The Role of Relative Lymphocyte Count as a Biomarker for the Effect of Catumaxomab on Survival in Malignant Ascites Patients: Results From a Phase II/III Study

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STATEMENT OF TRANSLATIONAL RELEVANCE

Aim of study was to investigate the role of relative lymphocyte count (RLC: defined as the percentage of lymphocytes within the peripheral white blood cell count) as a potential new biomarker for the efficacy of catumaxomab. Catumaxomab is a trifunctional monoclonal antibody that is approved in the European Union for the intraperitoneal treatment of malignant ascites in patients with epithelial cell-adhesion molecule (EpCAM)-positive carcinomas.

The relative lymphocyte count before therapy was found to be a potential biomarker for catumaxomab treatment efficacy. Predicting the response to cancer therapy is an increasingly important area of clinical research. For targeted therapies such as catumaxomab, biomarkers could potentially lead to significant improvements in current oncology practice by providing the ability to define optimal time schedules and to predict efficacy and tailor treatment to individual patients.

ABSTRACT

Purpose

We report the role of relative lymphocyte count (RLC) as a potential biomarker with prognostic impact for catumaxomab efficacy and overall survival (OS) based on a post-hoc analysis of the pivotal phase II/III study of intraperitoneal catumaxomab treatment of malignant ascites.

Experimental Design

The impact of treatment and RLC on OS was evaluated using multivariate Cox models. Kaplan-Meier and log-rank test were used for group comparisons. Survival analyses were performed on the safety population (patients with paracentesis plus ≥1 dose of catumaxomab [n=157] and paracentesis alone [n=88]). Determination of the optimal cut-off value for RLC was based on five optimality criteria.

Results

OS was significantly longer with catumaxomab versus paracentesis alone (P= .0219). The 6-month OS rate with catumaxomab was 28.9% versus 6.7% with paracentesis alone. RLC had a positive impact on OS and was an independent prognostic factor (P< .0001). In patients with a RLC >13% (n = 159: catumaxomab 100; control 59), catumaxomab was associated with a favorable effect on OS versus paracentesis alone (P= .0072), with a median/mean OS benefit of 41/131 days and an increased 6-month survival rate of 37.0% versus 5.2%, respectively. In patients with a RLC ≤13% at screening (n = 74: catumaxomab: 50; control: 24), the median (mean) OS difference between the catumaxomab and the control group was 3 (16) days, respectively, (P= .2561).

Conclusions

OS was significantly improved after catumaxomab treatment in patients with malignant ascites. A RLC >13% at baseline was a significant prognostic biomarker.

INTRODUCTION

Catumaxomab is a trifunctional monoclonal antibody that is approved in the European Union for the intraperitoneal treatment of malignant ascites in patients with epithelial cell-adhesion molecule (EpCAM)-positive carcinomas (1). The trifunctional mode of action of catumaxomab occurs by binding to epithelial tumor cells via EpCAM, to T-cells via CD3, and activation of Fcγ-receptor I-, IIa- and III-positive accessory cells via its functional Fc domain (2-5). The activation of different immune effector cells at the tumor site by catumaxomab leads to improved tumor-cell elimination by a variety of immunologic killing mechanisms (4, 6) and the presence of a functional immune system is key to its activity (7). In addition to malignant ascites(8), catumaxomab has also shown efficacy in the treatment of peritoneal carcinomatosis (9) and ovarian cancer (10).

The efficacy of intraperitoneal catumaxomab in the treatment of malignant ascites was demonstrated in a pivotal phase II/III study (8). In this randomized study of patients with malignant ascites due to different epithelial cancers, catumaxomab plus paracentesis significantly prolonged puncture-free survival (median 46 versus 11 days; HR, 0.254; $P < .0001$) and time to next paracentesis (median 77 versus 13 days; HR, 0.169; $P < .0001$) compared with the control arm (paracentesis alone). In addition, in the original analysis of this study, there was a trend for improvement in overall survival (OS) with catumaxomab versus paracentesis alone (median 72 versus 68 days; HR, 0.723; $P = .0846$) in the overall population and a significant difference in patients with gastric cancer (n = 66; median 71 versus 44 days; HR, 0.469; $P = .0313$).

An OS benefit of catumaxomab was also demonstrated in an analysis of patients with peritoneal carcinomatosis due to colon, gastric, or pancreatic cancer (11). In this post-hoc matched-pair analysis, 24 patients with peritoneal carcinomatosis treated with catumaxomab in a clinical study were compared with an equally sized control group of patients with peritoneal carcinomatosis treated with conventional intravenous chemotherapy. The median OS from the time of diagnosis of peritoneal carcinomatosis was 502 days with catumaxomab versus 180 days in the control group (HR, = 0.421; *P* = .0083). The potential survival benefit of catumaxomab is being investigated in further clinical studies.

Predicting the response to cancer therapy is an increasingly important area of clinical research, with numerous attempts to identify biomarkers that correlate with therapeutic effects to better select those patients who benefit most from the treatment (12-16). For targeted therapies, biomarkers could potentially lead to significant improvements in current oncology practice. By providing the ability to predict the efficacy of a specific therapy, biomarkers can guide treatment decision making for individual patients.

