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Deterioration in quality of life (QoL) in patients with malignant ascites: results from a phase II/III study comparing paracentesis plus catumaxomab with paracentesis alone

P. Wimberger¹, H. Gilet^{2*}, A-K. Gonschior³, M. M. Heiss⁴, M. Moehler⁵, G. Oskay-Oezcelik⁶, S-E. Al-Batran⁷, B. Schmalfeldt⁸, A. Schmittel⁹, E. Schulze¹⁰ & S. L. Parsons¹¹

¹Gynaecology and Obstetrics Clinic, University of Duisburg-Essen, Essen, Germany; ²Mapi Consultancy, Lyon, France; ³Pricing, Reimbursement and Market Access, Fresenius Biotech GmbH, München; ⁴Department of Surgery, Cologne-Merheim Medical Center, Köln; ⁵1st Medical Clinic and Policlinic, Johannes-Gutenberg University, Mainz; ⁶Quality of Life Working Group of the North-Eastern German Society of Gynecological Oncology (NOGGO), Berlin; ⁷Department of Hematology and Oncology, Krankenhaus Nordwest, Frankfurt; ⁸Department for Obstetrics and Gynecology, Technical University of Munich, München; ⁹Department of Hematology, Oncology and Transfusion Medicine, Charité University Hospital Berlin, Berlin; ¹⁰Medical Affairs, Fresenius Biotech GmbH, München, Germany; ¹¹Department of Surgery, Nottingham University Hospitals NHS Trust, Nottingham, UK

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Background: Malignant ascites (MA) is associated with poor prognosis and limited palliative therapeutic options. Therefore, quality of life (QoL) assessment is of particular importance to demonstrate new treatment value. Following the demonstration of the superiority of catumaxomab and paracentesis over paracentesis on puncture-free survival, this analysis aimed at comparing deterioration in QoL between both the treatment options.

Patients and methods: In a randomised, multicentre, phase II/III study of patients with MA due to epithelial cell adhesion molecule (EpCAM) positive cancer, the QoL was evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30) questionnaire at screening, 1, 3 and 7 months after treatment and in the case of re-puncture on the day of paracentesis. Time to first deterioration in QoL was defined as a decrease in the QoL score of at least five points and compared between the catumaxomab ($n = 160$) and control ($n = 85$) groups using the log-rank test and Cox proportional hazards models adjusted for baseline score, country and primary tumour type.

Results: Deterioration in QoL scores appeared more rapidly in the control than in the catumaxomab group (median 19–26 days versus 47–49 days). The difference in time to deterioration in QoL between the groups was statistically significant for all scores ($P < 0.01$). The hazard ratios ranged from 0.08 to 0.24 ($P < 0.01$).

Conclusions: Treatment with catumaxomab delayed deterioration in QoL in patients with MA. Compared with paracentesis alone, catumaxomab enabled patients to benefit from better QoL for a prolonged survival period.

Key words: deterioration, malignant ascites, quality of life

*Correspondence to: Mrs H. Gilet, Mapi Consultancy, 27 rue de la Villette, 69003 Lyon, France. Tel: +33-4-72-13-59-78; Fax: +33-4-72-13-51-40; E-mail: hgilet@mapi-group.com

introduction

Ascites is an abnormal accumulation of fluid in the abdominal cavity due to the unbalanced plasma flow into and out of the blood and lymphatic vessels. Malignant ascites (MA) is caused by peritoneal carcinomatosis, and is related to a poor prognosis in cancer patients [1, 2]. Primary tumours associated with MA include ovarian, gastrointestinal, breast, pulmonary, uterine and cervical cancer. Patients suffering from MA experience a number of burdensome symptoms accompanied with reduced performance status, which may negatively impact their health-related quality of life (HRQL). In this palliative situation, particular attention should thus be paid to HRQL assessment in cancer trials [3].

