Final Report

Name	Phase II study to document the efficacy of once weekly administration of a docetaxel/carboplatin or cisplatin/cetuximab combination (DCC) in patients with advanced squamous cell carcinoma of the oropharynx and oral cavity
EudraCT No.	2007-007034-18
Phase	II
Study coordination	Dr. Dr. Jan D. Raguse Charité Universitätsmedizin Berlin – CVK Klinik und Poliklinik für Mund-, Kiefer- und Gesichtschirurgie [*Department of Oral and Maxillofacial Surgery*] Augustenburger Platz 1 D-13353 Berlin Phone: 030 – 450 655 213 Fax: 030 – 450 555 901
Sponsor	Charité Universitätsmedizin Berlin – CVK
Principal investigator	Dr. Dr. Jan D. Raguse Charité Universitätsmedizin Berlin – CVK

Introduction

The incidence of squamous cell carcinomas of the head and neck (SCCHN) is increasing. It has come to be the sixth most frequent malignant disease accounting for over 500,000 newly diagnosed patients each year world wide (1). Despite great progress in primary therapy, local or locoregional relapses are reported in up to 60% and distant metastases in up to 25% of cases, in general (2).

The prognosis of patients with recurrent SCCHN after exploitation of all surgical and radiological therapy options is poor. Various studies state their median survival to be 4 to 6 months with the 1-year survival rate being below 20% (3, 4, 5).

Methotrexate, cisplatin, 5-FU and docetaxel are the most frequently used cytostatics in SCCHN. Single-agent therapy with methotrexate is reported to achieve response rates of 8-16% (3, 4), with cisplatin 16-44% (5, 6), 5-FU 15-22% and with docetaxel 24-45% (7, 8).

By combination of the different agents above, higher response rates can be achieved. The combination of cisplatin and 5-FU as a 5-day continuous infusion had, for long, been the standard regimen achieving response rates between 30 and 40% in phase I and phase II studies (9, 10). The improved response rate did, however, not have any positive influence on survival which, in the past years, has remained almost unchanged at 6 to 9 months.

Progress was achieved with respect to survival only after adding a third substance from the list above.

The addition of docetaxel has been described to increase the efficacy of the standard combination of cisplatin and 5-FU. In a phase I/II study in chemonaive patients, a response rate of 100% was achieved. This treatment was, however, associated with high toxicity mainly attributable to 5-FU. The same study also demonstrated that reduction of the administration period of 5-FU from five to four days alone was sufficient to markedly diminish typical adverse reactions such as mucositis and oesophagitis without compromising the efficacy of the regimen (11).

Even 4-day continuous infusion still markedly reduces the quality of life of the patients affected by the treatment, an effect not deemed justified in the context of palliative objectives in relapsing SCHNN. This is particularly true since, as described above, any real benefit in terms of efficacy remains doubtful (12).

Various phase II studies choosing docetaxel instead of 5-FU as a combination partner for cisplatin - initiated in the form of a three-week regimen at the standard dose of 75 mg/m² each - demonstrated results comparable to those achieved with the former standard therapy. At 40-54%, the remission rates were comparable to those seen with the combination of cisplatin plus 5-FU. At 10- 11 months, survival was improved even when taking into account the relevance of a phase II study (13, 14, 15). In this study, the imposition of several days‘ continuous infusion, associated with hospitalisation of the patients or at least restrictions, could additionally be omitted favouring a higher quality of life.

Several phase III studies as well as two meta-analyses using docetaxel weekly at reduced single doses (35 mg/m²) in patients with metastatic bronchial carcinoma demonstrated comparable efficacy to the three-week regimen. This split-course design served, in particular, to significantly improve the profile of haematological adverse reactions (16, 17, 18).

In another two studies in patients with relapsing SCHNN, this regimen of weekly administration of reduced single doses of docetaxel (35 mg/m²) plus cisplatin (25 mg/m²) also demonstrated good efficacy with response rates comparable to those of the three-week regimen (ORR 42%) (19, 20). This split-course design also markedly reduced toxicity particularly with respect to cumulative peripheral neuropathy and myelosuppression.

Most recently, the addition of cetuximab to the previous standard combination of cisplatin plus 5-FU (NEJM 2008), for the first time, achieved significant improvement of total survival from 7.4 to 10.1 months without increasing clinically relevant toxicity (21). Cetuximab seems to be an ideal partner for the docetaxel plus cisplatin regimen as it does not cause cumulative toxicity in its usual dose of initially 400 mg/m^2 and 250 mg/m² with weekly administration (22).

Materials and methods

An open prospective, multicentre phase II study was designed to evaluate whether the combination of cisplatin and docetaxel in the split-course design with cetuximab as add-on achieved promising efficacy. Given the palliative context of these patients, their quality of life was to be taken into account by being prepared to reduce the individual doses while not compromising the therapy's efficacy.

Patients

This prospective multicentre phase II study was initiated after approval by the competent ethics committee of Berlin dated January 21, 2009. Between 2009 and 2011 patients with a signed informed consent and relapsing and/or metastatic squamous cell carcinoma of the oral cavity and adjoining oropharynx were included. The following inclusion criteria were defined: age > 18 years, at least one measurable lesion according to RECIST criteria, ECOG performance status of 0 or 1 as well as sufficient bone marrow reserve, liver function and renal excretion.

Exclusion criteria: Radiation therapy within the past six months, preceding systemic chemotherapy apart from chemoradiotherapy, therapy with antibodies or tyrosine kinase inhibitors, other serious diseases (established heart failure, higher-grade cardiac arrhythmia such as first-degree AV block, myocardial infarction within the past six months, severe neurological or psychiatric diseases) as well as contraindications to the study medications. Pregnant women or women not employing sufficient contraceptive measures were not included.

Study objectives

The rate of progression-free survival after 16 weeks treatment was defined as the primary efficacy parameter. The results of the phase III study (EXTREME) with cisplatin + 5-FU versus cetuximab + Cisplatin + 5-FU were used as historical reference (21). If successful, the study would achieve a 15% higher rate of progression-free patients after 16 weeks (i.e. 60%) than the former standard arm of cisplatin + 5-FU (45%).The progression-free survival rate after 16 weeks was defined as the period from first administration of the study medication to first radiological confirmation of disease progression or death of any cause within 60 days after last contact or randomisation.

