SCIENTIFIC DISCUSSION (MODULE 8B OF THE EPAR)

1. Introduction

Erbitux contains cetuximab, a chimeric monoclonal antibody of the immunoglobulin G_1 class that is directed against the human epidermal growth factor receptor EGFR. Cetuximab binds to the extra-cellular region of EGFR, thereby inhibiting ligand binding. Cetuximab is also thought to induce receptor internalisation and degradation and antibody-dependent cellular cytotoxicity. EGFR is known to be overexpressed in many human tumours, including head neck cancer where its overexpression has been seen in more than 90% of cases.

Erbitux was approved in June 2004 for use in combination with irinotecan in the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

The MAH now applies for an extension of the indication to include also squamous cell cancer of the head and neck (SCCHN) as follows:

- Erbitux in combination with radiation therapy is indicated for the treatment of patients with locally advanced squamous cell cancer of the head and neck.

In patients with locally advanced squamous cell cancer of the head and neck, cetuximab is used concomitantly with radiation therapy. It is recommended to start cetuximab therapy one week before radiation therapy and to continue cetuximab therapy until the end of the radiation therapy period.
A second indication for the monotherapy treatment of patients who have failed chemotherapy for recurrent and/or metastatic squamous cell cancer of the head and neck was initially proposed but was withdrawn by the MAH at the time of the responses to the CHMP list of questions.

2. Preclinical aspects

In the new proposed indications cetuximab is to be administered in the same way as in the already authorized colorectal cancer (CRC) indication, i.e. once weekly as an intravenous (IV) infusion with an initial dose of 400 mg/m^2 in week 1 followed by subsequent weekly doses of 250 mg/m^2 from week 2 on. The maximum duration of treatment with cetuximab is either shorter than in CRC (8 weeks when used in combination with radiotherapy in SCCHN patients) or of the same length (to be used until progression of the underlying disease when used as monotherapy in SCCHN patients). For these reasons, no new pharmacology studies were performed, but the MAH has provided a summary of published data. Cell proliferation, cell survival, cell motility, cell invasion and tumour angiogenesis have all been shown to be affected by cetuximab in preclinical *in vitro* and *in vivo* SCCHN models, and the available data provides a strong basis for testing cetuximab against SCCHN in clinical studies.

3. Clinical aspects

Surgery and radiotherapy (RT) are the two curative treatment modalities available for head neck cancers. The total dose and fractionation are important factors in determining outcome of RT. "Standard-of-care" RT for subjects with locally advanced head and neck malignancies is still evolving. Although RT is essential in treating SCCHN, attempts have been made to improve efficacy by combining it with chemotherapy. Chemotherapy is also used in the recurrent and metastatic situation. Several large randomized trials have been published comparing concomitant chemoradiotherapy (CRT), predominantly using platinum analogues and 5-FU, with RT alone. Survival rates with CRT were 10–20% higher than with RT alone. CRT also significantly improves loco regional control (LRC) rates.
Currently, combined modality therapy with CRT is more frequently used and accepted as standards in spite of the varying degrees of increased local mucosal toxicity resulting in significant morbidity.

3.1. Clinical pharmacology

Population pharmacokinetic analysis was performed on a database including dosing information and plasma concentration data from the different SCCHN studies. The main objectives were to describe the pharmacokinetics in patients with SCCHN compared with other cancer types, to identify predictors of exposure to cetuximab and to estimate inter-patient variability.

The SCCHN database included 2866 observations from 446 patients, of which 412 received the standard regimen of a loading dose of 400 mg/m2 followed by weekly doses of 250 mg/m2. PK sampling was performed in all of the nine SCCHN studies, although in some studies only e.g. for trough concentrations, and all patients who had at least one PK sample and available dosing information were included in the population pharmacokinetic database.

Demographic data that were included as co-variates were age, weight, height, body surface area (BSA), sex, race, creatinine clearance and different markers for hepatic function. Concomitant medication, EGFR status and the manufacturing process for the various cetuximab lots administered in the studies were also included in the dataset as categorical variables.