Besides a clear efficacy in ascites control in the pivotal study (8), prolonged OS could be observed in about 50% of the patients after catumaxomab treatment. Therefore it was of interest, if those patients with benefit in OS could be identified by prognostic biomarkers. As the proposed mode of action of catumaxomab involves the activation of immune effector cells, these cells could be potential biomarkers for the efficacy of catumaxomab. An independently performed hypothesis-generating analysis was conducted to identify potential biomarkers predicting a positive effect of

catumaxomab on OS in patients with peritoneal carcinomatosis. The impact of the the following parameters was investigated: Age, Karnofsky Index (KI), relative (RLC) and absolute lymphocyte count, relative and absolute granulocyte count, T-cell subsets, NK cells, and monocytes before catumaxomab therapy. Correlation analysis, Kaplan-Meier curves, ROC calculation, and multivariate regression were used for statistical analysis. Karnofsky Index ($p=0.002$) and relative lymphocyte count (RLC: defined as the percentage of lymphocytes within the peripheral white blood cell count) before treatment ($p=0.039$) were found to be of prognostic value, being positively correlated with OS (17). Therefore, RLC and other potential biomarkers were investigated for their impact on response to catumaxomab treatment in this study with focus on OS. This analysis was performed post-hoc in a subset of patients in the pivotal study who received at least one dose of catumaxomab (safety population).

PATIENTS AND METHODS

Study Design

This post-hoc analysis of the impact of RLC on OS and puncture free survival (PuFS) used data from the two-arm, randomized, open-label, pivotal phase II/III study (EudraCT number: 2004-000723-15; ClinicalTrials.gov identifier: NCT00836654) of catumaxomab in patients with symptomatic malignant ascites secondary to epithelial cancers requiring symptomatic therapeutic paracentesis (8). In this study, patients were randomized in a 2:1 ratio to either paracentesis plus catumaxomab (catumaxomab n = 170) or paracentesis alone (control n = 88) and stratified by cancer type (ovarian n = 129 and non-ovarian n = 129). Patients in the control group who fulfilled the eligibility criteria and had two therapeutic punctures after paracentesis on day 0 were permitted to receive catumaxomab in a subsequent, single-arm, crossover period. The primary endpoint for this study was PuFS. After the end of the study, patients were followed up until death. After the end of the study, patients were followed up until death. Despite the primary endpoint for this study was PuFS this post-hoc analysis focused on the secondary endpoint OS, the most relevant clinical parameter in oncology studies.

Potential Biomarkers for Catumaxomab Outcome

In the hypothesis-generating analysis, the RLC at screening was identified as a potential biomarker for a survival benefit of catumaxomab therapy. Among a number different parameters investigated, including absolute lymphocyte count (ALC), CD4+ T-cells, CD8+ T cells, CD19+ B cells and natural killer cells, RLC and Karnofsky

index were the only prognostic parameters that significantly correlated with OS(17). Based on these findings, the data of the pivotal study were analyzed for the impact of RLC as a predictive biomarker for the effect of catumaxomab treatment. In addition to the impact of RLC, the impact of the absolute numbers of lymphocytes, granulocytes, and monocytes in the peripheral blood and the Karnofsky index (KI) before treatment (screening) was evaluated.

Safety Population for OS Analysis

The intent-to-treat population of the pivotal phase II/III study comprised 258 patients(8). The survival analyses reported in the current paper were performed primarily on the safety population (n = 245), i.e. patients who received at least one dose of catumaxomab (n = 157) or were treated with paracentesis alone (control group, n = 88). Thirteen patients (7.6%) randomized to the catumaxomab group (five ovarian and eight non-ovarian cancer) did not receive catumaxomab and were excluded from the analysis of the safety population. Four patients died between randomization and first treatment with catumaxomab, five patients withdrew their consent, and four patients were excluded for other reasons, including a serious adverse event (ileus), failure to meet inclusion criteria, and problems with ascites drainage. Exclusion of these patients from the analysis of OS was considered as appropriate and consistent with statistical principles for clinical trials (18, 19).

Statistical Analysis

Of the 245 patients (catumaxomab n = 150; control n = 83) in the safety population, 233 had evaluable screening data for the parameters of interest and were included in the statistical biomarker analysis. The parameters analyzed as potential biomarkers

were derived from the peripheral blood cell counts before the start of treatment: RLC, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), and absolute monocyte count (AMC). Furthermore, the KI at screening was analyzed for its prognostic impact. The impact of treatment and of the potential biomarkers was evaluated using various Cox models, including separate Cox models for the two treatment groups. For assessing the heterogeneity of treatment effects among the levels of a potential biomarker and for assessing the predictive value, a statistical test for interaction was performed within the Cox model, which is consistent with recommendations for reporting subgroup analyses in clinical trials (20).

To identify the optimal RLC cut-off-value a cutpoint determination method for survival analysis was applied (21) – together with further optimality criteria, which were applied for various RLC cut-offs. These optimality criteria included the p-value (for the log-rank test comparing the treatment effects above and below the cut-offs), the Hazard ratio (for assessing the treatment effects above and below the cut-offs), the OS-medians (for patients above the cut-offs –separately for each treatment group), and the sample size (of patients above the cut-offs). All statistical analyses were explorative in nature; therefore P values should be interpreted descriptively.

