European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT FOR ERBITUX

International non-proprietary name/Common name: cetuximab

Procedure No. EMEA/H/C/558/II/0026

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. Introduction

Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer
• in combination with chemotherapy
• as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.
Erbitux in combination with radiation therapy is indicated for the treatment of patients with locally advanced squamous cell cancer of the head and neck.
This indication is now revised as follows (new in **bold**):
Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck
• in combination with radiation therapy for locally advanced disease
• **in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.**

2 Clinical aspects

Early-stage Squamous Cell Carcinoma of Head and Neck (SCCHN) is curable with surgery and/or radiotherapy, but about 75% of SCCHN patients present with locally advanced disease and with current therapy 50 to 60% of these patients will experience a locoregional or distant relapse within 2 years of initial treatment. This is the target population for this application: recurrent and/or metastatic (R/M) SCCHN.

Clinical Studies Supporting the Efficacy off Cetuximab in the First-line Treatment of R/M SCCHN

Study	Phase	Study treatments	No. subjects treated	Submission	
				Current	Previous
EMR 62 202-002 (pivotal)	III	5-FU+cisplatin or carboplatin vs Cetuximab+5-FU+cisplatin or carboplatin	215 219	X	
EMR 62 202-008 (supportive, pilot for EMR 62 202-002)	I/II	Cetuximab+5-FU+cisplatin vs Cetuximab+5-FU+carboplatin	27 25		X *
ECOG E5397 (supportive)	III	Placebo + cisplatin vs Cetuximab+cisplatin	60 57		X **

ECOG=Eastern Cooperative Oncology Group, 5-FU=5-fluorouracil

* Report included in initial SCCHN dossier for evaluation of pharmacokinetics and safety but not for evaluation of efficacy.
** Report included in initial SCCHN dossier for evaluation of safety but not for evaluation of efficacy.

2. 1. Clinical efficacy

Main study **EMR 62 202-002** ("EXTREME")

The study was an open-label, randomized (1:1), multicenter (80 centers in Europe) study in R/M SCCHN comparing cetuximab + cisplatin or carboplatin + 5-FU versus cisplatin or carboplatin + 5-FU as first-line therapy for R/M SCCHN.
Group A: 1 treatment cycle consisted of dosing with chemotherapy (CTX) plus cetuximab on day 1, and doses of cetuximab on days 8 and 15, with follow-up through to day 20 of the cycle.
Group B: 1 treatment cycle consisted of dosing with CTX on day 1 with follow-up through to day 20 of the cycle.
Groups A and B received the same CTX regimen **every 21 days**. The regimen was based on cisplatin or carboplatin + 5-FU.

Order of administration	Drug	Dose
First	**Cisplatin** 60-min infusion on day 1	100 mg/m²
Or	**Carboplatin** 60-min infusion on day 1	AUC 5
Then	**5-Fluorouracil** day 1 to day 4	1000 mg/m²/day continuous infusion

Cetuximab every 7 days	First infusion	All subsequent infusions
Cetuximab	400 mg/m² intravenous infusion over 120 min	250 mg/m² intravenous infusion over 60 min

Treatment was continued until PD, symptomatic deterioration, or unacceptable toxicity.
Subjects with unacceptable toxicity on cisplatin could be switched to carboplatin. CTX was given for a maximum of 6 cycles and cetuximab was continued in subjects without PD as monotherapy after the end of CTX in subjects in the cetuximab + CTX group.
Subjects were stratified according to previous CTX (defined as neoadjuvant or induction CTX, adjuvant CTX or CTX in combination with concomitant radiotherapy as therapy for locally advanced disease) (yes/no) and Karnofsky performance score (KPS) (<80/≥80).

Tumour response assessments using modified World Health Organization (WHO) criteria were based on computed tomography (CT) or magnetic resonance imaging (MRI) every 6 weeks and evaluated at study sites.

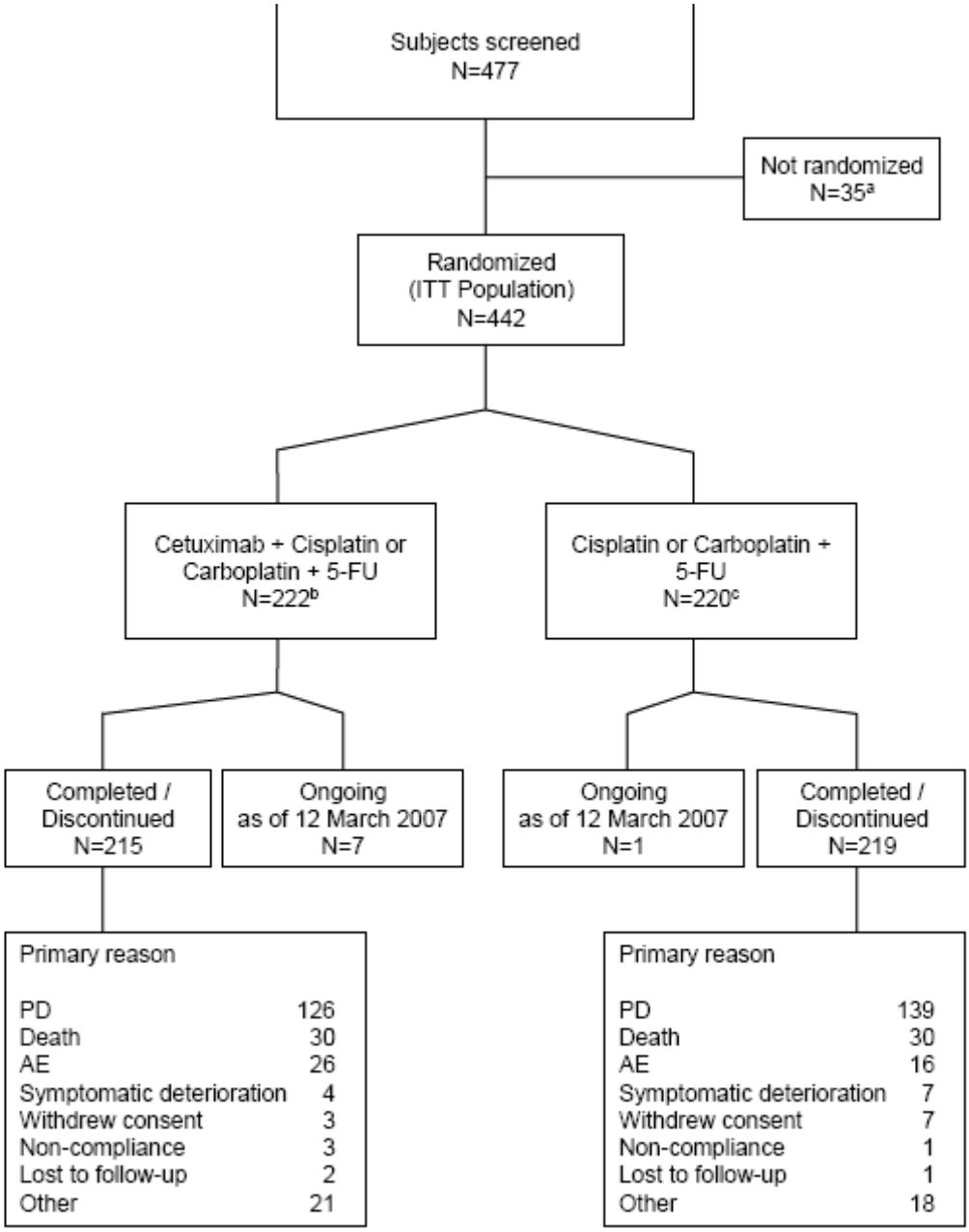
PD and survival status were assessed every 3 months after the end-of-study visit.