Secondary study objectives were tumor response according to RECIST criteria (ORR, response rate), progression-free survival (PFS), median survival period, quality of life as

determined by FACT-H&N questionnaires and toxicity profile of the combination of cetuximab, docetaxel, cis- or carboplatin.

Statistical analysis

The ITT population is used for primary evaluation of the efficacy variables. Evaluation of the per-protocol population was regarded to be a supportive analysis. Based upon the results of the EXTREME study (21) for the treatment arm without cetuximab, a progression-free survival rate of 45% at four months is considered insufficient while a rate of 60% or higher is rated as good response. A two-step design with 45 patients each per step is chosen in order to test the zero hypothesis P (PFS at month 4) ≤ 0.45 against the alternative hypothesis P (PFS at month 4) = 0.6 based upon a significance level alpha =0.05 and a type II error = 0.15. If at least 22 patients of the first step are progression-free at month 4, the second step will be initiated. In the case of 21 or less progression-free patients in the first step, recruitment of further patients will be stopped due to poor efficacy. If at the end of the second step at least 49 of the 90 treated patients are progression-free at month 4, the zero hypothesis will be rejected. If the zero hypothesis P (PFS at month 4) = 0.45 is valid, the probability of a recruitment stop after the first step is 65% and the expectation of the sample size 61. In addition, the 95% confidence interval for the probability of progression-free survival after four months is determined.

Kaplan-Meier estimates are used for evaluating secondary target variables, overall survival period and progression-free survival period. The 95% confidence interval is determined for the median periods.

With respect to the secondary target variable ORR (complete or partial tumor response acc. to RECIST), the following zero hypothesis P(ORR) ≤ 0.2 is tested against the alternative hypothesis P(ORR) = 0.35 based upon the response rates determined in the study by Vermorken et al. A one-sample X^2 test with a two-sided significance level of 0.05 has the power of 0.90 under the alternative hypothesis to reject the zero hypothesis.

The following statistical evaluations are performed to describe the toxicity:

- Determination of the frequency of patients with at least one adverse event stratified according to CTC Index Terms, severity, causal relationship with cetuximab, measures performed as well as outcome of the AE.
- Determination of the frequency of adverse events that lead to withdrawal from the study or reduction of the study medication.
- Determination of the frequency of deaths and other serious adverse events.
- In a first step, the incidence of “abnormal” laboratory values within the course of the study is determined as part of the statistical evaluation. In addition, the absolute and the relative change from baseline is quantitatively described for all parameters stratified according to cycle. The documented laboratory values are categorised according to CTCAE version 3.0 and thus made available for standardised counting of incidence as a function of severity.

Toxicity evaluations are performed stratified for both patients and cycles.

The EORTC-QLC C30 quality of life questionnaires are analysed in accordance with the corresponding evaluation manual. Non-parametric test methods are used for exploratory assessment of the treatment course.

Treatment schedule

The study medication was administered in four-week cycles. Cetuximab was given at a weekly dose of 250 mg/m² (day 1, 8, 15, 21) (initial dose 400 mg/m²), docetaxel at a dose of 35 mg/m² on days 1, 8 and 15 and cisplatin or carboplatin at a dose of 25 mg/m² or AUC 2 on days 1, 8 and 15 of each cycle. Pretreatment comprised 4 mg dimetindine, 50 mg ranitidine and 8 mg dexamethasone administered intravenously. Cetuximab was administered intravenously over a period of 60 minutes, followed by flushing with 500 ml NaCl; docetaxel was administered intravenously over a period of 30 minutes and cisplatin or Carboplatin over 30 minutes, again followed by final flushing with NaCl. Diuresis was to be supported as specified by the center with mannitol or furosemide. In addition, the patients received 8 mg oral dexamethasone at the day before and on the evening of the infusions. The next cycle started on day 28. Patients were to be treated for a maximum of 6 cycles of chemotherapy with two additional cycles being allowed if the patient did not show tumor

progression. Therapy with cetuximab was to be continued independent of chemotherapy at the same dose until tumor progression.

Results

Patients

45 patients with relapsing and/or metastatic squamous cell carcinoma of the oral cavity and adjoining oropharynx were included at 11 participating study centers between 2009 and 2011. The median period from initial diagnosis to study inclusion was 20 months (range 0-155). Table 1 gives a summary of the demographic data.

Patient characteristics		
	Number (n)	**Percent (%)**
Gender		
male	33	73
female	12	27
Age		
median	64	
range	41-81	
ECOG		
0	12	27
1	33	73
BMI		
median	22	
range	16-26	
Primary tumor location		
oral cavity	27	60
oropharynx	18	40
Extent of disease		
local	27	60
locoregional	23	51
distant metastases	24	53
lung	20	44
malignant pleural eff.	21	47
bone	6	13
liver	4	7
Previous therapy		
surgery	32	71
radiation therapy	43	96
salvage surgery	22	49
chemotherapy	29	64

Table 1: Patient characteristics

Forty four of the 45 patients could be evaluated with respect to survival. Evaluable statements regarding therapy response are available for 27 p atients (60%) only. Correspondingly, data regarding the progression-free interval are also available from 27 patients only. For assessment of the ITT population, the missing value was replaced by the date of death. 43 patients could be evaluated regarding toxicity. Insufficient data were available after termination of the study for assessment of quality of life which was to be recorded by EORTC-QLC C30 questionnaires.

Treatment

The patients received a median of 7 administrations of chemotherapy (range 1-32). In 23 patients (51%), less than two complete cycles were performed; Five patients (11%) only received six cycles as scheduled.16 patients (36%) were treated for less than 4 weeks. The most frequent reason for discontinuing therapy was insufficient compliance (17 patients – 38%), with no differentiation made between compliance of the patient or the treating physician, followed by progressive disease and death of the patient in seven cases (16%). Toxicity was stated as the cause for discontinuation in four cases (9%).

Response

27 patients were evaluable for tumor response. Complete remission was achieved in three of these patients (11%) and partial response in another 11 patients (41%) resulting in an overall response rate of 52%. Stable disease was achieved in 9 patients (33%) leading to a tumor control rate of 85% (Table 2).