Until recently, therapeutic options were limited to repeated paracentesis, systemic or intraperitoneal chemotherapy. The trifunctional antibody catumaxomab received European marketing authorisation for the treatment of MA in patients with epithelial cell adhesion molecule (EpCAM)-positive carcinomas where a standard therapy is not available or no longer feasible [4]. Its superiority over paracentesis was demonstrated in terms of puncture-free survival in a randomised clinical trial: puncture-free survival was significantly longer in the catumaxomab group (median 46 days) than in the control group (median 11 days), and overall survival showed a positive trend for the catumaxomab group [5].

The HRQL was also investigated in this study. The interest in the evaluation of HRQL in cancer trials has increased over the past decades and is now considered as important to complement the conventional end points such as survival or time to progression. Patient perspective, as measured by patient-reported outcomes questionnaires, can provide valuable information on the efficacy of an intervention and its possible detrimental effects [6]. In the catumaxomab study, the HRQL was assessed to show that prolonged puncture-free survival was not associated with deterioration in HRQL. This article presents the effects of paracentesis and catumaxomab compared with paracentesis alone in terms of HRQL, with the objective of evaluating whether catumaxomab is associated with a sustained HRQL in addition to a prolonged puncture-free survival.

materials and methods

study design

This study was a two-arm, randomised (2:1), open-label, multicentre European phase II/III study carried out in EpCAM positive cancer patients with symptomatic MA to compare paracentesis and catumaxomab (catumaxomab group) with paracentesis alone (control group). Patients with ovarian and non-ovarian cancer were two predefined strata. The primary objective of the study was to demonstrate the superiority of treatment with catumaxomab over treatment with paracentesis alone in terms of puncture-free survival. The assessment of patients' HRQL in both the groups was one of the secondary objectives of the trial. Catumaxomab was administered on days 0, 3, 7 and 10. Up to five visits were then scheduled during the follow-up period on day 8 and 1, 3, 5 and 7 months (end of study), following last infusion for the catumaxomab group and after day 0 for the control group. The end of study was reached when the patient required a therapeutic ascites re-puncture, died, needed an

antitumour treatment due to progression of disease, dropped out for any other reasons, and otherwise 7 months after treatment. More details can be found in Heiss *et al.* [5].

A total of 129 patients with ovarian cancer and 129 patients with non-ovarian cancer were included in the study. These 258 patients were randomised to the treatment groups in a 2:1 ratio, i.e. 170 in the catumaxomab group and 88 in the control group. Patients were recruited in 13 European countries: Austria, France, Germany, the Netherlands and the UK for Western Europe, and Czech Republic, Estonia, Latvia, Lithuania, Poland, Romania, Russian Federation and Ukraine for Eastern Europe.

The study was approved by an independent ethics committee at each study centre and conducted in compliance with the Declaration of Helsinki. All patients gave written informed consent before participation.

study end points

Patients' HRQL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30) questionnaire at screening, 1, 3 and 7 months after treatment and in the case of therapeutic ascites re-puncture on the day of paracentesis. The EORTC QLQ-C30 is a well-recognised HRQL questionnaire designed for use in a wide range of cancer patient populations and considered as a reliable and valid measure of HRQL [7, 8]. It was also shown to be appropriate for the evaluation of symptom relief after paracentesis in symptomatic ascites [9]. The EORTC QLQ-C30 was developed to measure the HRQL of cancer patients participating in international clinical trials; it has thus been translated into and validated in more than 80 different languages. It includes 30 items grouped into 6 functional and quality of life (QoL) scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning and global QoL), and 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact). All scores range from 0 to 100, with a higher score corresponding to a better level of functioning or QoL for the functional and QoL scales, and to a higher level of symptoms for the symptom scales. Thresholds for the interpretation of EORTC QLQ-C30 scores were established by Osoba *et al.* [10]: a change in the score from 5 to 10 can be interpreted as a small change in the HRQL, a change in the score from 10 to 20 can be interpreted as a moderate change in the HRQL and a change in the score above 20 can be interpreted as a large change in the HRQL. Reference values have been published for QLQ-C30 scores by the EORTC QoL group for all cancer types grouped together [11].