The previously developed population pharmacokinetic model, which was discussed during the assessment of the first marketing authorisation application for Erbitux and comprised a two-compartment model with saturable first-order elimination, provided a good prediction of the observed plasma concentration-time data for each of the new SCCHN studies. Given the limited dose range in the SCCHN studies, a two-compartment model with linear elimination adequately described the combined SCCHN data. The estimations for Volume of the central and peripheral compartments (3.52 L and 1.86 L, respectively) and for inter-compartment flow, Q (0.0437 L/h), were in good agreement with the estimations obtained with the previous population pharmacokinetic analysis on data from other tumour types. Clearance of cetuximab in SCCHN patients was estimated to be 0.322 L/h. BSA was determined to be a significant co-variate for clearance as well as central volume of distribution. Clearance of cetuximab was found to be approximately 16% lower after administration of batches manufactured to intermediate scale.

Discussion on clinical pharmacology

As expected, there were no obvious differences in the pharmacokinetics of cetuximab in patients with SCCHN compared with the results from the previous analysis of a database containing data from various tumour types. The previously observed non-linear elimination of cetuximab was seen at lower doses (<250 mg/m2). In the SCCHN studies, most patients received the standard dose of 400 mg/m2 loading dose and weekly maintenance doses of 250 mg/m2. At these doses cetuximab pharmacokinetics has been shown to be linear, and it is not surprising that a model with linear elimination adequately described the SCCHN data. As also previously observed, BSA had a significant impact on the clearance of cetuximab. No PK/PD analyses have been submitted
EGFR expression has been demonstrated to be polymorph. This may affect receptor-mediated clearance of cetuximab. It is assumed that samples for pharmacogenetic analyses are available and will be used to further elucidate the pharmacokinetics and pharmacodynamics of cetuximab.

3.2 Clinical efficacy

Clinical trial EMR 62 202-006: **add-on to definitive radiotherapy in patients with SCCHN.**
This is a multinational (36 US, 37 non-US sites [EU, South Africa, Israel, Australia, Switzerland]) open-label, phase III study. Subjects (n=424) were randomized 1:1 to RT alone or RT + cetuximab. Randomization was stratified by Karnofsky Performance Score (KPS) (60–80; 90–100%), nodal stage (N0; N+), tumour stage (T1–T3; T4 [AJCC]), and RT regimen (once daily; twice daily; concomitant boost) (dynamic allocation according to Pocock). Study period: First/last subject in: April 1999/March 2002. Clinical/survival cut-offs: 30 April/31 August 2004.

Objectives: Primary – Difference in locoregional disease control (LRC). Secondary –Overall survival (OS), tumour response (RR), acute and late toxicity, progression-free survival (PFS), quality of life; to assess EGFR levels in the treatment groups.
The primary evaluation of efficacy endpoints was made by an Independent Clinical Review Committee (ICRC), which was blinded to treatment group. The ICRC ascertained the dates of first documented locoregional failure, distant metastasis, or second primaries. It also determined the overall response at 8 weeks post-RT.
Main criteria for inclusion were:

- Measurable disease.
- Pathologically demonstrated squamous cell carcinoma of the oropharynx, hypopharynx, or larynx.
- Stage III or IV disease with an expected survival of ≥12 months.
- Medically able to withstand a course of definitive RT.
- KPS ≥60%.
- Neutrophils ≥1.5 x 10^9/l; platelets ≥100 x 10^{12}/l; bilirubin ≤25 μM/l; ALAT, ASAT ≤2 x the upper limit of normal; serum creatinine ≤133 μM/l, or estimated creatinine clearance ≥50 ml/min; normal serum calcium.
- Tumour tissue available for immunohistochemical assay of EGFR expression.
- No evidence of distant metastatic disease.