Cut-off value defined treatment groups were compared for OS and PuFS
by Kaplan-Meier curves and associated estimates, by log-rank-test and HR including 95% confidence interval (CI). Patients randomized to the control group who crossed over to catumaxomab treatment were censored at the date of crossover, i.e. any OS component observed after crossover was not considered for the OS analysis, as it may have been influenced by catumaxomab treatment.

RESULTS

Follow-Up OS Data

Ten patients were alive at the cut-off used for reporting the OS results of the phase II/III study (8). This cut-off was 8 months (ovarian cancer) and 7 months (non-ovarian cancer) after last patient out (LPO). Nine of those 10 patients had been randomized to catumaxomab (seven ovarian, one gastric, and one uterine cancer) and one patient (ovarian cancer) to paracentesis alone. The latter patient crossed over to catumaxomab after reaching the primary endpoint of the study. The KI, ALC, AMC, ANC, and RLC at screening of these patients were comparable to those patients considered for the OS cut-off applied in the phase II/III study (data not shown) (8). The median RLC at screening of these 10 patients was 19.9% (range, 14.3% to 49.0%). At the follow-up analysis 35 months (ovarian cancer) and 34 months (non-ovarian cancer) after LPO, one catumaxomab-treated patient with non-ovarian cancer was alive. Follow-up survival results in the ITT and safety populations are shown in Table 1. In the safety population, there was a statistically significant benefit in OS for catumaxomab-treated patients compared with control patients (P = .0219; HR, 0.649; 95% CI, 0.446 to 0.943) (Figure 1A). The 6-month OS rate in catumaxomab-treated patients was 28.9%, compared with 6.7% in the control group.

The following results are based on the follow-up analysis of the safety population.

Biomarkers with OS Impact

The Cox analysis showed that treatment with catumaxomab and RLC at screening had a strong positive impact on OS (Table 1). There was a strong correlation between RLC and OS in catumaxomab-treated patients but this was not seen in the

control group (Figure 1B and 1C). A significant positive impact on OS (P < .0001) was also observed for KI at screening (Table 1). The effect of catumaxomab treatment on OS remained significant (P = .0060) after adjustment for RLC. According to this model, catumaxomab treatment resulted in a HR of 0.582, corresponding to a catumaxomab-related risk reduction of 41.8%. An increase of 1% in RLC was associated with a risk reduction of 3.8% (HR, 0.962). In contrast, RLC had no significant effect on OS in control patients (P = .0974).

In a sensitivity analysis we further investigated the impact of the RLC-components (i.e. absolute values of WBC) to OS (Table 1). It turned out that ALC had a positive impact on OS (P = .0260). The impact of ANC (P < .0001) and AMC (P = .0425) at screening on OS was also significant but negative, i.e. OS was worse with increasing numbers of neutrophils and monocytes.

Plotting median OS against various RLC cut-offs (Figure 2A) showed that the difference between the catumaxomab and control groups in median OS increased with a RLC of >13%. In addition, a RLC of 13% was the first cut-off at which a substantial difference between the medians was observed, associated with a low P value of .0072 (Figure 2B) for catumaxomab versus the control group and a corresponding HR of 0.5180 (Figure 2C). These observations were supported by the results of a cutpoint determination method for survival analysis (Table 2). Therefore, 13% was selected as the RLC cut-off for subgroup analysis.

In the subgroup of patients with a RLC >13% at screening (n = 159 [64.9%]: catumaxomab n = 100 [63.7%]; control n = 59 [67.0%]), catumaxomab treatment was associated with a prolonged OS compared with the control group (*P* = .0072; HR, 0.518; 95% CI, 0.318 to 0.844), with a median (mean) of 109 (209) versus 68 (78) days (Figure 3a). The 6-month and 1-year survival rates were 37.0% versus 5.2% and 18.5% versus 0.0%, respectively. In patients with a RLC ≤13% at screening (n = 74: catumaxomab n = 50; control n = 24), the median (mean) OS of the catumaxomab and the control groups was 52 (76) and 49 (60) days, respectively (*P* = .2561; HR, 0.695; 95% CI, 0.368 to 1.311) (Figure 3b).

Cut-off value definition at a RLC of 13% had also an impact on PuFS.. Compared to control-patients, catumaxomab treatment prolonged PuFS in patients with low RLC (<=13%) and high RLC (>13%) patients. However, catumaxomab patients with a RLC >13% had a significantly prolonged PuFS compared to patients with RLC <=13% (p= .0027, HR 0.555, Table 3). In control patients, the difference between high and low RLC was not significant (p= .265, HR 0.760; log-rank).

KI had a significant positive impact on OS (Table 1). The study inclusion criteria included patients with a KI of ≥60. A total of 135 (86%) patients (86% catumaxomab; 86% control) had a KI ≥70. In patients with a KI ≥70, OS was statistically significantly longer in catumaxomab-treated patients compared with controls (median 84 versus 62 days, respectively; *P* = .0053; HR, 0.567). In patients with a KI ≥90 (23% of catumaxomab-treated patients, 20% of controls), median OS was 203 days in catumaxomab-treated patients versus 68 days in controls (*P* = .0162; HR, 0.372).