Fatigue, nausea and vomiting, pain, dyspnoea, sleep disturbance and appetite loss symptoms are the common symptoms associated with MA [12, 13] and were considered of primary importance for MA patients [9]. Emotional and global QoL scores were also considered of primary interest in this study as Husain *et al.* [14] highlighted the importance of measuring HRQL and emotional symptoms, such as depression and anxiety, in studies conducted on MA.

statistical analysis

For each EORTC QLQ-C30 score, deterioration in HRQL was defined as a decrease in the score from screening of at least five points, the threshold proposed by Osoba *et al.* as a small but meaningful change in HRQL. Time to first deterioration in HRQL was then analysed using survival methods with the log-rank test and Cox proportional hazards models adjusting for the baseline value of the EORTC QLQ-C30 score, country and primary tumour type. Patients with no deterioration in EORTC QLQ-C30 scores were censored at the end of study, re-puncture time or death time.

A sensitivity analysis was conducted using a decrease of 10 points to define deterioration in HRQL. Analyses were conducted on all randomised patients who completed at least one item of the EORTC QLQ-C30 at screening (Full QoL analysis set, FQoLAS). Sensitivity analyses were also conducted on all patients who received at least one dose of treatment in the catumaxomab group or all randomised patients in the control group, and who completed at least one item of the EORTC QLQ-C30 at screening (Safety QoL analysis set, SQoLAS). All analyses were carried out using SAS software for Windows version 9.2 (SAS Institute, Cary, NC, USA).

results

description of the population

Among the 258 patients enrolled in the study, 245 completed the EORTC QLQ-C30 questionnaire at screening and constituted the FQoLAS. Among them, 160 were randomised to the catumaxomab group and 85 to the control group (Figure 1). The catumaxomab and control groups were similar at screening in terms of sociodemographics and clinical data, with a mean age of 58 years and about 80% being female (Table 1). In terms of HRQL at screening, the overall distribution of EORTC QLQ-C30 scores of primary interest was similar for the catumaxomab and control groups for global QoL, fatigue, sleep disturbance and appetite loss, indicating a similar HRQL and level of symptoms in both the treatment groups (Table 2). For the emotional functioning, nausea and vomiting, pain and dyspnoea, scores reflected a slightly better HRQL and level of symptoms for the catumaxomab group than for the control group, with differences in mean scores between the catumaxomab and control groups >5 points but <10 points (5.3, 6.7, 5.5 and 9.2, respectively). For both the treatment groups, the mean scores at screening reflected an impaired HRQL and level of symptoms compared with reference data of all cancer sites pooled together [11]. For the catumaxomab group, the mean HRQL scores were similar for ovarian and non-ovarian cancer patients, while for the control group, ovarian cancer patients

reported a better level of symptoms such as fatigue, pain, dyspnoea and appetite loss.

A total of 234 patients were included in the SQoLAS population; this population did not differ substantially from the FQoLAS population.

time to first deterioration in HRQL

For scores of primary interest, deterioration in HRQL scores appeared more rapidly in the control group than in the catumaxomab group (Figure 2): the median time to first deterioration ranged from 19 to 26 days in the control group, while it ranged from 47 to 49 days in the catumaxomab group. The Kaplan–Meier curves also showed that the deterioration in HRQL appeared sooner in the control group than in the catumaxomab group (Figure 3). The difference in time to first deterioration in HRQL between the treatment groups was statistically significant for all EORTC QLQ-C30 scores of primary interest with log-rank tests ($P < 0.001$ for all scores). Results were confirmed by using Cox proportional hazards models when adjusting for the baseline value of score, country and primary tumour type (Table 3). The hazard ratios ranged from 0.08 for nausea and vomiting score to 0.24 for emotional functioning score. Regarding covariables included in the models to adjust for potential confounding factors (baseline value of the EORTC QLQ-C30 score, primary tumour type and country), the baseline value of the score was found to have a significant impact on the deterioration of HRQL for all scores of primary interest ($P < 0.05$), except for the fatigue score ($P = 0.214$): the better the level of QoL or the lower the level of symptoms at baseline, the greater the risk of experiencing a deterioration in QoL or symptoms during the study (hazard ratio of 1.02 for QoL scores and between 0.97 and 0.99 for symptom scores). Contrary to the baseline value of the score, primary tumour type and country tended to show no significant impact on time to deterioration in HRQL ($P > 0.05$). All results were similar for other EORTC QLQ-C30 scores.