Primary endpoint: Survival
Secondary endpoints: PFS, RR, duration of response, QoL

Main Inclusion Criteria:
- Histologically or cytologically confirmed diagnosis of SCCHN
- Recurrent (locoregional) and/or metastatic SCCHN, not suitable for local therapy
- At least 1 bi-dimensional lesion measurable by either CT or MRI
- KPS of ≥70 at study entry
- Total bilirubin ≤2 xupper limit of normal range (ULN); aspartate aminotransferase
- (AST) and alanine aminotransferase (ALT) ≤3 xULN
- Tumor tissue available for evaluation of EGFR

Important Main Exclusion Criterion:
- Prior systemic CTX **except** if given as part of a multimodal treatment for locally advanced disease which was completed **more than 6 months** before study entry (i.e. neoadjuvant or induction CTX, adjuvant CTX or CTX in combination with concomitant radiotherapy as therapy for locally advanced disease)

Disposition of Subjects:



a) 6 subjects who were not eligible were randomized
b) 3 not treated
c) 5 not treated
AE=adverse event; 5-FU=5-fluorouracil; ITT=intention-to-treat; N=number of subjects; PD=progressive disease

Baseline Characteristics

Characteristic		Cetuximab + CTX (N=222)	CTX (N=220)
Gender (N, %)	Male	197 (88.7)	202 (91.8)
	Female	25 (11.3)	18 (8.2)
Age (years)	Mean ± SD	57.1 ± 8.0	56.7 ± 8.7
	Median	56	57
	Q1-Q3	51-62	51-62
Age categories (years)			
<65		183 (82.4)	182 (82.7)
≥65		39 (17.6)	38 (17.3)
Height (cm)	Mean ± SD	170.0 ± 8.1	170.4 ± 8.3
	Median	170	171
	Q1-Q3	165-175	165-176
Weight (kg)	Mean ± SD	65.1 ± 13.2	64.6 ± 13.4
	Median	64	64
	Q1-Q3	56-73	56-71

Characteristic		Cetuximab + CTX (N=222)	CTX (N=220)
Duration of SCCHN (months; mean ± S.D.)			
From initial diagnosis to IC	(N=216, 218)	26.9 ± 33.1	27.1 ± 34.8
From R/M to IC	(N=221, 220)	2.1 ± 4.7	2.4 ± 6.6
From initial diagnosis to R/M	(N=215, 218)	25.0 ± 33.0	24.7 ± 33.7
Site of primary tumor (No. subjects [%])			
Oropharynx		80 (36.0)	69 (31.4)
Hypopharynx		28 (12.6)	34 (15.5)
Larynx		59 (26.6)	52 (23.6)
Oral cavity		46 (20.7)	42 (19.1)
Other		9 (4.1)	23 (10.5)
Type of primary tumor (No. subjects [%])			
Recurrent, not metastatic		118 (53.2)	118 (53.6)
Metastatic, including recurrent		104 (46.8)	102 (46.4)
Histology of tumor (No. subjects [%])			
Well differentiated		35 (15.8)	40 (18.2)
Moderately differentiated		93 (41.9)	101 (45.9)
Poorly differentiated		46 (20.7)	46 (20.9)
Not specified/missing		48 (21.6)	33 (15.0)
AJCC stage at first diagnosis (No. subjects [%])			
0		1 (0.5)	0
I		15 (6.8)	9 (4.1)
II		28 (12.6)	24 (10.9)
III		44 (19.8)	47 (21.4)
IV		127 (57.2)	131 (59.5)
Unknown/missing		7 (3.2)	9 (4.1)

Karnofsky Performance Status (%)	Number of subjects (%)	
	Cetuximab + CTX (N=222)	CTX (N=220)
100	37 (16.7)	37 (16.8)
90	69 (31.1)	62 (28.2)
80	89 (40.1)	96 (43.6)
75	1 (0.5)	1 (0.5)
70	25 (11.3)	24 (10.9)
50	1 (0.5)	0
<80	27 (12.2)	25 (11.4)
≥80	195 (87.8)	195 (88.6)

Type of previous therapy[a]	Number of subjects (%)[b]	
	Cetuximab + CTX (N=222)	CTX (N=220)
Previous therapies/regimens	202 (91.0)	201 (91.4)
Radiotherapy	189 (85.1)	190 (86.4)
Radiotherapy (excluding palliative)	174 (78.4)	176 (80.0)
Surgery	143 (64.4)	135 (61.4)
Chemotherapy	90 (40.5)	80 (36.4)
Radiochemotherapy (excluding palliative)	69 (31.1)	60 (27.3)
Neoadjuvant chemotherapy	24 (10.8)	33 (15.0)
Other	1 (0.5)	2 (0.9)
Adjuvant, neoadjuvant or palliative therapy	146 (65.8)	159 (72.3)
Adjuvant	108 (48.4)	114 (51.8)
Neoadjuvant	32 (14.4)	42 (19.1)
Palliative	30 (13.5)	33 (15.0)

a) Multiple mentions possible
b Table is sorted on cetuximab + CTX column

Best Response to Prior Therapy

Nature of response	Number of subjects (%)	
	Cetuximab + CTX (N=222)	CTX (N=220)
Response known	164 (73.9)	170 (77.3)
Complete response	136 (61.3)	143 (65.0)
Partial response	20 (9.0)	17 (7.7)
Stable disease	7 (3.2)	4 (1.8)
Progressive disease	1 (0.5)	6 (2.7)
Not known	58 (26.1)	50 (22.7)

Efficacy Results

Summary of Primary Analysis of Overall Survival Time (ITT Population)

Response variable[a]	Number (%) of subjects	
	Cetuximab + CTX (N=222)	CTX (N=220)
Number of deaths (%)	167 (75.2)	176 (80.0)
Log rank p value (stratified)[b]	0.036	
Hazard ratio (stratified) [95% CI] [b, c]	0.797 [0.644, 0.986]	
Overall survival time *(months, median [95% CI])* [d]	10.1 [8.6, 11.2]	7.4 [6.4, 8.3]
Number of subjects at risk/survival rates up to [95% CI][d]		
3 months	184 84% [79, 89]	173 81% [75, 86]
6 months	153 71% [65, 77]	127 60% [53, 66]
12 months	82 39% [32, 45]	65 31% [24, 37]
18 months	30 24% [18, 30]	19 16% [10, 21]

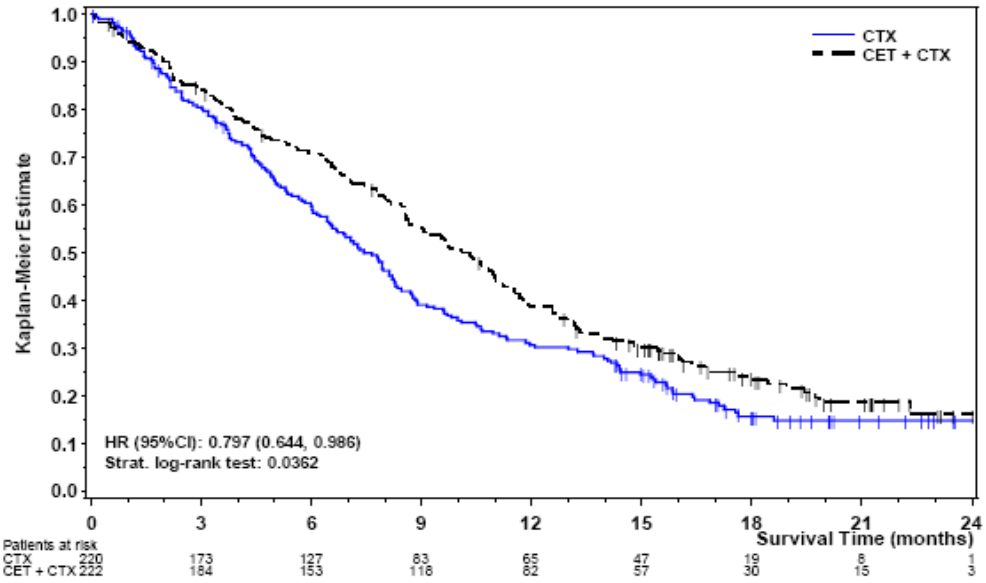
Source: *Table 14.2-1.1*

[a] Analysis based on 28 March 2007 snapshot

[b] Stratification based on previous chemotherapy and Karnofsky Performance Status as per IVRS