DISCUSSION

RLC was found to be a biomarker with a positive prognostic impact on OS with catumaxomab treatment. In patients with a RLC >13% at screening, catumaxomab treatment was associated with a pronounced beneficial effect on OS versus the control group (*P* = .0072) and a seven-fold higher 6-month survival rate (37.0% versus 5.2%). This statement is also true regarding puncture free survival PuFS, which represented the primary endpoint in the pivotal phase II/III trial. Here, the cut-off value of RLC >13% allowed to select patients with prolonged PuFS (49 vs. 31 days, median, p=0.0027, log-rank) in the catumaxomab treatment group.

These results were achieved by investigating the relevance of RLC as a potential biomarker for catumaxomab treatment based on a retrospective analysis of an independent, smaller, descriptive study. The results of this hypothesis-generating analysis showed that RLC at screening was a prognostic biomarker, being positively correlated with OS, and that patients with a high RLC (>13%) showed an increased OS after catumaxomab treatment versus patients with a RLC ≤13% (mean 14.5 versus 7.1 months, respectively; *P* = .04)(17). In addition, our analysis shows that catumaxomab was associated with a statistically significant OS benefit in the safety population of the pivotal phase II/III study versus paracentesis alone (P = .0219, HR, 0.649). It should be noted that all the patients who were alive at the first cut-off for OS analysis had a RLC >13% (8).

The results are consistent with the proposed immunologic mode of action of catumaxomab (3-6), which requires a functional immune system for its anti-tumor activity. Ott et al. showed that there was a strong correlation between early humoral

immunologic response to catumaxomab, as shown by the development of human antimouse antibodies (HAMAs), and clinical outcome (7). Patients who developed HAMAs after catumaxomab treatment showed significant improvements in the three clinical outcome parameters investigated (OS, puncture-free survival, time to next therapeutic paracentesis). This indicates that the ability of a patient to mount a rapid immunologic response, i.e. the presence of a functional immune system, is key to catumaxomab's positive effects on OS. Different immunologic mechanisms are induced after intraperitoneal administration of catumaxomab, e.g., immediate T-cell mediated cytotoxicity is involved in the reduction of malignant ascites (22). Complex immunological mechanisms in addition to the direct and local effects of catumaxomab may be involved in its mode of action (23). Cellular and humoral immune responses to antigens other than EpCAM (e.g. human epidermal growth factor receptor 2 [HER2] or cancer testis antigens) as well as the detection of catumaxomab-induced long-term-activated T cells and the expansion of preexisting EpCAM-specific T cells after catumaxomab therapy indicate the initiation of persistent systemic immunologic anti-tumor activity (22, 24).

An increased lymphocyte count has also been shown to be a prognostic factor for OS in patients with gastric and colorectal cancer (25, 26). In addition, lymphocyte subsets have been shown to be predictive markers for immunotherapy in cancer patients (14, 27).Characiejus et al. concluded that the pretreatment level of CD8+ T cells could be a predictive biomarker for the response to cancer immunotherapy (14).

The positive impact of RLC on OS was supported by the sensitivity-analysis-results for ALC, which also showed a significant positive impact on OS (P = .0260). The

reason for the stronger signal of RLC versus ALC may be because the RLC includes all peripheral blood cells, including lymphocytes, neutrophils, and monocytes, as it represents the relation of the ALC to all peripheral blood cell populations (17). A number of studies on the neutrophil/lymphocyte ratio (NLR, analogous to the RLC) in different tumor types, including gastric, colorectal, and ovarian, showed that a high NLR (corresponding to a low RLC) is a poor prognostic parameter (28-30). This could result from impaired immunologic function due to a low number of lymphocytes and also from inflammatory processes caused by inhibitory neutrophils that can lead to stimulation of the tumor. Neutrophils secrete vascularization factors, such as vascular endothelial growth factor (VEGF), which promote tumor growth (31). In addition, neutrophils are also known to inhibit the specific immune system (32). An et al. therefore suggested that the NLR could represent the balance between pro-tumor inflammatory status and anti-tumor immune status (33). The findings of the present study, that the ANC and AMC have a negative impact on OS, support this interpretation. The advantage of using RLC is that it is easy to assess using an established routine diagnostic method. The results of the analysis of the outcome of catumaxomab-treated patients according to their performance status can be regarded as consistent with the RLC results, as a functional immune system is generally associated with an adequate performance status. Moreover, as RLC could be shown to be an independent prognostic marker, it can be concluded that both RLC and KI may complement one another with regard to treatment decision making.

In conclusion, a RLC >13% could be used as a pre-therapeutic biomarker for enhanced efficacy of catumaxomab treatment, regarding both PuFS and overall survival. These benefits in patients with a RLC >13% indicate that treatment with

catumaxomab in this subgroup may also result in effects on disease outcome, in addition to symptom control. Appropriate patient selection is therefore important for achieving a maximum treatment effect with catumaxomab, including a potential survival benefit. Moreover, the RLC may be used to define the optimal timepoint to start catumaxomab treatment in context of multimodal treatment. As RLC is a dynamic and easily accessible marker, it allows not only to select appropriate patients, but also optimal time management in context with systemic chemotherapy. Therefore, early use of catumaxomab in selected patients in the course of disease could increase the OS benefit in addition to the symptom relief provided.