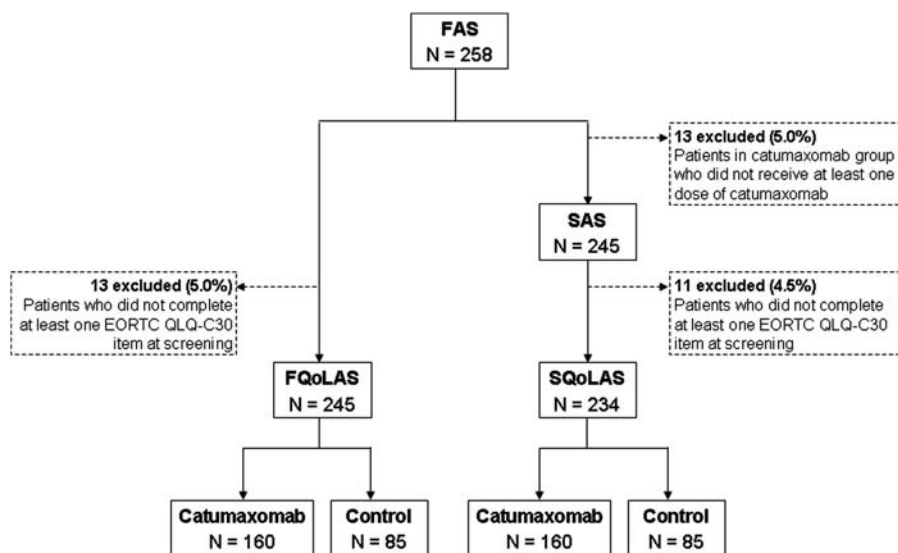


Figure 1. Flow chart of analysis sets. FAS, full analysis set; SAS, safety analysis set; FQoLAS, full QoL analysis set; SQoLAS, safety QoL analysis set.

Table 1. Sociodemographic and clinical characteristics of patients at screening (full QoL analysis set, FQoLAS).

Variable	Catumaxomab (n = 160)	Control (n = 85)
Age		
n	160	85
Mean (SD)	58.2 (10.6)	58.5 (11.6)
Median	58.0	58.0
Min–Max	23.0–85.0	31.0–85.0
Gender		
Male, n (%)	33 (20.6)	16 (18.8)
Female, n (%)	127 (79.4)	69 (81.2)
Country ^a		
Western Europe, n (%)	47 (29.4)	25 (29.4)
Eastern Europe, n (%)	113 (70.6)	60 (70.6)
Main tumour type		
Gastric cancer, n (%)	44 (27.5)	19 (22.4)
Breast cancer, n (%)	4 (2.5)	8 (9.4)
Ovarian cancer, n (%)	81 (50.6)	43 (50.6)
Other ^b , n (%)	31 (19.4)	15 (17.6)
Abdominal girth (cm)		
n	155	85
Mean (SD)	97.0 (13.2)	98.4 (11.5)
Median	95.5	99.0
Min–Max	67.0–140.0	75.0–125.0
Ascites mass (g)		
n	156	84
Mean (SD)	3627.3 (2528.1)	3724.9 (2491.4)
Median	3240.0	3479.5
Min–Max	82.0–13 000.0	100.0–14 350.0
Number of punctures before randomisation		
n	160	85
Mean (SD)	2.1 (2.0)	2.0 (2.1)
Median	1.0	1.0
Min–Max	1.0–10.0	1.0–10.0

^aWestern Europe includes Germany, Great Britain, Austria, France and the Netherlands; Eastern Europe includes Poland, Ukraine, Russian Federation, Romania, Estonia, Lithuania, Czech Republic and Latvia.

^bIncluding colon, pancreas, lung, endometrial and other carcinomas.