Based upon the ITT population of 45 patients and CR in 7%, PR in 24% and SD in 20%, the tumor response amounted to 31% and the tumor control rate to 51%.

Summary of response rates				
	ITT population		**Patients evaluable**	
	Number (n)	Percent (%)	Number (n)	Percent (%)
Patients	44	100	27	100
ORR	**14**	**32**	**14**	**52**
CR	3	7	3	11
PR	11	25	11	41
SD	9	20	9	33
PD	4	9	4	15
NA	17	39	-	-

Table 2: Response rates in the ITT and the evaluable population

Progression-free survival (PFS)

Based upon the results of the EXTREME-Study (21), the primary target objective of the study was to achieve a progression-free survival rate of 60% at 4 months after the start of therapy in the ITT population. Evaluation of the per-protocol populations was regarded to be a supportive analysis. A two-step design was chosen with 45 patients each per step. At least 22 patients of step one had to be progression-free at month 4 in order to continue with therapeutic step two.

At the defined point in time – 4 months after the start of therapy – a progression-free survival rate of 50% was achieved in the ITT population in 22 progression-free patients out of 44

evaluable patients. The first step of the two stage design for the primary objective was principally fulfilled, but owing to the poor data caused by the insolvent CRO, the study was discontinued in accordance with the protocol after the first step (Fig. 1).

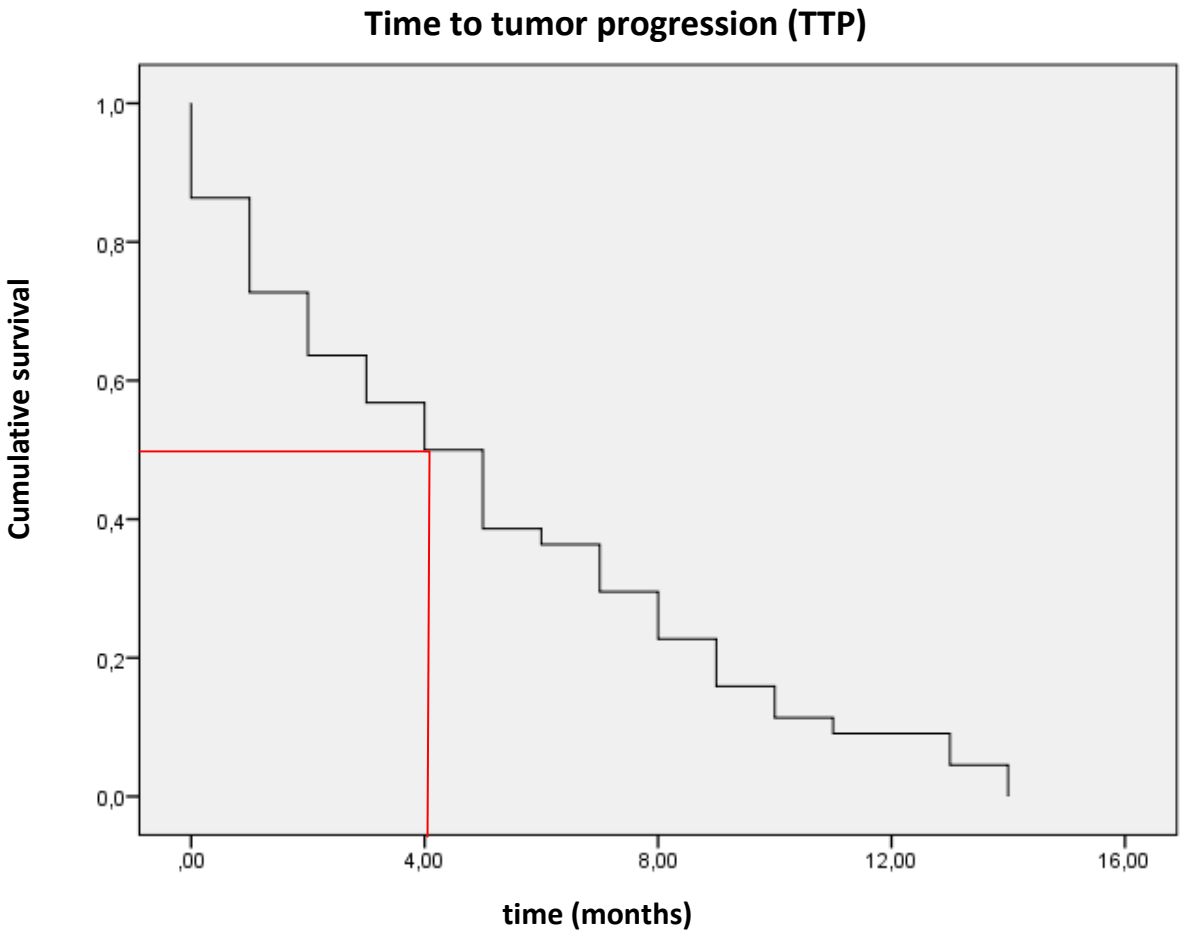

Figure 1: PFS in the ITT population

Therapy was discontinued in 16 patients within the first four weeks of therapy. The main cause was lack of compliance in 75% (n = 12) of the cases. Four patients died within the first week of inclusion with death not being related to therapy. When comparing these patients with those in whom therapy lasted longer than four weeks, the difference in progression-free survival was highly significant ($p < 0.005$). In the per-protocol population the progression-free survival rate at four months was 71% (Fig. 2) and the median PFS was 7.0 months (95% CI 4.4-9.6), as opposed to less than 2 months for those patients receiving less than 4 weeks treatment..