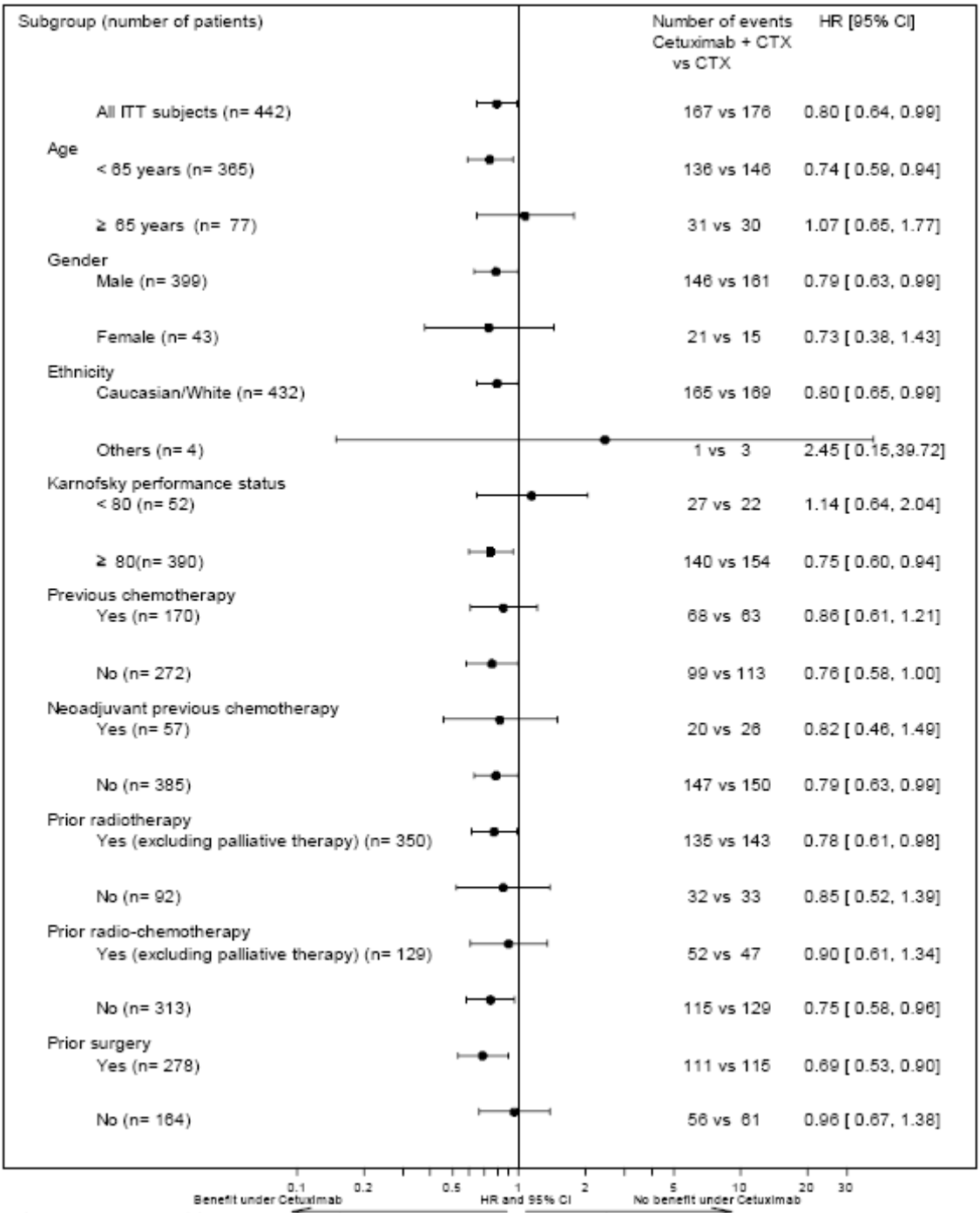
[c] Hazard ratio of cetuximab + CTX over CTX

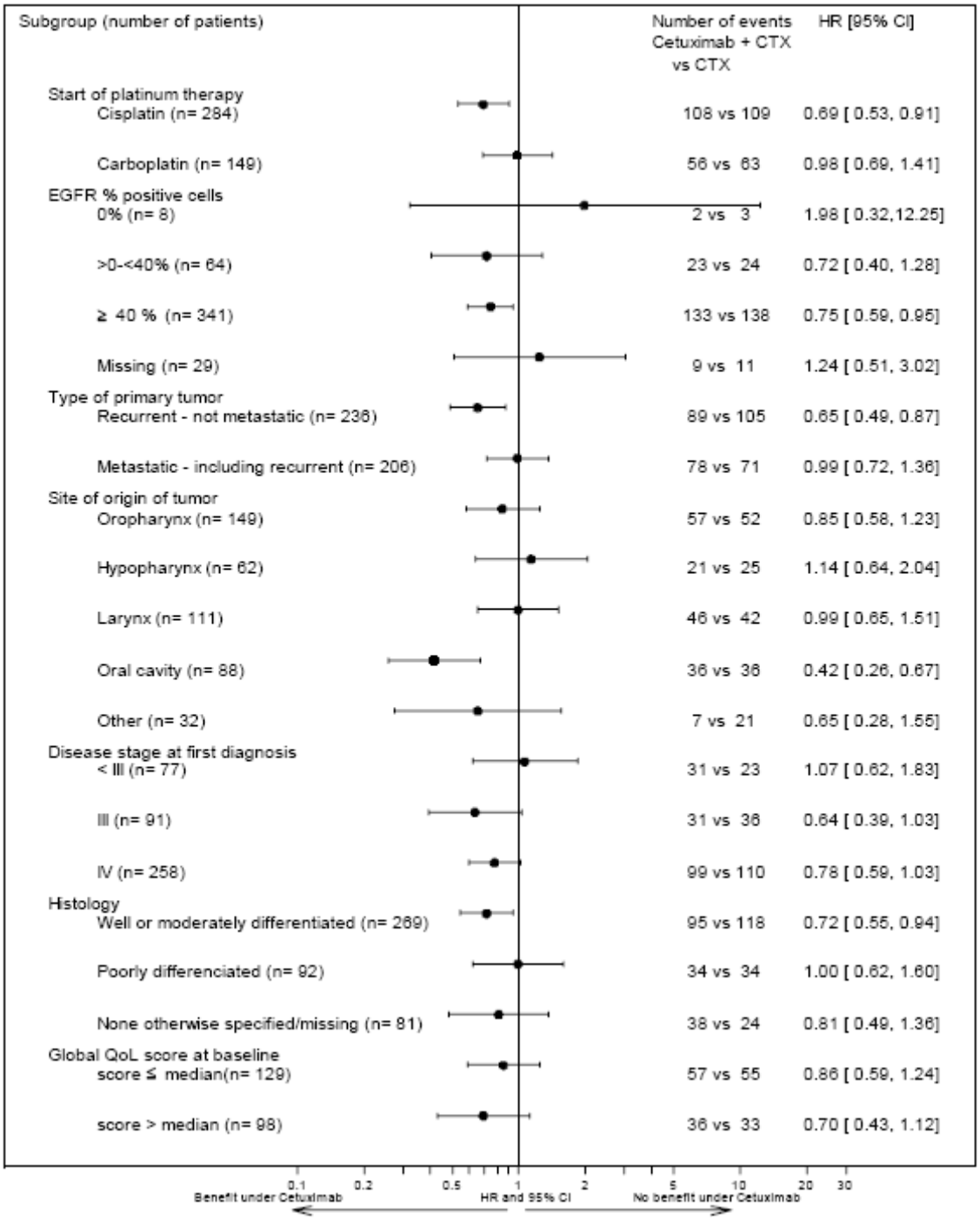
[d] Product-limit (Kaplan-Meier) estimates