Dose and duration of treatment

- RT (all patients): 6-7 weeks once-daily (70 Gy in 35 fractions), twice-daily (72.0–76.8 Gy in 60–64 fractions), or concomitant boost (72.0 Gy total in 42 fractions).
- Cetuximab (RT + cetuximab group): 400 mg/m^2 initial dose in week 1, then weekly doses of 250 mg/ m^2 for 7-8 weeks.

Statistical methods:
Distributions of time-to-event variables were estimated using the Kaplan-Meier product-limit method. Median times-to-event and 1-, 2- and (for overall survival) 3-year estimates (including 95% CIs).
The log-rank test, stratified by randomization stratum was the primary analysis for treatment comparison. A Cox proportional hazards model, stratified as above, estimated hazard ratios (HR) and their 95% CIs. Rates were compared using the Cochran-Mantel-Haenszel test, adjusted for randomization stratum as primary analysis.

Results

Table 1. Demographic and baseline characteristics (ITT population)

Characteristic	Radiotherapy alone (N=213)	Radiotherapy + cetuximab (N=211)
Gender, n (%)	**169 (79.3)**	**171 (81.0)**
Male		
Female	44 (20.7)	40 (19.0)
Age (years) Median	58	56
Range	35–83	34–81
<65 years	**148 (69.5)**	**166 (78.7)**
≥65 years	65 (30.5)	45 (21.3)
Race, n (%) White	175 (82.2)	177 (83.9)
Black	24 (11.3)	24 (11.4)
Asian	2 (0.9)	1 (0.5)
Hispanic	10 (4.7)	8 (3.8)
Other	2 (0.9)	1 (0.5)
Karnofsky 50	1 (0.5)	0 (–)
Performance 60	5 (2.3)	6 (2.8)
Score, n (%) 70	16 (7.5)	15 (7.1)
80	49 (23.0)	42 (19.9)
90	**103 (48.4)**	**112 (53.1)**
90–100	0 (–)	1 (0.5)
100	38 (17.8)	34 (16.1)
Unknown	1 (0.5)	1 (0.5)

Table 2. Primary tumour diagnosis at screening (ITT population)

Site of primary tumor	Number (%) of patients	
	Radiotherapy alone	Radiotherapy + cetuximab
Oropharynx	135 (63.4)	118 (55.9)
Hypopharynx	27 (12.7)	36 (17.1)
Larynx	51 (23.9)	57 (27.0)

Table 3. Pretreatment and AJCC staging

Element of staging	Number (%) of subjects			
	Radiotherapy alone		Radiotherapy + cetuximab	
AJCC overall stage				
II	1	(0.5)	0	(–)
III	51	(23.9)	55	(26.1)
IV	161	(75.6)	156	(73.9)
AJCC T stage				
T1	17	(8.0)	13	(6.2)
T2	50	(23.5)	50	(23.7)
T3	81	(38.0)	85	(40.3)
T4	65	(30.5)	62	(29.4)
TX	0	(–)	1	(0.5)
AJCC N stage				
N0	38	(17.8)	42	(19.9)
N1	39	(18.3)	42	(19.9)
N2a	21	(9.9)	12	(5.7)
N2b	47	(22.1)	48	(22.7)
N2c	44	(20.7)	52	(24.6)
N3	24	(11.3)	15	(7.1)

Efficacy

Locoregional control (ICRC, ITT, primary endpoint) was defined as "The time from randomization to the first documented progression or recurrence of locoregional disease, or death due to any cause. … Primary analysis – ICRC assessment: The event date will be the date of locoregional disease progression per ICRC, or the date of death, in the absence of locoregional progression. If no event exists, then LRC will be censored per the ICRC assessment. LRC of living patients with no ICRC assessment will be censored at randomization." Results are presented in table 4.