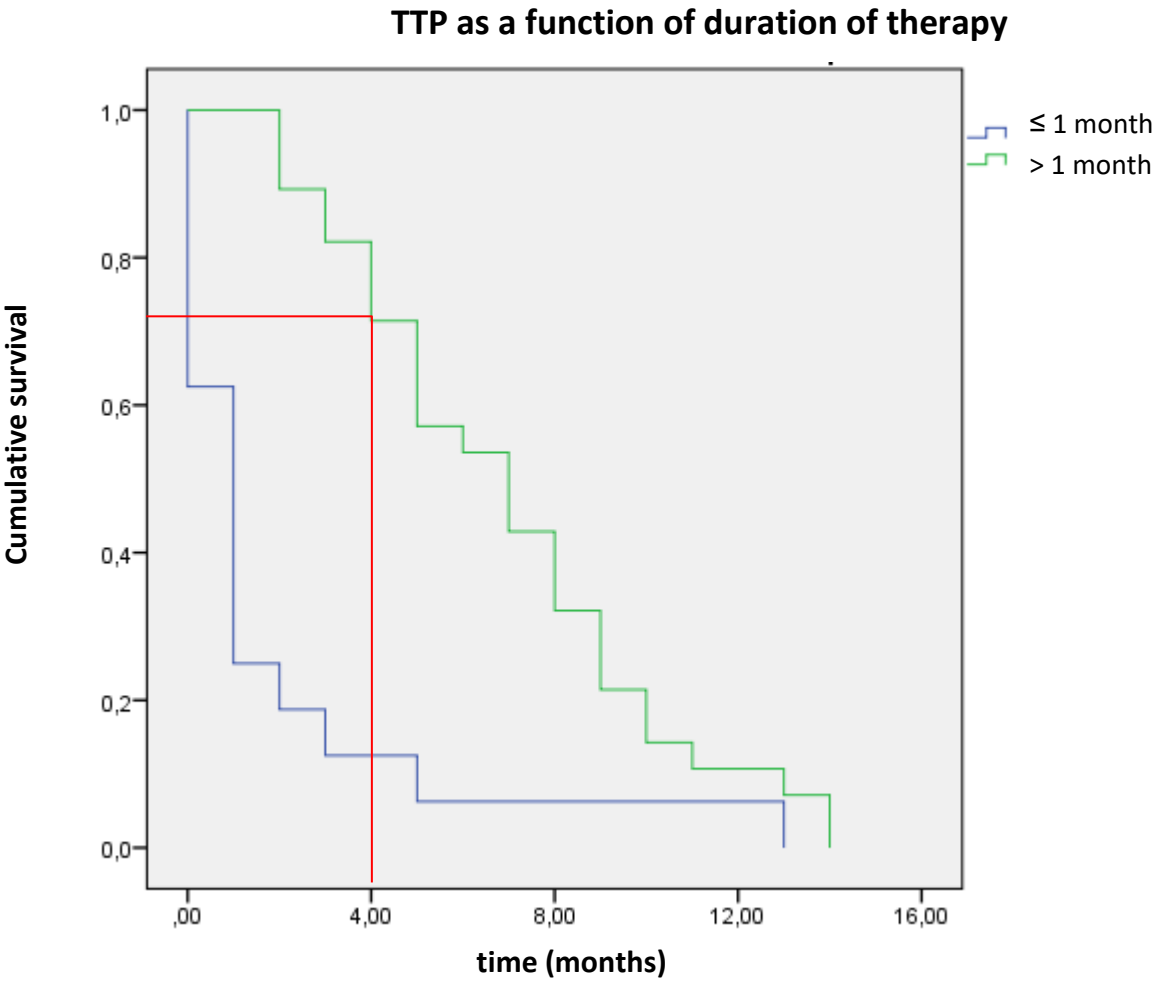

Figure 2: PFS as a function of duration of therapy

A highly significant difference ($p < 0.005$) was also found when comparing the patients who received an effective antitumor dose of chemotherapy which is presumed to be two cycles. Patients who received more than two cycles of chemotherapy had a progression-free survival rate at four months of 76% (Fig. 3 and the median PFS was 7.0 months (95% CI 4.8-9.2).

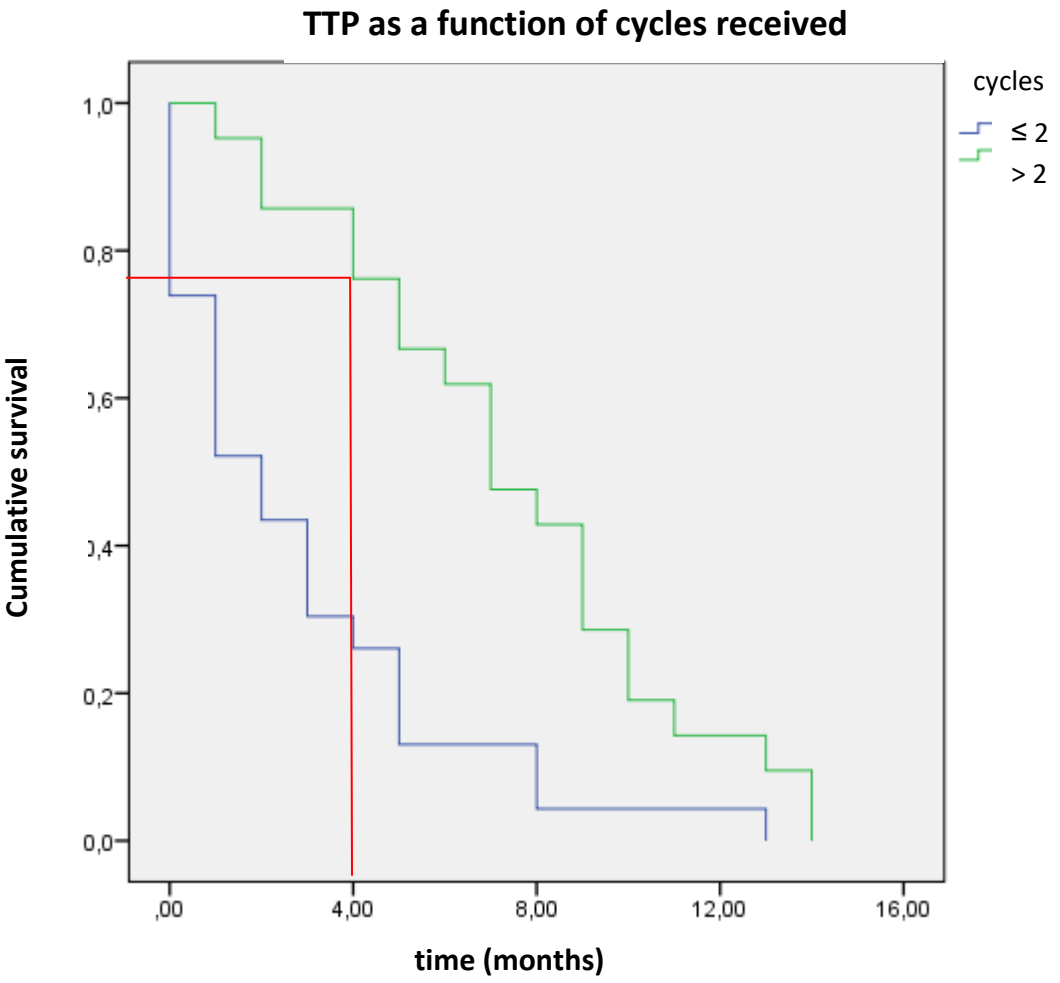

Figure 3: PFS as a function of cycles performed

Overall survival (OS)

In the ITT population with 44 evaluable patients the median survival was 5 months (95%CI 5.01-8.4) (Fig. 4). 43% of the patient population was still alive after six months and 20% after 12 months.

