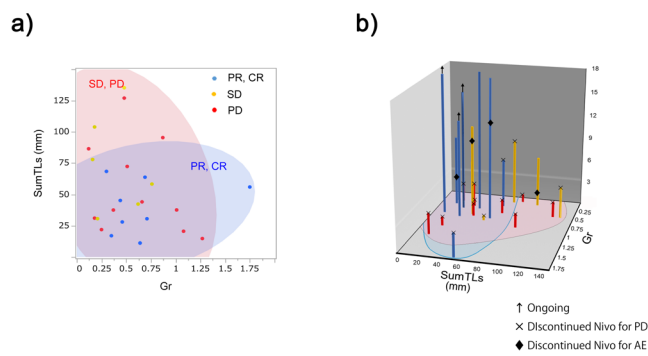
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Fig. 2



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Fig. 3

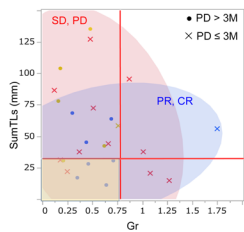


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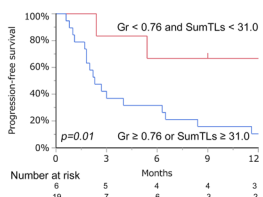
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Fig. 4

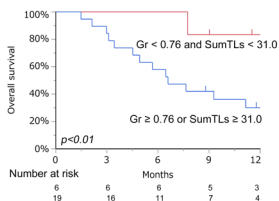
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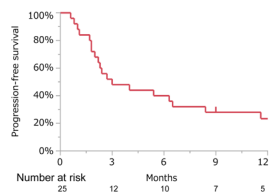
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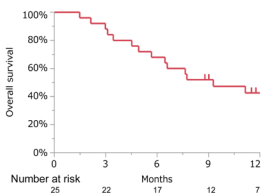
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Supplemental Fig.1

a)



b)



422

423

424 **Table 1: Patient demographics (N=25)**
425
426

Age	Median, range		65.0 (52- 79)
Gender	Male		20 (80.0%)
	Female		5 (20.0%)
ECOG performance status	0-1		21 (84.0%)
	2		4 (16.0%)
Number of metastatic sites	≤ 2		18 (72.0%)
	≥ 3		7 (28.0%)
Site of primary	Oral		11 (44.0%)
	Pharynx		9 (36.0%)
	Larynx		3 (12.0%)
	Paranasal		2 (8.0%)
Platinum-free interval (m)	Median (Range)		2.3 (0.2–9.2)
No. of previous lines of systemic cancer therapy	1		8 (32.0%)
	2		12 (48.0%)
	≥ 3		5 (20.0%)
Previous receipt of cetuximab	Yes		15 (60.0%)
	No		10 (40.0%)
Smoking or tobacco use	Current or former		19 (76.0%)
	Never		6 (24.0%)
Subsequent treatment	Yes		7 (24.0%)
	No		18 (76.0%)
Sum of diameters of target lesions	Median (mm), range		44.1 (11.2–135.3)
Tumor growth rate	Median (Range)		0.48 (0.12–1.75)
Biochemical examination of blood	Neutrophil/lymphocyte ratio	Median, range	5.90 (2.15–25.1)
	LDH		186 (124–978)
	CRP		2.02 (0–12.62)

Table 2. PFS and OS in 25 patients: univariate and multivariate analyses

Factor		PFS				OS			
		Univariate		Multivariate		Univariate		Multivariate	
		Relative risk (95% CI)	P value	Relative risk (95% CI)	P value	Relative risk (95% CI)	P value	Relative risk (95% CI)	P value
Gender	Female Male	reference 0.34 (0.12–1.10)	0.07	0.14 (0.04–0.51)	<0.01				
ECOG performance status	0-1 2	reference 3.88 (1.05–11.7)	0.04			reference 6.12 (1.56–20.9)	0.01		
Number of metastatic sites	≤ 2 ≥ 3					reference 2.05 (0.69–5.72)	0.19		
Previous of receipt of cetuximab	Yes No					reference 0.45 (0.14–1.25)	0.13		
Subsequent treatment	No Yes					reference 0.34 (0.07–1.07)	0.07	reference 0.20(0.04–0.87)	0.04
Biochemical examination of blood CRP		9.49 (1.25–63.1)	0.03			12.7 (1.52–92.8)	0.02		
Sum of diameters of target lesions		3.15 (0.63–14.2)	0.16			10.3 (1.81–56.6)	<0.01		
Gr and SumTLs Gr ≥ 0.76 or SumTLs ≥ 31.0 mm Gr < 0.76 and SumTLs < 31.0 mm		reference 0.20 (0.03–0.71)	0.01	reference 0.13 (0.03–0.65)	<0.01	reference 0.13 (0.01–0.65)	<0.01	reference 0.08 (0.01–0.71)	0.02

*PFS, progression-free survival; OS, overall survival; Gr, tumor growth rate; SumTLs, the sum of the diameters of the target lesions.

Supplementary table. PFS and OS in 25 patients: univariate analyses

Factor		PFS		OS	
		Relative risk (95% CI)	P value	Relative risk (95% CI)	P value
Age		0.73 (0.12–4.47)	0.74	1.52 (0.19–12.6)	0.69
Gender	Female	reference		Reference	
	Male	0.34 (0.12–1.10)	0.07	0.49 (0.16–1.81)	0.26
ECOG performance status	0–1	reference		Reference	
	2	3.88 (1.05–11.7)	0.04	6.12 (1.56–20.9)	0.01
Number of metastatic sites	≤ 2	reference		Reference	
	≥ 3	1.26 (0.44–3.20)	0.65	2.05 (0.69–5.72)	0.19
Platinum-free interval (m)		1.56 (0.23–9.24)	0.64	1.17 (0.15–7.37)	0.88
No. of previous lines of systemic cancer therapy					
	1	reference		Reference	
	≥ 2	1.02 (0.40–2.90)	0.97	1.82 (0.62–6.60)	0.28
Previous receipt of cetuximab	Yes	reference		Reference	
	No	0.78 (0.29–1.91)	0.59	0.45 (0.14–1.25)	0.13
Subsequent treatment	No	reference		Reference	
	Yes	0.85 (0.27–2.25)	0.75	0.34 (0.07–1.07)	0.07
Smoking or tobacco use	Current or former	reference		Reference	
	Never	1.76 (0.57–4.64)	0.30	1.34 (0.37–3.86)	0.62
Sum of diameters of target lesions (SumTLs)		3.15 (0.63–14.2)	0.16	10.3 (1.81–56.6)	< 0.01
Tumor growth rate (Gr)		1.87 (0.22–10.9)	0.53	0.67 (0.06–4.25)	0.69
Biochemical examination of blood	NLR	1.26 (0.19–5.56)	0.79	1.32 (0.18–6.26)	0.76
	LDH	1.00 (0.08–5.42)	1.00	1.60 (0.18–7.60)	0.62
	CRP	9.49 (1.25–63.1)	0.03	12.7 (1.52–92.8)	0.02
Gr and SumTLs					
	Gr < 0.76 and SumTLs < 31.0 mm	0.20 (0.03–0.71)	0.01	0.13 (0.01–0.65)	< 0.01
	Gr ≥ 0.76 or SumTLs ≥ 31.0 mm	reference		reference	