Sensitivity analyses conducted with a 10-point threshold instead of 5-point threshold for the definition of deterioration in HRQL provided similar results with a statistically significant difference in time to deterioration in HRQL in favour of the catumaxomab group for all scores (hazard ratios ranging from 0.08 to 0.23 with $P < 0.001$ for scores of primary interest) (Supplementary Table S1, available at *Annals of Oncology online*). The same results were found when sensitivity analyses were conducted on the SQoLAS population, whatever the threshold for the definition of deterioration in HRQL (data not shown).

discussion

The HRQL of patients suffering from MA is certainly impacted as patients have to face a number of burdensome symptoms that are associated with reduced performance status. In addition, due to the palliative nature of treatment of MA, demonstrating the benefits of a new treatment in terms of prolonged survival or other traditional clinical end points may not be enough to show the whole benefit for patients. That is why HRQL assessment in cancer trials has become of major interest in the last few decades.

In order to complement the efficacy and safety results of catumaxomab [5, 4], this study aimed to demonstrate that catumaxomab was associated with a sustained HRQL in addition to a prolonged puncture-free survival, compared with paracentesis alone. The first deterioration in HRQL appeared more rapidly in the control group than in the catumaxomab group for all HRQL scores defined as of primary interest, with median time to first deterioration between 47 and 49 days in the catumaxomab group and between 19 and 26 days in the control group. Differences in time to first deterioration in HRQL between the treatment groups were found to be statistically significant, and a consistent pattern was observed across the results of all analysis methods used. The analysis of HRQL scores not defined as of primary interest, as well as different sensitivity analyses, led to the same conclusions.

Table 2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30) scores of primary interest at screening (full QoL analysis set, FQoLAS)--Mean (SD)

EORTC QLQ-C30 score	Catumaxomab (n = 160)			Control (n = 85)			Reference data: all cancer sites [11] ^b (n = 23 553)
	Ovarian (n = 81)	Non-ovarian ^a (n = 79)	Total (n = 160)	Ovarian (n = 43)	Non-ovarian ^a (n = 42)	Total (n = 85)	
Emotional functioning	60.1 (25.8)	63.3 (24.1)	61.6 (25.0)	57.0 (25.2)	55.6 (29.3)	56.3 (27.2)	71.4 (24.2)
Global quality of life (QoL)	40.5 (18.9)	41.8 (17.7)	41.1 (18.2)	38.5 (17.1)	39.2 (18.2)	38.9 (17.5)	61.3 (24.2)
Fatigue	59.0 (22.7)	61.3 (23.4)	60.1 (23.0)	60.7 (25.0)	66.1 (21.4)	63.4 (23.3)	34.6 (27.8)
Nausea and vomiting	26.1 (27.6)	23.2 (24.2)	24.7 (26.0)	29.1 (30.2)	33.7 (22.8)	31.4 (26.8)	9.1 (19.0)
Pain	39.3 (28.1)	38.0 (25.9)	38.6 (26.9)	41.5 (28.7)	46.8 (25.3)	44.1 (27.1)	27.0 (29.9)
Dyspnoea	35.4 (29.5)	35.9 (32.1)	35.6 (30.7)	38.0 (29.6)	52.0 (28.9)	44.8 (29.9)	21.0 (28.4)
Sleep disturbance	41.3 (31.9)	40.5 (30.5)	40.9 (31.1)	38.8 (34.1)	38.9 (30.3)	38.8 (32.1)	28.9 (31.9)
Appetite loss	50.2 (33.4)	52.1 (34.2)	51.2 (33.7)	50.4 (35.9)	60.3 (32.3)	55.3 (34.3)	21.1 (31.3)

^aIncluding gastric, breast, colon, pancreas, lung, endometrial and other carcinomas.

^bIncluding all cancer sites and not only MA.