Table 4, fig 1: Duration of locoregional control in months (ITT population)

Locoregional control	Radiotherapy alone	Radiotherapy + cetuximab
Number of events (%)	**134 (62.9)**	**110 (52.1)**
Median duration (months) 95% CI	14.9 11.8;19.9	24.4 15.7;45.1
One-year rate 95% CI	55.3% 48.5;62.2%	63.2% 56.5;69.8%
Two year rate 95% CI	40.7% 33.8;47.5%	50.3% 43.4;57.3%
Stratified log-rank p value	0.005	
Stratified hazard ratio	0.680	
95% CI	0.520;0.890	

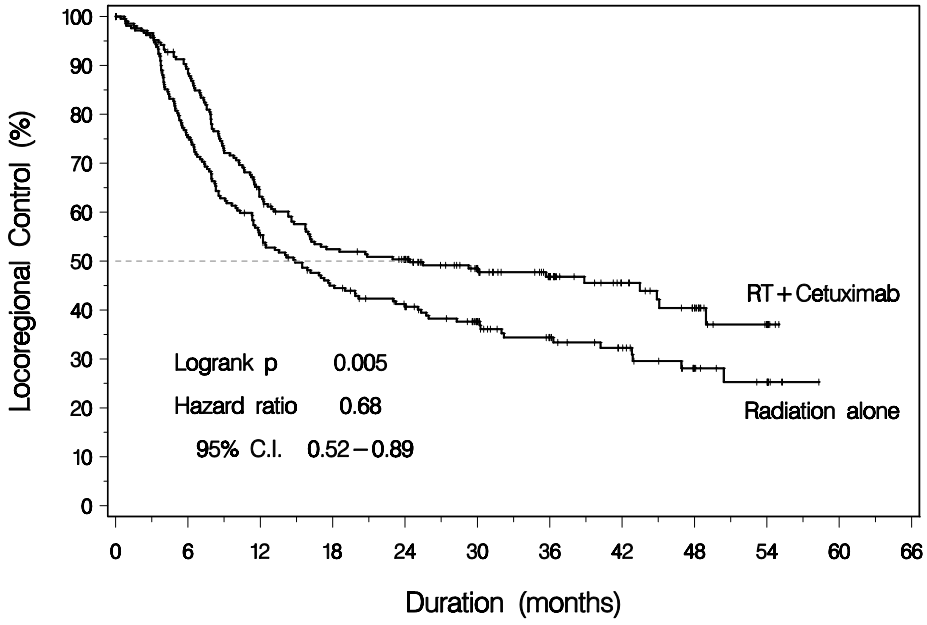


Table 5, fig 2: Overall survival (ITT population)

Overall survival	Radiotherapy alone	Radiotherapy + cetuximab[a]
Number of events (%)	121 (56.8)	101 (47.9)
Median follow-up, months	45.7	45.0
Median survival, months (95% CI)	29.3(20.6; 42.8)	49.0(32.8; 62.6+)
One-year rate (95% CI)	73.8(67.9; 79.8)	77.6(72.0; 83.3)
Two year rate (95% CI)	55.2(48.4; 62.0)	62.2(55.6; 68.7)
Three-year rate (95% CI)	45.0(38.2; 51.9)	56.1(49.3; 62.8)
Log rank p value	0.032	
Hazard ratio (95% CI)	0.74 (0.56; 0.97)	