Cox regression with a stepwise selection procedure identified only one additional potential prognostic baseline factor, namely the type of primary tumour. Adjustment for the most important prognostic variables confirmed the primary analysis on OS time: HR=0.786, 95% CI: 0.636, 0.973.

Overall Survival Time: Results of Subgroup Analyses (ITT Population)




Subgroup (number of patients)
Number of events Cetuximab + CTX vs CTX
HR [95% CI]
Start of platinum therapy
Cisplatin (n= 284) 108 vs 109 0.69 [0.53, 0.91]
Carboplatin (n= 149) 56 vs 63 0.98 [0.69, 1.41]
EGFR % positive cells
0% (n= 8) 2 vs 3 1.98 [0.32,12.25]
>0-<40% (n= 64) 23 vs 24 0.72 [0.40, 1.28]
≥ 40 % (n= 341) 133 vs 138 0.75 [0.59, 0.95]
Missing (n= 29) 9 vs 11 1.24 [0.51, 3.02]
Type of primary tumor
Recurrent - not metastatic (n= 236) 89 vs 105 0.65 [0.49, 0.87]
Metastatic - including recurrent (n= 206) 78 vs 71 0.99 [0.72, 1.36]
Site of origin of tumor
Oropharynx (n= 149) 57 vs 52 0.85 [0.58, 1.23]
Hypopharynx (n= 62) 21 vs 25 1.14 [0.64, 2.04]
Larynx (n= 111) 46 vs 42 0.99 [0.65, 1.51]
Oral cavity (n= 88) 36 vs 36 0.42 [0.26, 0.67]
Other (n= 32) 7 vs 21 0.65 [0.28, 1.55]
Disease stage at first diagnosis
< III (n= 77) 31 vs 23 1.07 [0.62, 1.83]
III (n= 91) 31 vs 36 0.64 [0.39, 1.03]
IV (n= 258) 99 vs 110 0.78 [0.59, 1.03]
Histology
Well or moderately differentiated (n= 269) 95 vs 118 0.72 [0.55, 0.94]
Poorly differenciated (n= 92) 34 vs 34 1.00 [0.62, 1.60]
None otherwise specified/missing (n= 81) 38 vs 24 0.81 [0.49, 1.36]
Global QoL score at baseline
score ≤ median(n= 129) 57 vs 55 0.86 [0.59, 1.24]
score > median (n= 98) 36 vs 33 0.70 [0.43, 1.12]
0.1
0.2
0.5
1
2
5
10
20
30
Benefit under Cetuximab
HR and 95% CI
No benefit under Cetuximab

Summary of Analysis of Progression-free Survival Time (ITT Population)

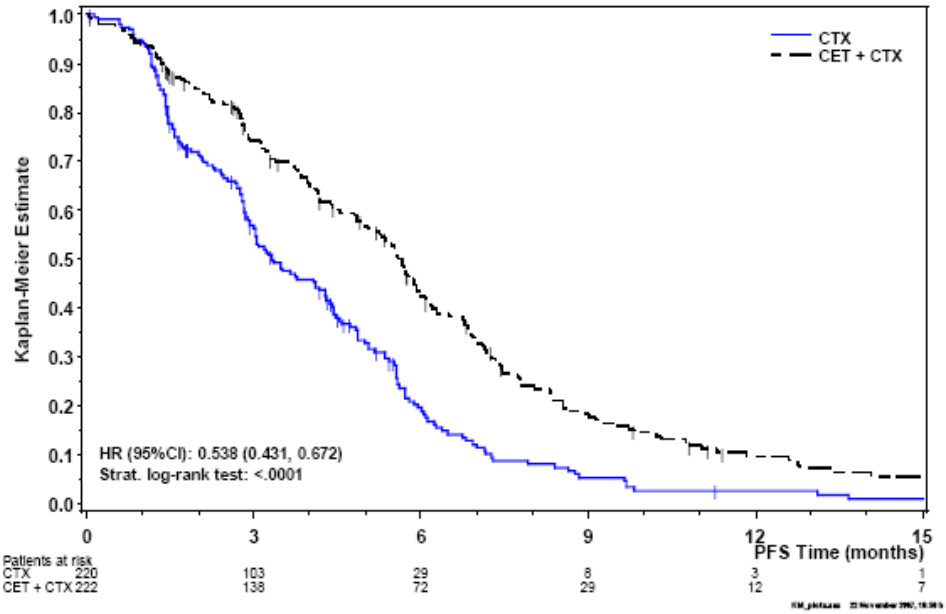
Response variable	Number (%) of subjects	
	Cetuximab + CTX (N=222)	CTX (N=220)
Number of PDs and deaths (%)	168 (75.7)	173 (78.6)
Log rank p value (stratified)[a]	<0.0001	
Hazard ratio (stratified) [95% CI][a, b]	0.538 [0.431, 0.672]	
Progression-free survival time *(months, median [95% CI])*[c]	5.6 [5.0, 6.0]	3.3 [2.9, 4.3]
Number of subjects (%) at risk/survival rates up to [95% CI][c]		
3 months	138 (74%) [68, 80%]	103 (56%) [49, 63%]
6 months	72 (42%) [35, 49%]	29 (20%) [14, 26%]
12 months	12 (10%) [5, 14%]	3 (3%) [0, 5%]
18 months	3 (5%) [1, 8%]	0 (1%) [0, 3%]