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TABLES

Table 1

Follow-up overall survival in the intent-to-treat (ITT) and safety populations				
	ITT population		Safety population[§]	
	Catumaxomab (n = 170)	Control (n = 88)	Catumaxomab (n = 157)	Control (n = 88)
3-month survival rate	43.7%	23.6%	45.3%	23.6%
6-month survival rate	27.5%	6.7%	28.9%	6.7%
1-year survival rate	11.4%	3.4%	12.0%	3.4%
2-year survival rate	2.9%	0%	3.1%	0%
Median overall survival, days	72	68	79	68
p-value	.0783		.0219	
Hazard ratio (95% CI)	0.718 (0.495 to 1.041)		0.649 (0.446 to 0.943)	

Impact of catumaxomab-treatment, RLC and KI on overall survival (Cox model)		
Parameter	*p*-value	Hazard ratio (95% CI)
Catumaxomab treatment versus control	.0060	0.582 (0.395 to 0.856)
RLC*	< .0001	0.962 [a] (0.945 to 0.980)
KI*	< .0001	0.963 [b] (0.94 to 0.976)

Impact of catumaxomab-treatment, and other relevant absolute counts of WBC-baseline characteristics on overall survival (Cox model)		
Parameter	*p*-value	Hazard ratio (95% CI)
Catumaxomab treatment versus control	.0328	0.648 (0.435 to 0.965)
ALC*	.0260	0.784 [c] (0.632 to 0.971)
ANC*	< .0001	1.116 [d] (1.060 to 1.175)
AMC*	.0425	1.758 [e] (1.019 to 3.031)

Annotations and abbreviations:
RLC, relative lymphocyte count; KI, Karnofsky index; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; AMC, absolute monocyte count.
[§] Patients who received at least one dose of catumaxomab and were included in the catumaxomab arm.
*At screening.

[a]Increasing RLC by 1% results in a risk decrease of 3.8%; [b]Increasing KI by 1% results in a risk decrease of 3.7%; [c]Increasing ALC by 1000/µl results in a risk decrease of 31.6%; [d]Increasing ANC by 1000/µl results in a risk increase of 11.6%; [e]Increasing AMC by 1000/µl results in a risk increase of 75.8% corresponding to a risk increase of 7.58% with an AMC increase by 100/ µl.

Table 2:
Cutpoint determination for RLC by a survival tree analysis according to Mandrekar et al. (20). [a]

Observation	Cut point RLC (%)	P-value
19	10.00	P>0.30
20	10.10	P>0.30
21	10.20	P>0.30
22	11.00	0.2602
23	11.10	0.1749
24	11.20	0.1213
25	11.50	0.101
26	11.70	0.095
27	12.40	0.0822
28	12.50	0.0694
29	12.60	0.0423
30	12.70	0.0288
31	12.80	0.0228
32	12.90	0.0084
33	13.00	0.0047
34	13.50	0.0013
35	14.00	0.0003
36	14.30	0.0001
37	14.40	0.0004
38	14.50	0.0003
39	14.90	0.0003
40	15.00	0.0002
41	15.10	0.001
42	15.70	0.0025
43	16.00	0.0033
44	16.40	0.0046
45	16.50	0.0029
46	16.70	0.0056
47	16.90	0.0106
48	17.00	0.0031
49	17.20	0.0061
50	17.30	0.0035
51	17.50	0.0049
52	17.80	0.0028
53	17.90	0.0029
54	18.00	0.0031
55	18.20	0.0051
56	18.30	0.0094
57	18.40	0.006
58	18.50	0.0085
59	18.60	0.0114
60	18.80	0.0108
61	19.00	0.0501
62	19.10	0.0731
63	19.30	0.0498
64	19.60	0.0282
65	20.00	0.0302

[a]: This table is just an excerpt of the complete analyses, which focuses on the range of RLC-values relevant for the cut-off selection. However, the analyses were performed for the entire range of observed RLC-values (0.4 - 56.0)

Table 3:

Puncture- free Survival (PuFS): Comparison of RLC-Subgroups

	Catumaxomab versus control			
	RLC > 13%		RLC ≤ 13%	
	Catumaxomab (n=100)	Control (n=59)	Catumaxomab (n=50)	Control (n=24)
Median PuFS, days	49	15	31	9
HR (95%CI)	0.231 (0.153; 0.348)		0.331 (0.192; 0.572)	
p-value (log-rank test)	<0.0001		<0.0001	
	Catumaxomab: RLC >13% versus RLC ≤ 13%			
	RLC > 13% (n=100)		RLC ≤ 13% (n=50)	
Median PuFS, days	49		31	
HR (95%CI)	0.555 (0.375; 0.823)			
p-value (log-rank test)	0.0027			
	Control: RLC >13% versus RLC ≤ 13%			
	RLC > 13% (n=59)		RLC ≤ 13% (n=24)	
Median PuFS, days	15		9	
HR (95%CI)	0.760 (0461; 1.251)			
p-value (log-rank test)	0.2650			

FIGURE LEGENDS

FIGURE 1

Figure 1A: Overall survival of the safety population including long term follow up data

Figure 1B and 1C: Overall survival in relation to the relative lymphocyte count at screening in catumaxomab-treated (B) and control (C) patients

FIGURE 2

Figure 2A: Median Overall survival in patients treated with catumaxomab and control patients for various RLC cut-off values.

Figure 2B: Hazard Ratios for comparing treatment effects above/below various RLC cut-off values.