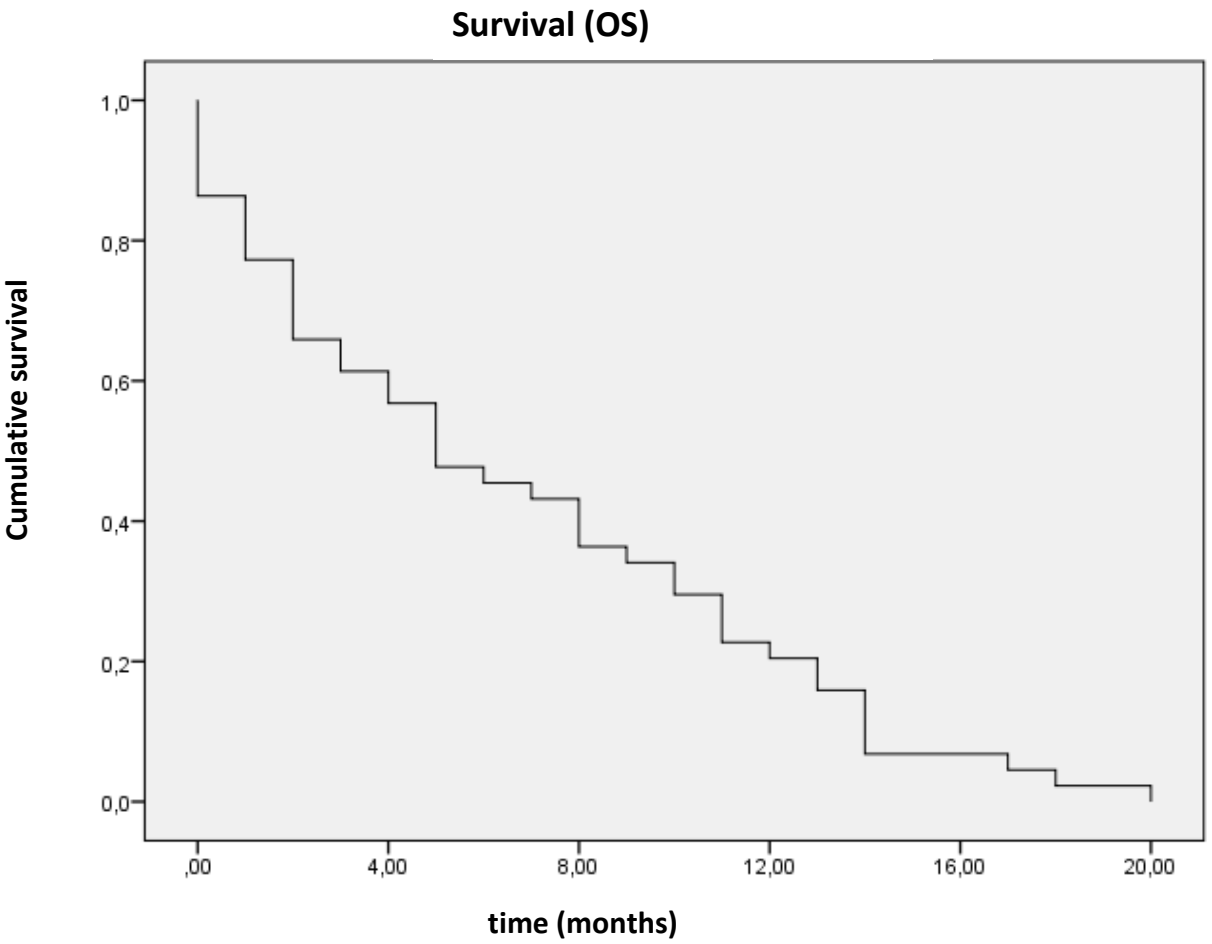

Figure 4: OS in the ITT population

When once more comparing those patients in whom therapy lasted longer than four weeks or had prematurely been discontinued, a highly significant difference ($p < 0.005$) was demonstrated also with respect to overall survival. In the per-protocol population, the median OS was 9 months (95%CI 5.9-12.1) vs. 1 month (95%CI 0.5-1.9) (Fig. 5). 64% of the patient population was still alive after six months and 29% after 12 months.