Source: *Table 14.2-2.1*

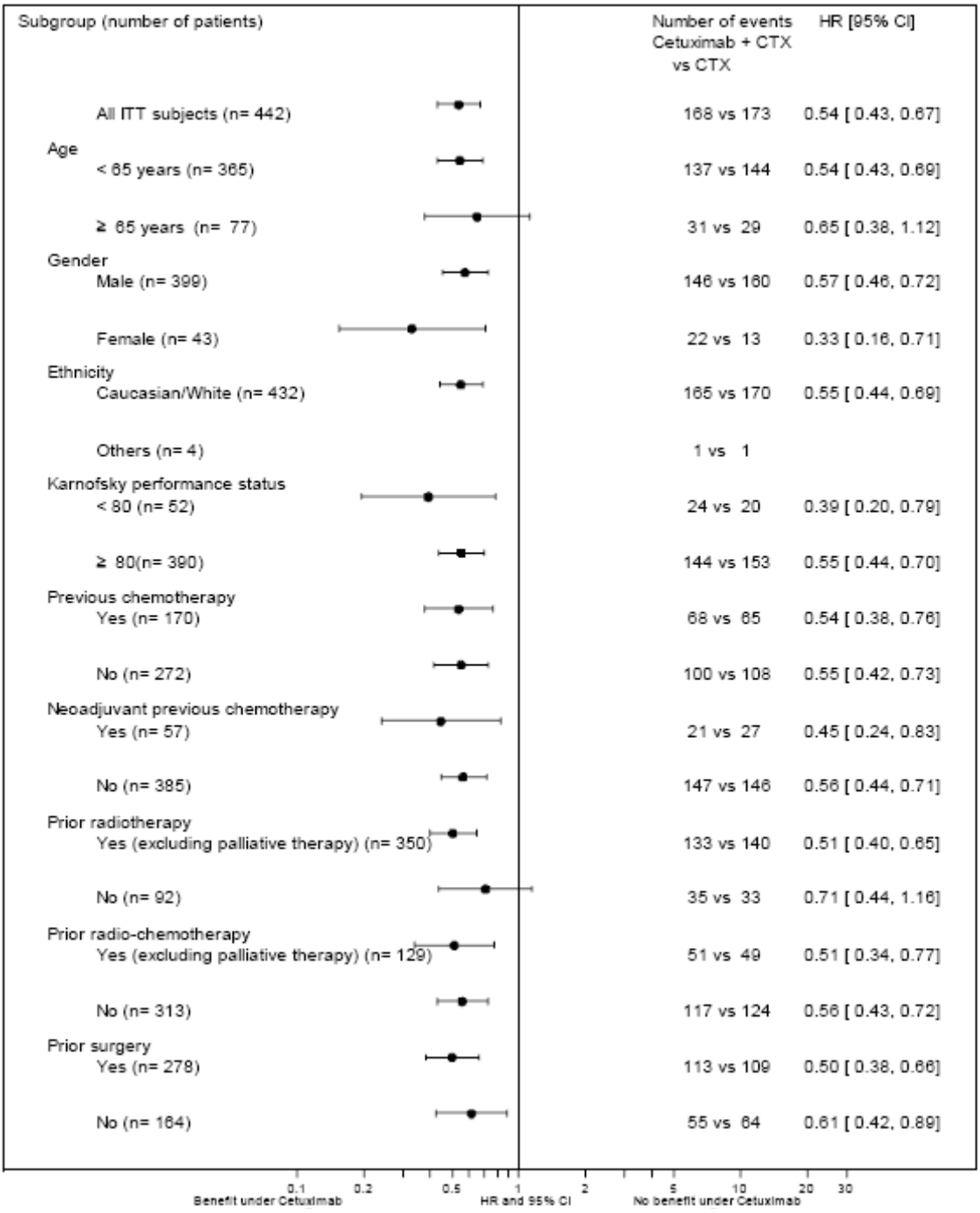
[a] Stratification based on previous chemotherapy and Karnofsky Performance Status as per IVRS

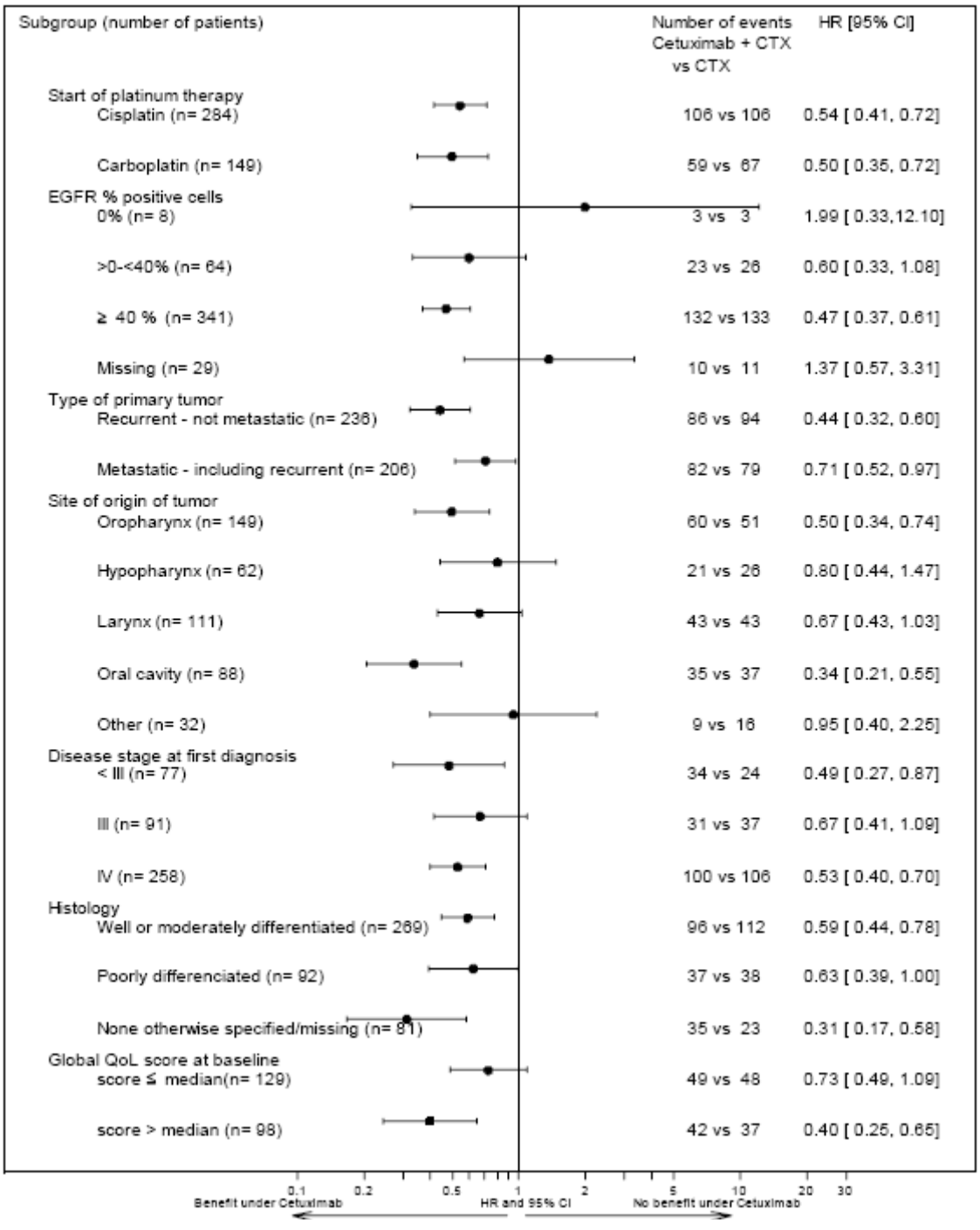
[b] Hazard ratio of cetuximab + CTX over CTX

[c] Product-limit (Kaplan-Meier) estimates



Progression-free Survival Time: Results of Subgroup Analyses (ITT Population)