Figure 2C: P-values Log rank Test comparing treatment effects above/below various RLC cut-off values.

Median, p-value and HR above / below cutoff refers to the comparison between the treatment groups (Catumaxomab vs. Control) for the subgroup of patients above (>) / below or equal (<=) the corresponding RLC cut-off displayed on the x-axis.

FIGURE 3:

Overall survival in patients with a relative lymphocyte count of >13% (A) and ≤13% (B) at screening (only patients with valid lymphocyte results were included in the analysis. Crossover patients were censored at the time of first catumaxomab infusion).

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Figure 1A

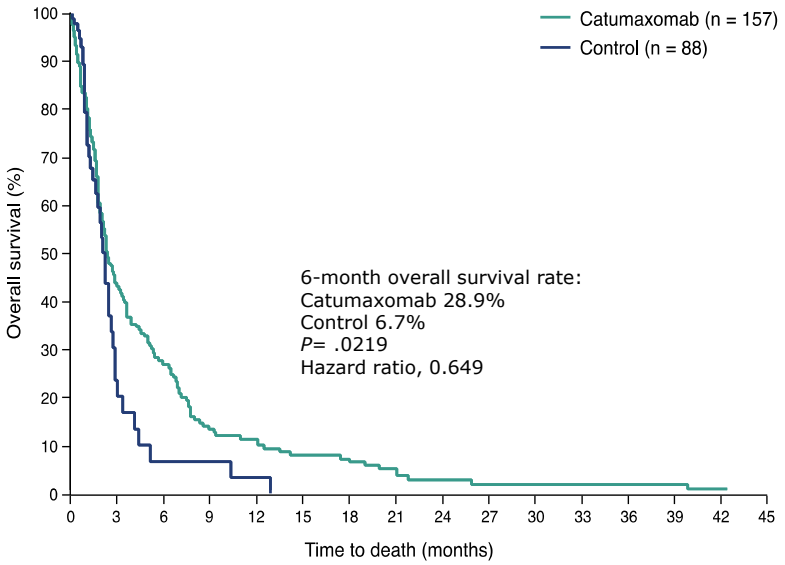

Figure 1B

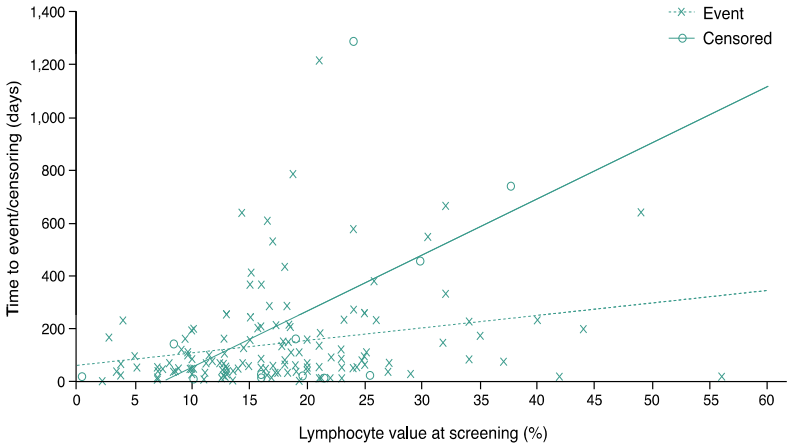

Figure 1C

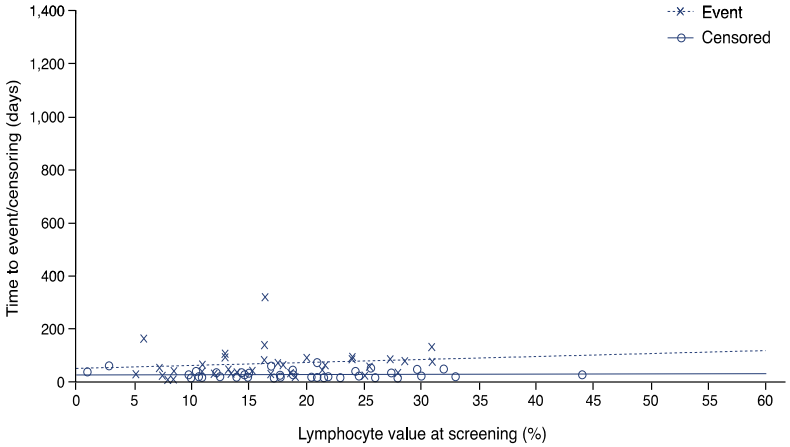

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Figure 2A

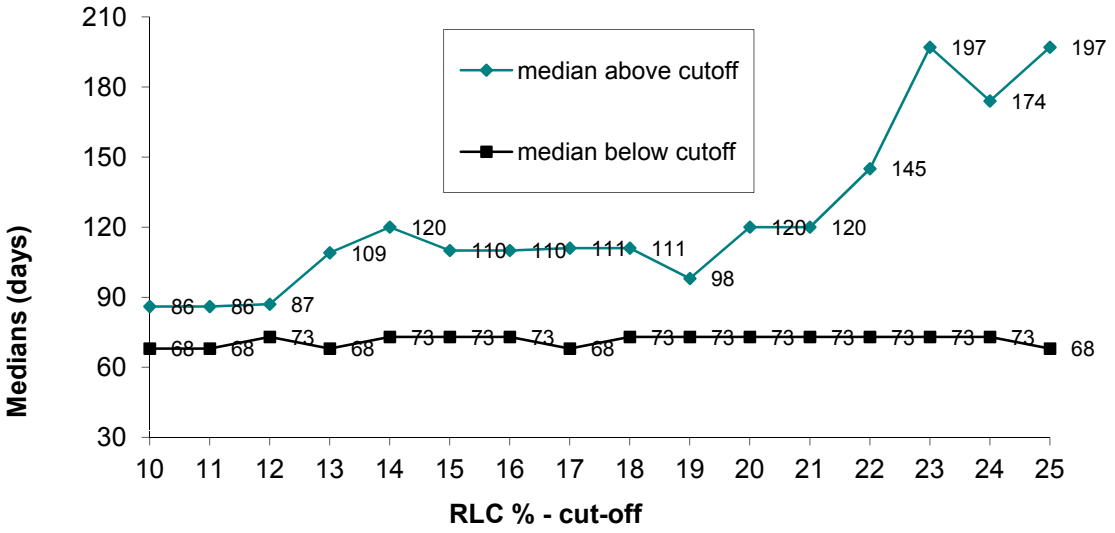

Figure 2B

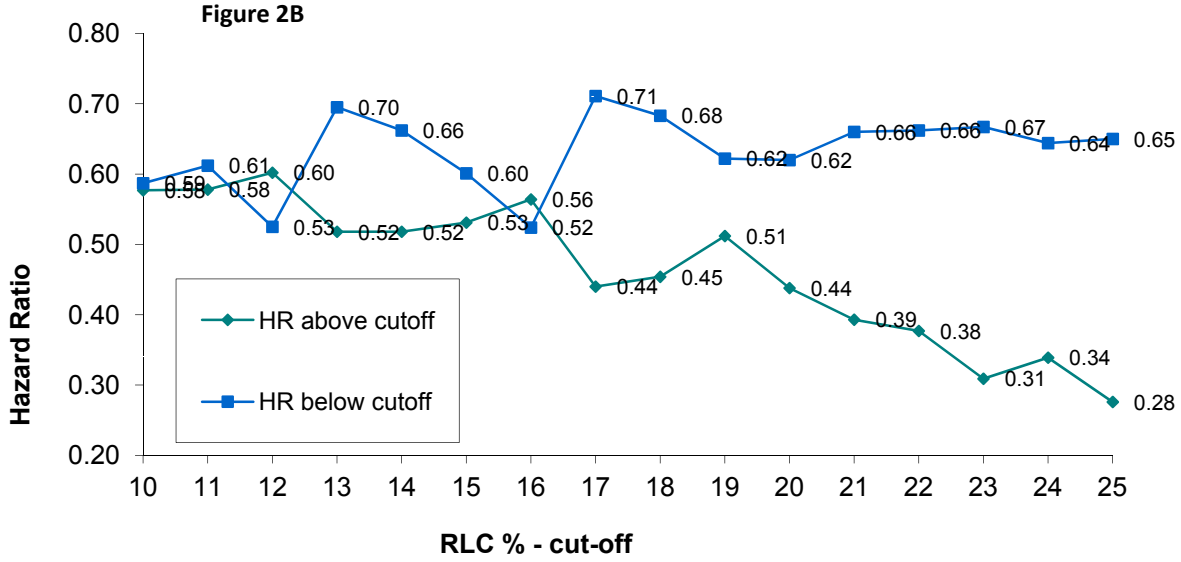