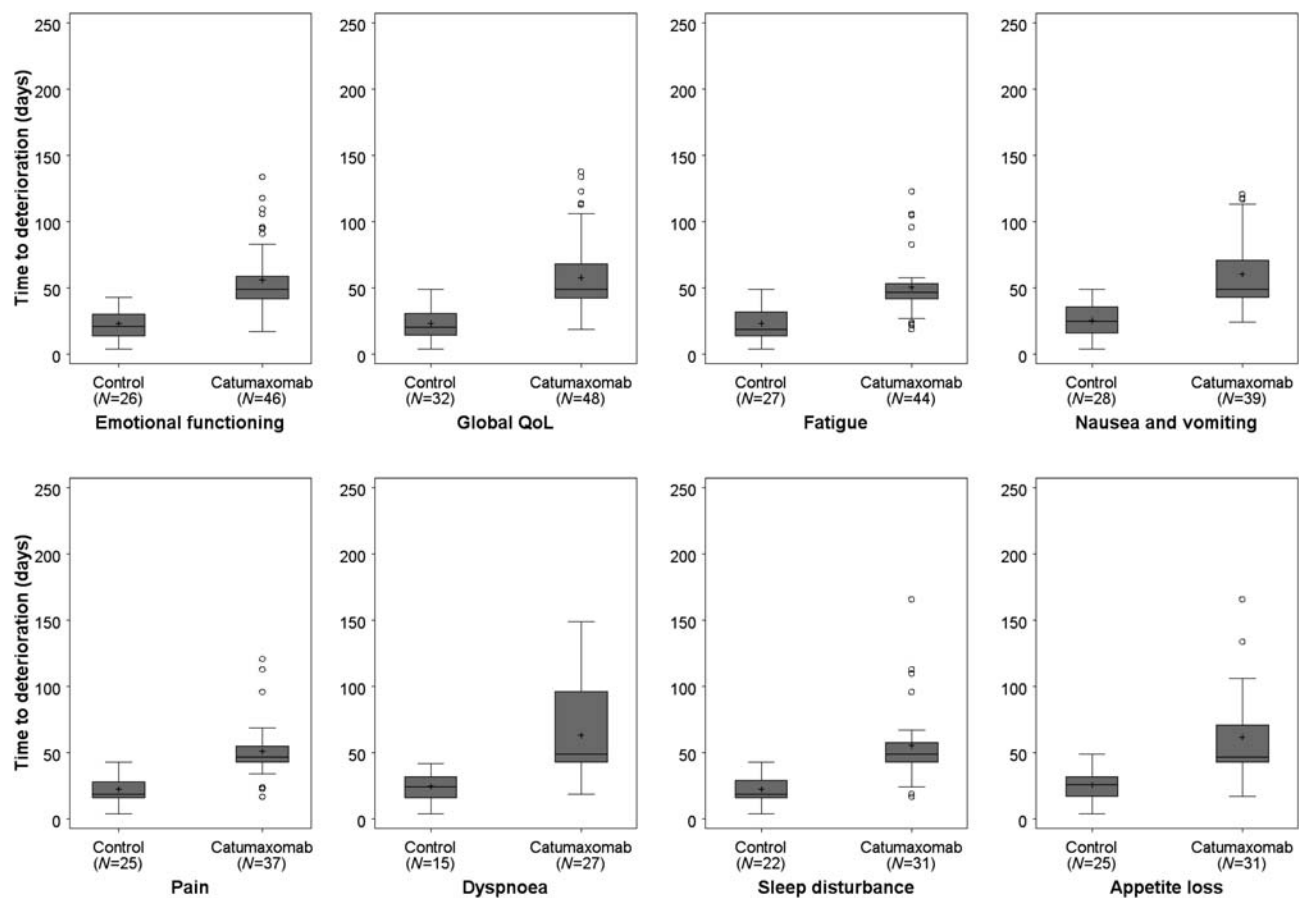


Figure 2. Time to first deterioration in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30) scores of primary interest, in days (full QoL analysis set, FQoLAS). Box for each score: interquartile range (Q1–Q3); +: mean; -: median; bottom and top bars: observed minimum and maximum values; ○: outliers (i.e. values that are outside the distance of 1.5 times the interquartile range from Q1 or Q3). Note: patients censored: $n = 112$ – 133 for catumaxomab, $n = 53$ – 70 for control.

Choosing the least restrictive threshold (decrease of at least five points in scores) for the main definition of deterioration in HRQL could have led to a rapid deterioration in scores observed for all patients, regardless of the treatment group, and thus to inconclusive results. However, we found a clear superiority of catumaxomab over control with this threshold, and the fact that similar findings resulted from the different sensitivity analyses conducted gave support to our main analysis and proved the robustness of our results.