Subgroup (number of patients)
Number of events Cetuximab + CTX vs CTX
HR [95% CI]
Start of platinum therapy
Cisplatin (n= 284) 106 vs 106 0.54 [0.41, 0.72]
Carboplatin (n= 149) 59 vs 67 0.50 [0.35, 0.72]
EGFR % positive cells
0% (n= 8) 3 vs 3 1.99 [0.33,12.10]
>0-<40% (n= 64) 23 vs 26 0.60 [0.33, 1.08]
≥ 40 % (n= 341) 132 vs 133 0.47 [0.37, 0.61]
Missing (n= 29) 10 vs 11 1.37 [0.57, 3.31]
Type of primary tumor
Recurrent - not metastatic (n= 236) 86 vs 94 0.44 [0.32, 0.60]
Metastatic - including recurrent (n= 206) 82 vs 79 0.71 [0.52, 0.97]
Site of origin of tumor
Oropharynx (n= 149) 60 vs 51 0.50 [0.34, 0.74]
Hypopharynx (n= 62) 21 vs 26 0.80 [0.44, 1.47]
Larynx (n= 111) 43 vs 43 0.67 [0.43, 1.03]
Oral cavity (n= 88) 35 vs 37 0.34 [0.21, 0.55]
Other (n= 32) 9 vs 16 0.95 [0.40, 2.25]
Disease stage at first diagnosis
< III (n= 77) 34 vs 24 0.49 [0.27, 0.87]
III (n= 91) 31 vs 37 0.67 [0.41, 1.09]
IV (n= 258) 100 vs 106 0.53 [0.40, 0.70]
Histology
Well or moderately differentiated (n= 269) 96 vs 112 0.59 [0.44, 0.78]
Poorly differenciated (n= 92) 37 vs 38 0.63 [0.39, 1.00]
None otherwise specified/missing (n= 81) 35 vs 23 0.31 [0.17, 0.58]
Global QoL score at baseline
score ≤ median(n= 129) 49 vs 48 0.73 [0.49, 1.09]
score > median (n= 98) 42 vs 37 0.40 [0.25, 0.65]
0.1
0.2
0.5
1
2
5
10
20
30
Benefit under Cetuximab
HR and 95% CI
No benefit under Cetuximab

Summary of Best Overall Confirmed Response in All Subjects (ITT Population)

Response variable	Number (%) of subjects, ITT population	
	Cetuximab + CTX (N=222)	CTX (N=220)
Best overall response		
Complete response	15 (6.8)	2 (0.9)
Partial response	64 (28.8)	41 (18.6)
Stable disease	101 (45.5)	89 (40.5)
Progressive disease	12 (5.4)	45 (20.5)
Not evaluable	30 (13.5)	43 (19.5)
Best overall response rate (% [95% CI])[a]	35.6 [29.3, 42.3]	19.5 [14.5, 25.4]
CMH test[b]		
p value	0.0001	
Odds ratio [95% CI][b]	2.326 [1.504, 3.600]	
Disease control rate (% [95% CI])[a]	81.1 [75.3, 86.0]	60.0 [53.2, 66.5]
CMH test[b]		
p value	<0.0001	
Odds ratio [95% CI][b]	2.881 [1.870, 4.441]	

Source: *Table 14.2-3.1*

[a] Best overall response rate is based only on subjects with CR and PR, and disease control rate is based on subjects with CR, PR and SD

[b] Stratification based on previous chemotherapy and Karnofsky Performance Status as per IVRS

Summary of Best Overall Confirmed Response in Subjects who Started Platinum Therapy with Cisplatin or Carboplatin (ITT Population)

Response variable	Number (%) of subjects, ITT population	
	Cetuximab + CTX	CTX
Therapy started with CISPLATIN	(N=149)	(N=135)
Best overall response rate (% [95% CI])[a]	38.9 [31.1, 47.2]	23.0 [16.2, 31.0]
p value (CMH test)[b]	0.0035	
Odds ratio [95% CI][b]	2.181 [1.289, 3.691]	
Disease control rate (% [95% CI])[a]	81.9 [74.7, 87.7]	63.0 [54.2, 71.1]
p value (CMH test)[b]	0.0004	
Odds ratio [95% CI][b]	2.631 [1.521, 4.551]	
Therapy started with CARBOPLATIN	(N=69)	(N=80)
Best overall response rate (% [95% CI])[a]	30.4 [19.9, 42.7]	15.0 [8.0, 24.7]
p value (CMH test)[b]	0.0267	
Odds ratio [95% CI][b]	2.452 [1.102, 5.458]	
Disease control rate (% [95% CI])[a]	84.1 [73.3, 91.8]	58.8 [47.2, 69.6]
p value (CMH test)[b]	0.0007	
Odds ratio [95% CI][b]	3.879 [1.735, 8.675]	

Source: *Tables 14.2-3.2* and *14.2-3.3*

[a] Best overall response rate is based only on subjects with CR and PR, and disease control rate is based on subjects with CR, PR and SD

[b] Stratification based on previous chemotherapy and Karnofsky Performance Status as per IVRS

Subgroup Analyses of Best Overall Response (ITT Population)

Subgroup	Best overall response rate					
	Cetuximab + CTX N=222			CTX N=220		
	N	%	95% CI	N	%	95% CI
Age (years)						
< 65	64/183	35.0	[28.1, 42.4]	37/182	20.3	[14.7, 26.9]
≥ 65	15/39	38.5	[23.4, 55.4]	6/38	15.8	[6.0, 31.3]
Gender						
Male	67/197	34.0	[27.4, 41.1]	41/202	20.3	[15.0, 26.5]
Female	12/25	48.0	[27.8, 68.7]	2/18	11.1	[1.4, 34.7]
Karnofsky Performance Status						
< 80	7/27	25.9	[11.1, 46.3]	1/25	4.0	[0.1, 20.4]
≥ 80	72/195	36.9	[30.1, 44.1]	42/195	21.5	[16.0, 28.0]
Previous chemotherapy						
Yes	25/90	27.8	[18.9, 38.2]	13/80	16.3	[8.9, 26.2]
No	54/132	40.9	[32.4, 49.8]	30/140	21.4	[14.9, 29.2]
Neoadjuvant previous chemotherapy						
Yes	7/24	29.2	[12.6, 51.1]	6/33	18.2	[7.0, 35.5]
No	72/198	36.4	[29.7, 43.5]	37/187	19.8	[14.3, 26.2]
Prior radiotherapy (excluding palliative therapy)						
Yes	61/174	35.1	[28.0, 42.6]	31/176	17.6	[12.3, 24.1]
No	18/48	37.5	[24.0, 52.6]	12/44	27.3	[15.0, 42.8]
Prior radiochemotherapy (excluding palliative therapy)						
Yes	19/69	27.5	[17.5, 39.6]	9/60	15.0	[7.1, 26.6]
No	60/153	39.2	[31.4, 47.4]	34/160	21.3	[15.2, 28.4]
Prior surgery						
Yes	51/143	35.7	[27.8, 44.1]	21/135	15.6	[9.9, 22.8]
No	28/79	35.4	[25.0, 47.0]	22/85	25.9	[17.0, 36.5]

Subgroup	Best overall response rate					
	Cetuximab + CTX N=222			CTX N=220		
	N	%	95% CI	N	%	95% CI
Start of platinum therapy						
Cisplatin	58/149	38.9	[31.1, 47.2]	31/135	23.0	[16.2, 31.0]
Carboplatin	21/69	30.4	[19.9, 42.7]	12/80	15.0	[8.0, 24.7]
EGFR % stained cells						
0	0/3	0.0	[0.0, 70.8]	1/5	20.0	[0.5, 71.6]
>0–<40	13/32	40.6	[23.7, 59.4]	13/32	40.6	[23.7, 59.4]
≥40	63/174	36.2	[29.1, 43.8]	25/167	15.0	[9.9, 21.3]
Missing	3/13	23.1	[5.0, 53.8]	4/16	25.0	[7.3, 52.4]
Type of primary tumor						
Recurrent, not metastatic	42/118	35.6	[27.0, 44.9]	17/118	14.4	[8.6, 22.1]
Metastatic, including recurrent	37/104	35.6	[26.4, 45.6]	26/102	25.5	[17.4, 35.1]
Site of origin of tumor						
Oropharynx	28/80	35.0	[24.7, 46.5]	13/69	18.8	[10.4, 30.1]
Hypopharynx	7/28	25.0	[10.7, 44.9]	6/34	17.6	[6.8, 34.5]
Larynx	21/59	35.6	[23.6, 49.1]	17/52	32.7	[20.3, 47.1]
Oral cavity	21/46	45.7	[30.9, 61.0]	2/42	4.8	[0.6, 16.2]
Other	2/9	22.2	[2.8, 60.0]	5/23	21.7	[7.5, 43.7]
Histology						
Well/moderately differentiated	41/128	32.0	[24.1, 40.9]	29/141	20.6	[14.2, 28.2]
Poorly differentiated	20/46	43.5	[28.9, 58.9]	9/46	19.6	[9.4, 33.9]
Missing/not specified	18/48	37.5	[24.0, 52.6]	5/33	15.2	[5.1, 31.9]
Global Quality of Life score at baseline						
≤ median	19/67	28.4	[18.0, 40.7]	7/62	11.3	[4.7, 21.9]
> median	22/54	40.7	[27.6, 55.0]	12/44	27.3	[15.0, 42.8]