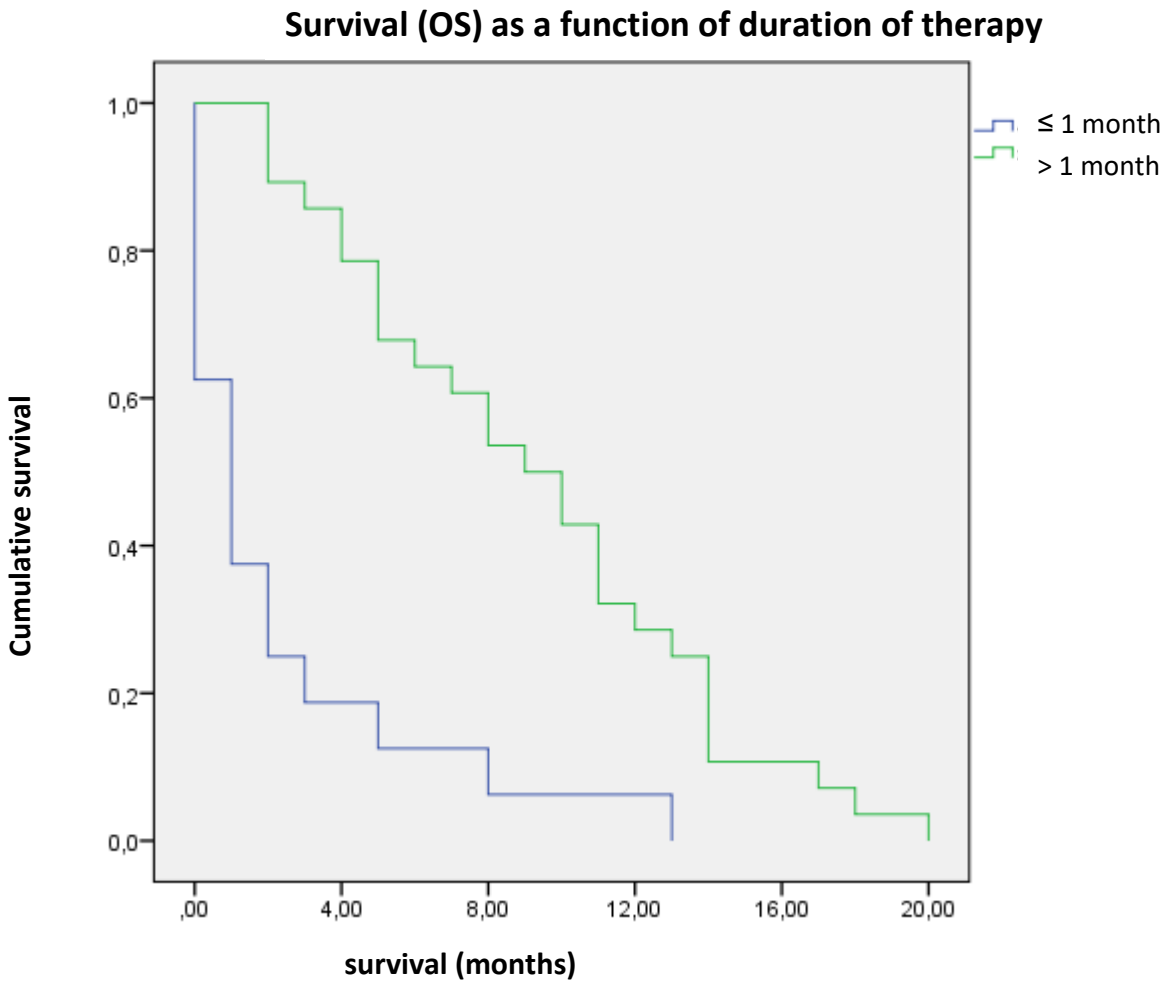

Figure 5: OS as a function of duration of therapy

Similar results were obtained for the comparison of patients who received more than 2 cycles versus those who received less than 2 cycles of therapy ($p<0.05$). Patients completing more than 2 cycles showed a median OS of 10.0 months (95 % CI, 8.2-11.8). At 6 months 71 % were still alive, and the 1-year survival rate was again 29 %.

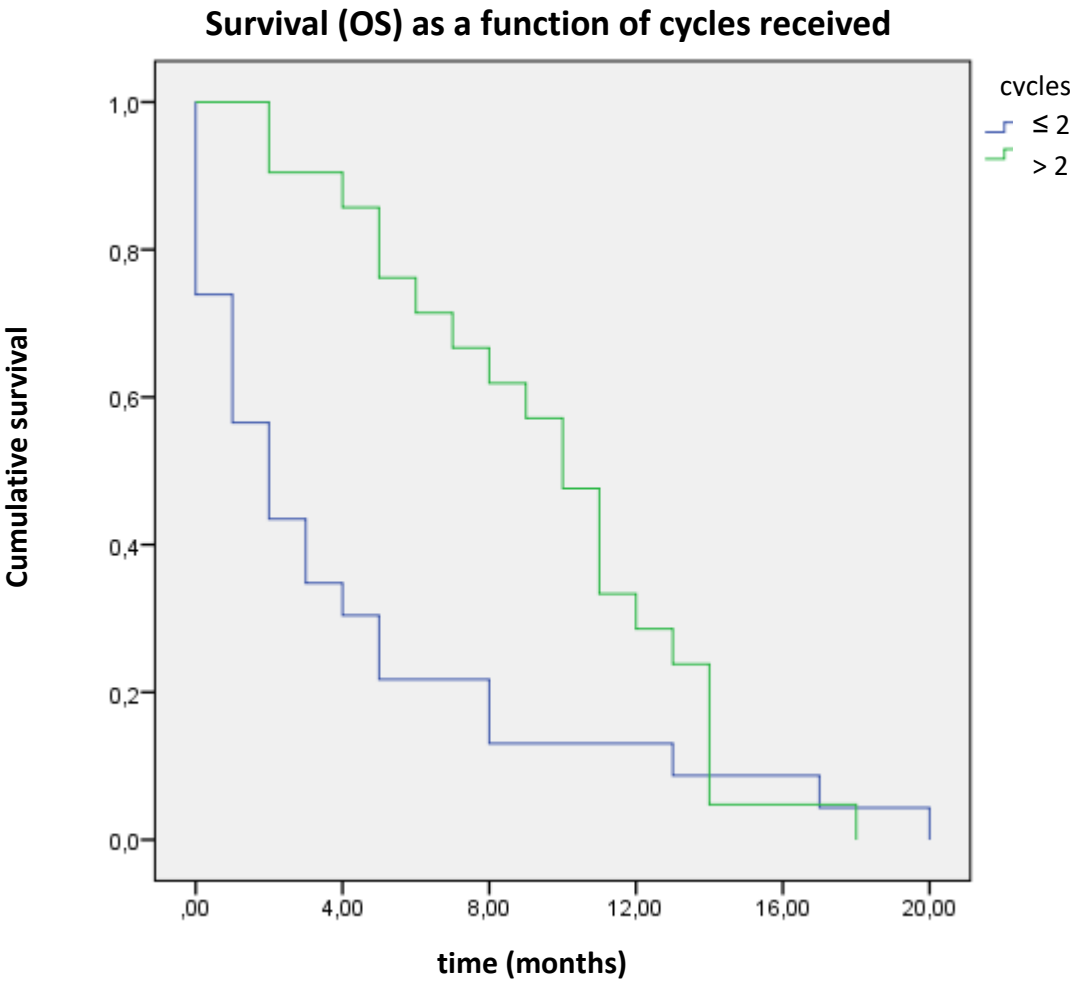

Figure 6: OS as a function of cycles received

Further significant differences were demonstrated for locoregional relapses and the presence of malignant pleural effusion in existing pulmonary metastases. These two factors were associated with significantly lower PFS and OS ($p < 0.005$) (Fig. 7).