Previously published results showed that catumaxomab was associated with both a prolonged puncture-free survival compared with control (median of 46 days versus 11 days, $P < 0.001$) [5], and less symptoms, with more patients in the catumaxomab group being free of symptoms compared with the control group (33.1% versus 11.4% 8 days after treatment, 19.7% versus 4.5% after 1 month, and 6.4% versus 0% after 3 months) [15]. Moreover, when considering the symptoms of ascites, abdominal pain, nausea and fatigue that are overlapping with typical adverse reactions of catumaxomab [5], already 8 days after treatment the percentage of patients free of these symptoms had increased compared with screening and was significantly higher compared with control [16]. Overall, the safety profile of catumaxomab has been shown to be

acceptable, with frequent, but manageable and generally reversible adverse events mainly related to its immunologic mode of action [5]. Therefore, catumaxomab enables patients to benefit not only from a longer puncture-free survival, but also from a better HRQL for a longer period of life and a prolonged reduction of ascites symptoms, with an acceptable tolerability. In order to complete the clinical, HRQL and safety evaluation of catumaxomab, investigations on costs per quality-adjusted life year, capturing both the quantity and quality of life related to the treatment, should be carried out to also examine catumaxomab's value from an economic perspective.

Symptomatic paracentesis is carried out primarily to relieve symptoms and it is of no surprise, therefore, that HRQL results seem to correlate with a delay in the need for symptomatic paracentesis. The clear delay to deterioration of HRQL seen in the catumaxomab patients compared with control emphasises the HRQL benefit to these patients and the validity of our primary end point puncture-free survival. It is not possible to determine whether the delay to deterioration of HRQL was also partly due to other effects of catumaxomab on the tumour.

In addition, the study was conducted using an open-label study design because of the lack of an approved active