Supportive studies

EMR 62 202-008 was an open-label, uncontrolled, randomized, multicenter phase I/II study on the safety and tolerability of escalating doses of infusional 5-FU in combination with cetuximab in the first-line treatment of subjects with R/M SCCHN combined with cisplatin or carboplatin . Altogether 53 subjects received the licensed dose of cetuximab in combination with 3-weekly cycles of cisplatin (100 mg/m²) or carboplatin (AUC 5), each in combination with a 5-day infusion of 5-FU at escalating doses of 600 (low dose), 800 (medium dose) or 1000 mg/m²/day (high dose). The frequency of dose-limiting toxicities (DLTs) in the first 2 cycles was acceptable according to the protocol definition for all regimens, for cetuximab in combination with either cisplatin or carboplatin given together with infusional 5-FU at a daily dose of 1000 mg/m².

As infusional 5-FU at 1000 mg/m², in combination with cisplatin (100 mg/m²) or carboplatin (AUC 5), is considered standard without cetuximab, this dose was selected for the confirmatory study. The pooled efficacy analysis of the study showed a median survival time of 9.8 months, a median PFS time of 5.1 months, and an overall response rate of 36%. These efficacy results and the safety profile of cetuximab in combination with either cisplatin (100 mg/m²) or carboplatin (AUC 5) given together with infusional 5-FU at a daily dose of 1000 mg/m² were the basis for the selection of this dose of 5-FU for further study.

Study ECOG E5397 was conducted in the first-line setting of R/M SCCHN. Cisplatin + cetuximab and cisplatin + placebo were compared in 117 subjects.

Time-related efficacy parameters tended to favour the cetuximab containing arm, although not reaching statistical significance (median OS time: 9.2 vs 8.0 months; median PFS time: 4.2 vs 2.7 months), and the overall response rate was superior (26 vs 10%, p=0.03). The safety profile of cisplatin was essentially not altered by add-on cetuximab.

Main study

EMR 62 202-002 – FISH analysis
The MAH was requested by the CHMP to provide further analyses of the outcome of the pivotal study in relation to EGFR gene copy number status (assessed by FISH) of the tumour using the most mature outcome data available and to discuss possible bias introduced by censoring. The clinical data cut-off for the study was 12 March 2007.

The “Colorado Score definition” and five additional FISH score definitions were tested to investigate a possible association of EGFR gene copy number status and cetuximab efficacy in EMR 62 202-002. No informative relationship was seen between EGFR gene copy number status and study outcome for overall survival, progression-free survival and response.

Therefore, it can be concluded that EGFR gene copy number status is not a predictive marker for cetuximab in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.

Discussion of Efficacy
Add-on efficacy of a magnitude normally considered clinically relevant has been demonstrated in the pivotal study. These data are supported by add-on activity demonstrated in a small ECOG study.

Survival benefit has not been consistently demonstrated in the subgroup analyses reported, but add-on activity in terms of response rate and PFS benefit was shown. This constitutes no major concern as it would be expected for an add-on therapy to show less activity in patients with affected performance status, more aggressive tumours, etc.

In the current SPC and in relation to the radiotherapy study the following is stated: "Patients with a good prognosis as indicated by tumour stage, Karnofsky performance status (KPS) and age had a more pronounced benefit, when cetuximab was added to radiation therapy. No clinical benefit could be demonstrated in patients with KPS ≤ 80 who were 65 years of age or older." The same situation applies similarly to the new study in combination with platinum-based chemotherapy.

Relevant add-on activity is seen for FISH positive and FISH negative tumours, where FISH status is defined according to the Colorado Scoring system definition. This seems to be the case also with respect to exploratory analyses.
Available data on KRAS mutation in SCCHN and evaluation of the feasibility of further investigations to address this issue, were discussed assuming that a mutated KRAS would have similar consequences in the SCCHN population as in mCRC. In contrast to mCRC where KRAS mutations are found in 30-40% of tumors, KRAS mutations in SCCHN are rare events. Therefore, KRAS mutational status does not appear to be a meaningful biomarker in SCCHN to identify patients who derive most benefit from cetuximab treatment.
Also, it has to be considered that the results from mCRC cannot automatically be extrapolated to other indications given the complexity of the EGFR and KRAS biology. The impact of KRAS mutations on cetuximab efficacy is most likely dependent on the relative importance of KRAS and its downstream mediators for EGFR mediated signalling in the respective indication vs. other (KRAS independent) EGFR triggered pathways such as PI3K/Akt or STAT signalling. Furthermore, the prominence of other EGFR signalling independent mechanisms such as ADCC could reduce the predictive power of KRAS mutations.

2.2 Clinical safety

EMR 62 202-002
Cetuximab was given as weekly infusions until PD, symptomatic deterioration or unacceptable toxicity. CTX was given in cycles of 21 days and subjects could receive up to 6 cycles of CTX provided that they did not show PD or unacceptable toxicity. Cetuximab could be continued in subjects without PD as monotherapy after the end of CTX in subjects in the cetuximab + CTX group.

Of the 442 randomized subjects, 219 subjects were exposed to cetuximab + CTX and 215 subjects were exposed to CTX only. Subjects in the cetuximab + CTX group received a median of 17 cetuximab infusions. A total of 100 subjects continued to receive cetuximab as monotherapy after CTX; the median number of cetuximab monotherapy infusions was 10 (interquartile range: 6–23, range: 1–71).

Overall, the median cumulative cetuximab dose was 4,139 mg/m². The median dose intensity for the weekly treatment was 241 mg/m² and thus very close to the target dose of 250 mg/m². Overall, 75.2% subjects achieved a relative dose intensity of ≥90%.