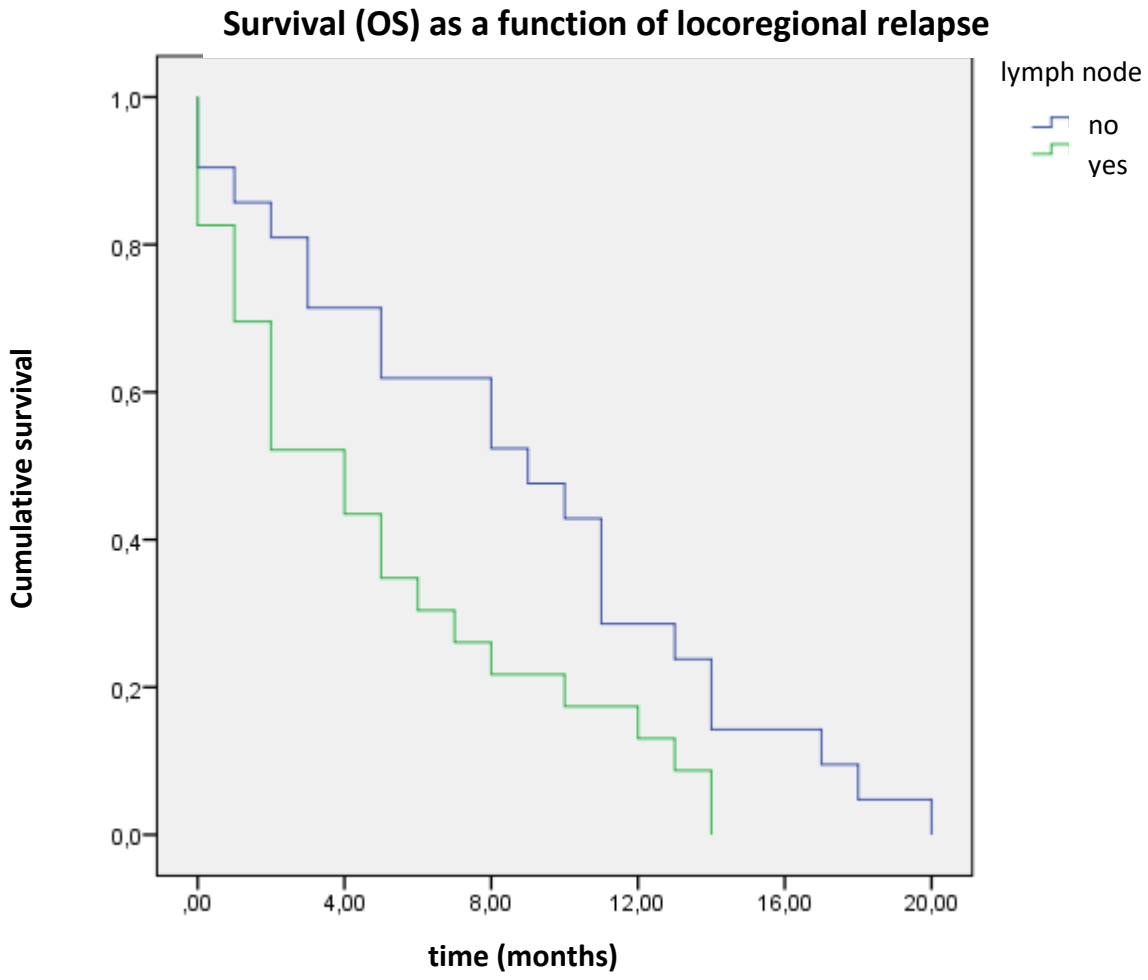

Figure 7: OS in lymph node metastases

Toxicity

Table 3 gives a summary of haematological toxicity. Myelosuppression in the sense of neutropenia of grade 4 (4 patients, 9%) and grade 3 (10 patients, grade 3) was the most frequent adverse reaction. Febrile neutropenia (defined as neutropenia grade 4 associated with fever > grade 1) was not observed. 79% of the patients developed grade 1/2 and 9% grade 3 anaemia during the course of the study. Higher-grade anaemia was not observed.

Summary of haematological toxicity						
	Grade 1/2		**Grade 3**		**Grade 4**	
	Number of pat.	%	Number of pat.	%	Number of pat.	%
Neutropenia	28	65	10	23	4	9
Thrombocytopenia	10	23	-	-	-	-
Anaemia	34	79	4	9	-	-

Table 3: Haematologic toxicity

Higher-grade non-haematological adverse reactions occurred in a total of 10 patients. No grade 4 toxicity was observed, however. The most frequent adverse reaction of grade 1/2 was diarrhoea in 65% of patients, followed by skin changes (58%) and nausea (56%). Low-grade exhaustion was reported by almost half of the patients. Neurological deficiencies were not recorded, however (Table. 4).

Summary of non-haematological toxicity						
	Grade 1/2		**Grade 3**		**Grade 4**	
	Number of pat.	%	Number of pat.	%	Number of pat.	%
Alopecia	13	30	1	2	-	-
Asthenia	21	49	-	-	-	-
Diarrhoea	28	65	-	-	-	-
Emesis	16	38	2	5	-	-
Nausea	24	56	2	5	-	-
Neurological deficiency	-	-	-	-	-	-
Skin	25	58	2	5	-	-
Nails	2	5	1	2	-	-
Dyspnoea	6	14	2	5	-	-

Table 4: Non-haematological toxicity

Discussion

The presented prospective multicentre phase II study was to evaluate whether the combination of reduced-dose cisplatin (25 mg/m²) and docetaxel (35 mg/m²) in the sense of a split-course design with cetuximab as add-on was capable of achieving promising efficacy. Given the palliative context of the patients, their quality of life was to be taken into account by reducing the individual doses while not compromising the therapy's efficacy.