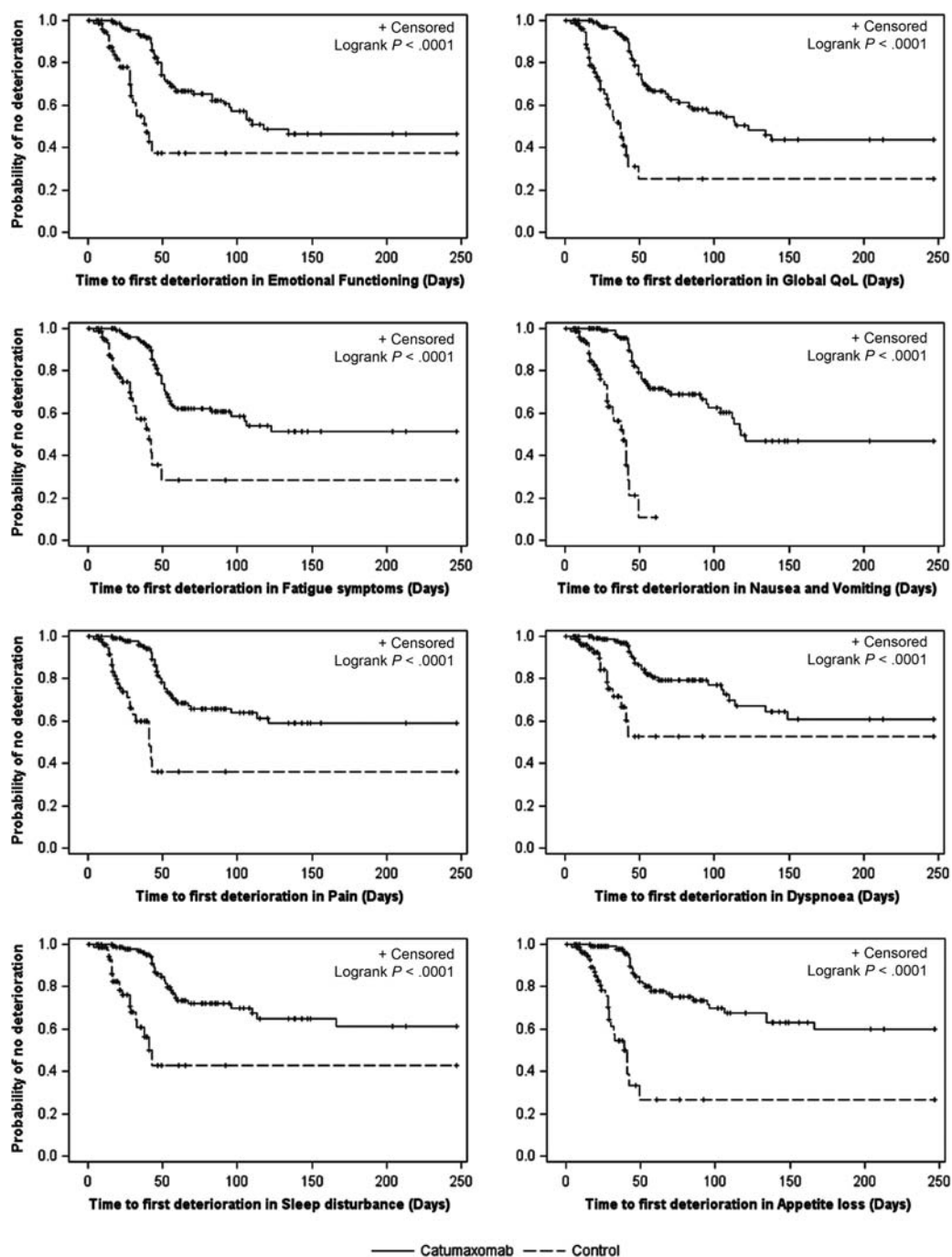


Figure 3. Kaplan–Meier curve and log-rank test for European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30) scores of primary interest (full QoL analysis set, FQoLAS).

comparator and the unethical aspect of exposing the control group to the risk of an infusion with a non-active agent. We acknowledge that the patients’ perspective regarding the HRQL and symptoms may have been influenced by the fact that patients knew which treatment they were taking during the study.

One could also argue that patients included in this study had to cope with different types of cancer alongside symptomatic MA, with potentially different cancer progression, which could have a substantial role in HRQL assessment. Indeed,

deterioration in HRQL could not exclusively be related to ascites but also to cancer progression, in particular for patients in the catumaxomab group who stayed longer in the study compared with the control group. The addition of primary tumour type as a covariate in the Cox proportional hazards models showed that the time to deterioration in HRQL was not significantly different in patients with gastric, breast, ovarian or other types of cancer. Further investigation would be necessary to accurately assess the specific impact of ascites and the impact of other potential parameters such as cancer stage, even

Table 3. Cox proportional hazards models^a for European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items (EORTC QLQ-C30) scores of primary interest (full QoL analysis set, FQoLAS)

EORTC QLQ-C30 score	Catumaxomab versus control	
	Hazard ratio ^b (95% CI)	<i>P</i> value
Emotional functioning	0.24 (0.14;0.42)	<0.001
Global quality of life (QoL)	0.17 (0.10;0.28)	<0.001
Fatigue	0.23 (0.13;0.39)	<0.001
Nausea and vomiting	0.08 (0.04;0.16)	<0.001
Pain	0.18 (0.10;0.32)	<0.001
Dyspnoea	0.17 (0.08;0.36)	<0.001
Sleep disturbance	0.14 (0.07;0.28)	<0.001
Appetite loss	0.11 (0.06;0.21)	<0.001

^aResults from Cox proportional hazards models adjusting for the baseline value of the score, country and primary tumour type; the baseline value of the score is the value of the score measured at screening.

^bHazard ratio <1 are in favour of the catumaxomab group compared with the control group.

n = 160 for the catumaxomab group and *n* = 85 for the control group.

In bold, *P* < 0.05

though the complexity of the impact of cancer symptoms and treatments may make this evaluation challenging.

In conclusion, deterioration in QoL was delayed by treatment with catumaxomab in patients suffering from MA, compared with paracentesis alone. Catumaxomab thus enables patients to benefit from better HRQL during a prolonged survival period.

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disclosure

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