Adverse events

Most Common Grade 3 or 4 AEs Occurring in >5% Subjects in Either Treatment Group of Study EMR 62 202-002

Preferred term	Number (%) of subjects[a]			
	Grade 3 or 4 events		Grade 4 events	
	Cetuximab+CTX N=219	CTX N=215	Cetuximab+CTX N=219	CTX N=215
Any event	179 (81.7)	164 (76.3)	67 (30.6)	66 (30.7)
Neutropenia	49 (22.4)	50 (23.3)	9 (4.1)	18 (8.4)
Anemia	29 (13.2)	41 (19.1)	2 (0.9)	2 (0.9)
Thrombocytopenia	24 (11.0)	24 (11.2)	0 –	3 (1.4)
Leukopenia	19 (8.7)	19 (8.8)	4 (1.8)	5 (2.3)
Hypokalemia	16 (7.3)	10 (4.7)	2 (0.9)	1 (0.5)
Vomiting	12 (5.5)	6 (2.8)	0 –	0 –
Anorexia	11 (5.0)	3 (1.4)	2 (0.9)	1 (0.5)
Asthenia	11 (5.0)	12 (5.6)	1 (0.5)	1 (0.5)
Hypomagnesemia	11 (5.0)	3 (1.4)	8 (3.7)	1 (0.5)
Rash	11 (5.0)	0 –	0 –	0 –
Dyspnea	9 (4.1)	17 (7.9)	2 (0.9)	5 (2.3)

Grade 3 or 4 AEs in <5% Subjects of Study EMR 62 202-002 with Higher Frequencies in the Cetuximab + CTX group (Relative Increase >2)

Preferred term	Number (%) of subjects[a]			
	Grade 3 or 4 events		Grade 4 events	
	Cetuximab+CTX N=219	CTX N=215	Cetuximab+CTX N=219	CTX N=215
Dehydration	8 (3.7)	3 (1.4)	1 (0.5)	1 (0.5)
Diarrhea	10 (4.6)	2 (0.9)	0 –	0 –
Hypocalcemia	9 (4.1)	2 (0.9)	5 (2.3)	0 –
Pneumonia	9 (4.1)	4 (1.9)	3 (1.4)	1 (0.5)
Sepsis	6 (2.7)	1 (0.5)	3 (1.4)	1 (0.5)
Septic shock	3 (1.4)	0 –	3 (1.4)	0 –

Serious adverse events and deaths

Deaths: The profile of primary reasons for death differed slightly between the 2 treatment groups with a lower frequency of deaths due to disease progression in the cetuximab + CTX group than in the CTX group (4.6 vs 7.0% subjects). Frequencies in the cetuximab + CTX group were higher for deaths due to intercurrent or unrelated illnesses (5.5 vs 2.8%) and deaths due to unknown causes (4.6 vs 0.9%). The primary reason for death was not considered to be due to cetuximab-related events in any of the subjects; 9 deaths were considered to be due to an AE related to CTX (2 in the cetuximab + CTX group, 7 in the CTX group).

SAEs were reported in both treatment groups in a similar proportion of subjects: 50.2% in the cetuximab + CTX group and 47.4% in the CTX group.

The following SAEs were more frequent in the cetuximab + CTX group than in the CTX group (relative increase >2): pneumonia (4.6 vs 1.9%), dehydration (4.1 vs 1.4%), sepsis (2.7 vs 0.5%), and septic shock (1.4 vs 0%).

Withdrawals due to AEs: Cetuximab was discontinued due to AEs in 44 (20.1%) of the 219 subjects in the cetuximab + CTX group; in 28 (12.8%) of these subjects, CTX was also discontinued.

The most frequent reason for discontinuation of cetuximab was hypersensitivity (1.8% subjects). The proportion of subjects in whom AEs led to discontinuations of CTX was higher in the cetuximab + CTX group compared to the CTX group: 22.8 vs 17.7% subjects. The most frequent AEs leading to discontinuation of CTX were neutropenia (2.7 vs 0.9%), mucosal inflammation (1.8 vs 0.9%), and general physical health deterioration (1.8 vs 0%).

Special AE Categories
In study EMR 62 202-002, the following AE categories were examined based on relevant MedDRA preferred terms as they represent known side effects of cetuximab:
skin reactions, acne-like rash, IRRs, mucositis, cardiac events (in combination with infusional 5-FU), and thromboembolic events.

In addition, events related to haemorrhage were analyzed. Frequencies of corresponding NCI-CTC terms and categories in study ECOG E5397 were also reviewed.
The coincidence of electrolyte imbalances and two categories of AEs (cardiac events or death of unknown cause, severe diarrhea) was also examined in study EMR 62 202-002.

Known Side Effects: Incidences and severities of skin reactions, acne-like rash, IRRs, deep vein thrombosis and pulmonary embolism, and cardiac events were in line with previous findings and consistent with the current product labeling.

Severe cardiac AEs occurred more often in the cetuximab + CTX group than in the CTX group (7.3 vs 4.2%). This was mainly due to AEs of ‘infarction/ischemia’ occurring primarily during the first 5-FU infusion, as well as ‘congestive heart failure’ and ‘sudden death’ due to unknown causes.

Other Safety Issues. The frequency of ‘hemorrhages’ was not increased by the combination of cetuximab with platinum-based CTX as compared to platinum-based CTX alone.

The data on coincidence of electrolyte imbalances with cardiac events, death of unknown cause, or severe diarrhoea were limited and did not allow clinically meaningful conclusions to be drawn.

Discussion of Safety

The safety profile of cetuximab as add-on to CTX is as expected and is dominated by acne-like rash, diarrhoea, electrolyte disturbances and infusion-related reactions.
Based on the increased incidence of grade 3 and 4 hypocalcaemia in study EMR 62202-002 in the cetuximab plus CTX group, it is at least possible that this is a cetuximab related event. It was agreed that cases of severe hypocalcaemia should be mentioned in the SPC.

As diarrhoea and mucositis are both known side effects of cetuximab irrespective of indication and combination therapy, this indicates that the occurrence of dehydration is not only limited to the combination with platinum-based therapy. Therefore it was agreed to include dehydration in particular secondary to diarrhoea or mucositis as a side effect of cetuximab in the product information.
It is very likely that the association of severe neutropenia (based on AE and laboratory values) to subsequent infectious complications, such as febrile neutropenia, pneumonia or sepsis is present in patients with SCCHNTherefore these findings were reflected in the product information.

3. OVERALL DISCUSSION AND Benefit-risk assessment

Benefit
Patients with recurrent or metastatic head and neck cancer (SCCHN) have a poor prognosis and treatment is administered with the aims to palliate symptoms and to prolong survival. In selected patients, cisplatin + infusional 5FU is considered standard therapy. In certain individuals, cisplatin is substituted with carboplatin due to its favourable safety profile. As add-on, cetuximab has shown increased anti-tumour activity in two studies and in the pivotal study also a survival benefit. The results of the pivotal study EMR 62 202-002 demonstrate a positive benefit-risk for combination therapy of cetuximab with platinum-based chemotherapy in terms of improvements in overall survival, progression-free survival, overall response rate, disease control rate, and time to treatment failure compared to platinum-based chemotherapy alone.
KRAS is typically not mutated in head and neck cancer and thus constitutes no concern.
Relevant add-on activity is seen for FISH positive and FISH negative tumours, also with respect to exploratory analyses and it can be concluded that no informative relationship is seen between FISH status and study outcome.

Risk
Patients with head and neck cancer are often elderly with co-morbidities and at time of recurrence or with metastatic disease, treatment is administered selectively. In patients deemed suitable for cisplatin/5FU the add-on toxicity of cetuximab is manageable and associated tolerability problems are foreseeable. The safety profile of cetuximab as add-on to CTX is as expected and is dominated by acne-like rash, diarrhoea, electrolyte disturbances and infusion-related reactions. Appropriate revisions of the SPC have been made to further clarify these safety aspects.

In certain subgroups, mainly groups with poor prognosis, benefit in terms of survival, seems not to be present. This, however, is rather what would be expected and there are no good reasons to restrict the indication from an efficacy perspective. This is already captured in the SPC section 5.1 in relation to cetuximab.

Balance
The benefit – risk relationship of adding cetuximab to standard platinum based chemotherapy in patients with recurrent or metastatic SCCHN is favourable.

4. CONCLUSION

On 23 October 2008 the CHMP considered this Type II variation to add “use of Erbitux in combination with platinum-based chemotherapy for recurrent or metastatic squamous cell cancer of the head and neck”, to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.