Based upon the results of the EXTREME-Study (21), the primary endpoint of the study was defined as a progression-free survival rate of 60% in the ITT population at 4 months after the start of therapy. Evaluation of the per-protocol population was regarded to be a supportive analysis. A two-step design was chosen with 45 patients each per step. At least 22 patients of step one had to be progression-free at 4 months in order to continue with step two of therapy.

A progression-free survival rate of 50% was demonstrated in the ITT population in 22 progression-free patients out of 44 evaluable patients. The first step of the two stage design for the primary objective was principally fulfilled, but owing to the poor data caused by the insolvent CRO, the study was discontinued in accordance with the protocol,

More detailed evaluation of the data revealed that therapy was discontinued in 16 out of 44 evaluable patients (36%) within the first four weeks of the study. The main reason for discontinuation was lack of compliance (12/16, 75%) with no differentiation between compliance of the patient or of the treating physician. Four patients died within the first week with death not being therapy-related. This may indicate inadequate selection of patients and casts doubt on the performance status (ECOG 0 and 1) as an adequate inclusion criterion.

A similar conclusion is suggested by the fact that23 out of 44 patients (52%) received less than 2 cycles of the scheduled therapy, i.e. chemotherapy at a dose unlikely to be tumor effective. This is particularly remarkable if one considers the fact that a split-course design with reduced single doses was used. Again, the reasons were mainly lack of compliance of the patients and the treating physicians alike. One reason for discontinuation was, for example, that a patient departed for a prolonged stay at a rehabilitation center.

In contrast to our study, Vermorken reports a median number of five cycles received in the cetuximab arm and four cycles in the chemotherapy arm. At the same time, 82% of the patients in the cetuximab arm received the scheduled maintenance therapy.

Even though evaluation of the per-protocol population was intended to be a supportive analysis only, it is the object of further discussion below, in order to assess the therapeutic regimen and to enable comparison with the EXTREME study (Table 5).

In the per-protocol population the progression-free survival (PFS) rate after four months was 71% in patients treated longer than four weeks and 76% in patients who received more than two cycles of therapy. With these results, the primary endpoint of the study (60%) is clearly exceeded. The median PFS was seven months in both groups (95% CI 4.4-9.6 and 95% CI 4.8-9.2).

In this population, the overall survival (OS) was 9 months (95% CI 5.9-12.1) (> 4 weeks of therapy) and 10 months (95% CI 8.2-11.8) (> 2 cycles), which taking into account the rather limited comparability of a phase II study is very close to the 10.1 months achieved in the historical cetuximab combination group of the EXTREME study.

The therapeutic response rate of 52% achieved in the set of evaluable patients is to be considered relatively high compared to the two arms of the EXTREME study.

Comparison of response and survival rates achieved in Extreme vs. DCC					
	EXTREME Cis/5-Fu/Cetux	EXTREME Cis/5-FU	DCC ITT population	DCC PP population (> 4 weeks)	DCC PP population (> 2 cycles)
Survival (months)					
OS	10.1 (8.6-11.2)	7.4 (6.4-8.3)	5.0 (5.0-8.4)	9.0 (5.9-12.1)	10.0 (8.2-11.8)
PFS	5.6 (5.0-6.0)	3.3 (2.9-4.3)	4.0 (3.8-6.3)	7.0 (4.4-9.6)	7.0 (4.8-9.2)
BOR (%)					
ORR	36	20	32	52	N/A
DCR	81	60	51	85	N/A

Table 5: Comparison of efficacy EXTREME vs. DCC (BOR – best overall respnse, ORR – overall response rate, DCR – disease control rate, NA – not available)

When comparing the patient populations of the EXTREME study and the DCC study (Table 6) the DCC population is clearly at disadvantage. Its median age was 10 years higher than that of the EXTREME study. Even though we used the ECOG scale in our population whilst the EXTREME study used the Karnofsky Index to determine the patients' performance status, our patient population was clearly the markedly more morbid of the two. In addition, about one-third more patients in our study population had metastatic disease and had received significantly more aggressive prior treatments (64 vs 41 % with prior chemotherapy in combination with radiotherapy, 96 vs 85% prior radiotherapy). Furthermore the high rate of previous surgical treatment in our study has to be estimated (71 % prior surgery, and 49 % additional prior salvage surgery)

Comparison of patient characteristics EXTREME vs. DCC			
	DCC	**EXTREME number (%)**	
	number (%)	**Cis/5-Fu/Cetux**	**Cis/5-Fu**
Age			
median	64	56	54
range	41-81		
ECOG Karnovsky			
0 > 80%	12 (27)	195 (88)	195 (89)
1 < 80%	33 (73)	27 (12)	25 (11)
Primary tumor location			
Oral cavity	27 (60)	46 (21)	42 (19)
Oropharynx	18 (40)	80 (36)	69 (31)
Other	-	96 (53)	99 (50)
Extent of disease			
locoregional	18 (40)	118 (53)	118 (54)
distant/ locoregional and distant	27 (60)	104 (47)	102 (46)
Previous therapy			
Surgery	32 (71)	N/A	-N/A
Radiation therapy	43 (96)	189 (85)	190 (86)
Salvage surgery	22 (49)	N/A	-N/A
Chemotherapy	29 (64)	90 (41)	80 (36)

Table 6: Comparison of patient populations of EXTREME vs. DCC

Conclusion

The presented prospective multicentre phase II study succeeded in demonstrating the general efficacy of reduced-dose cisplatin (25 mg/m²) and docetaxel (35 mg/m²) in combination with cetuximab (250 mg/m²) as add-on in the sense of a split-course design.

This results from the fact that, in the per-protocol population, progression-free survival (PFS) after 4 months was achieved in 71% (patients > 4 weeks of therapy) and 76% (> 2 cycles chemotherapy). These values exceed the historical results of the EXTREME study. The low compliance seen in this study is to be considered problematic with analysis of the exact reasons being, however, difficult in the context of a multicentre study. Bankruptcy of the clinical research organisation in charge during the course of the study was just as important a factor leading to difficulties in performance and evaluation in accordance with the study protocol. The fact that currently several study groups are investigating the presented concept of reduced single doses reflects the general value of the study. Publication of the results is, therefore, intended to follow in a timely manner.

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