Figure 2C

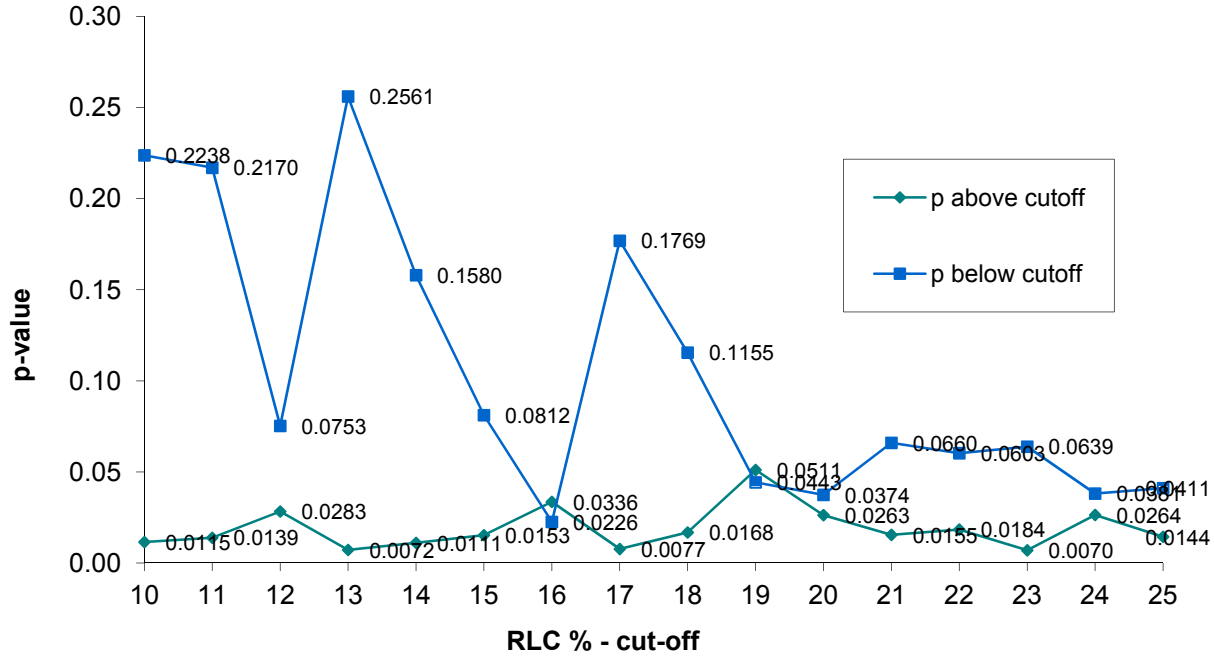

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FIGURE 3A

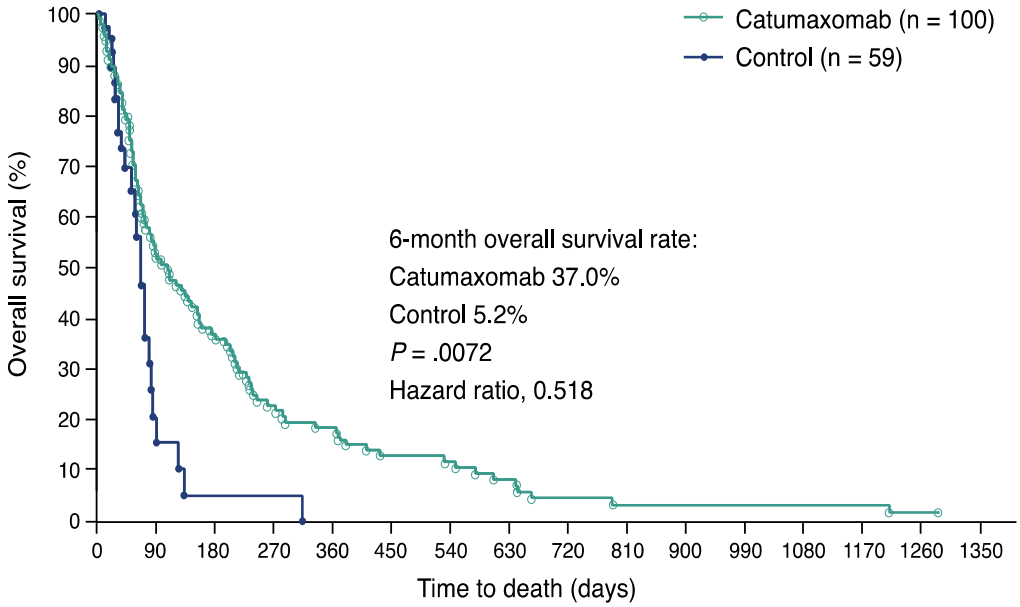
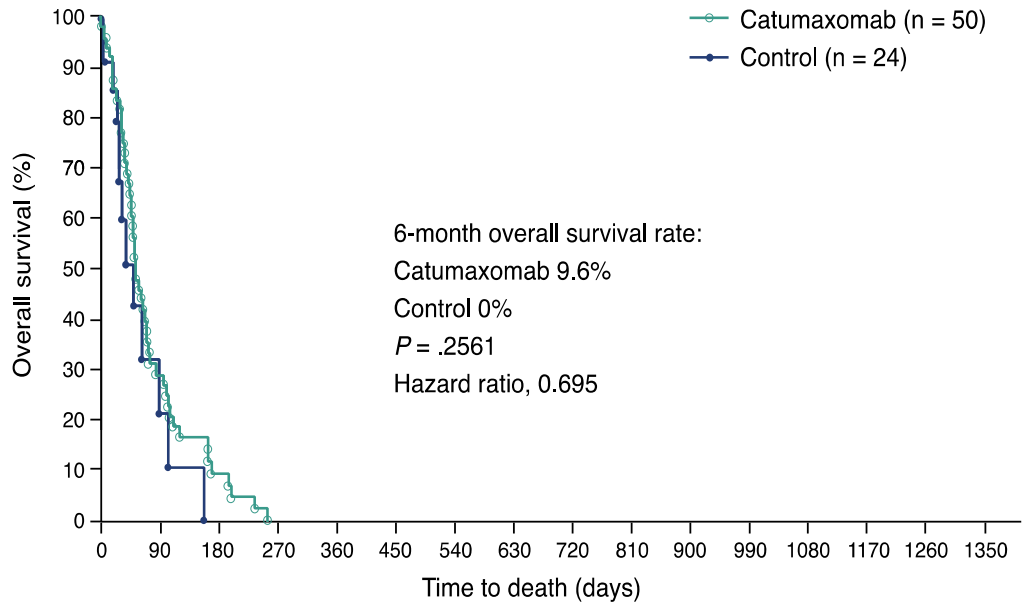


FIGURE 3B



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The Role of Relative Lymphocyte Count as a Biomarker for the Effect of Catumaxomab on Survival in Malignant Ascites Patients: Results From a Phase II/III Study

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