[a] '+' denotes that the upper bound limit had not been reached at cut-off

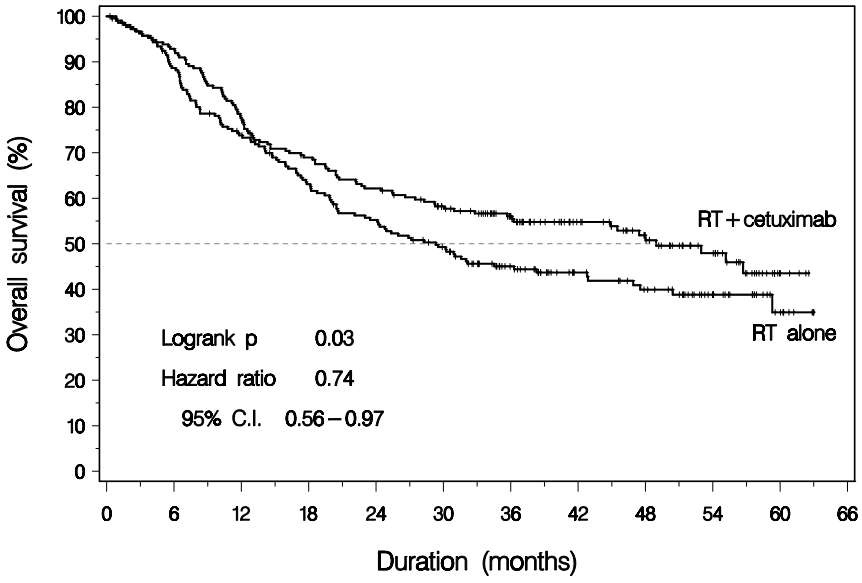
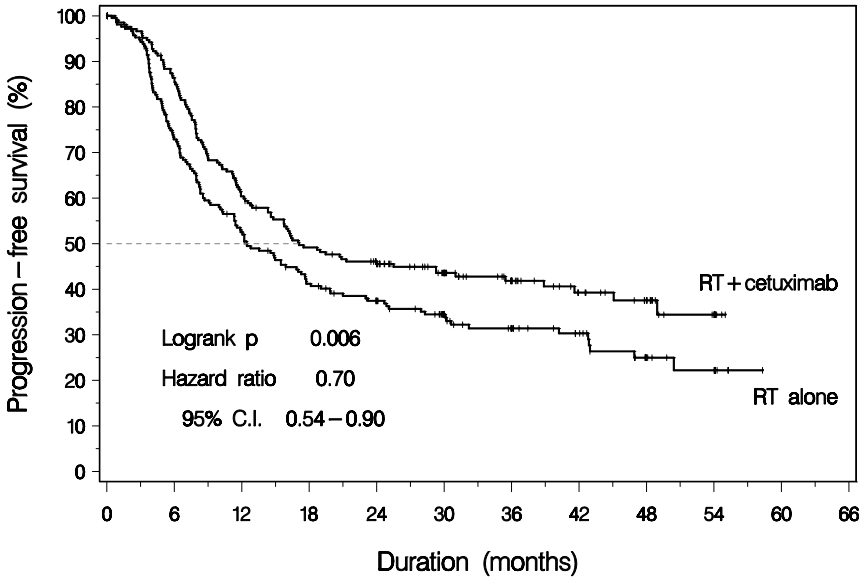


Table 6, fig 3:Progression-free survival as assessed by ICRC (ITT population)

Progression-free survival	Radiotherapy alone	Radiotherapy + cetuximab
Number of events (%)	141 (66.2)	119 (56.4)
Median number of months (95% CI)	12.4(10.3; 17.6)	17.1(14.6; 31.0)
One-year rate (95% CI)	52.5(45.6; 59.4)	60.4(53.7 ; 67.1)
Two year rate (95% CI)	37.4(30.7; 44.2)	46.1(39.2; 53.0)
Stratified log-rank p value	0.006	
Stratified hazard ratio (95% CI)	0.70 (0.54; 0.90)	



Tumour response rate

”The overall response to protocol treatment was determined by the investigator at each scheduled visit, using a modified version of the 1978 WHO criteria. A best overall response per patient, with confirmation of responses, will be derived from the investigator-determined overall response at scheduled time-points. The ICRC determined the overall tumor response at the 8-week post RT time-point only.” (SAP)

Table 7. Summary of overall response 8 weeks post-radiotherapy by ICRC (ITT population)

Response variable	Number (%) of subjects	
	Radiotherapy alone	Radiotherapy + cetuximab
Best response		
Complete response	95 (44.6)	95 (45.0)
Partial response	65 (30.5)	68 (32.2)
Stable disease	16 (7.5)	18 (8.5)
Progressive disease	11 (5.2)	5 (2.4)
Not evaluable	26 (12.2)	25 (11.8)
Overall response rate (CR+PR)	160 (75.1)	163 (77.3)
95% CI	68.8;80.8%	71.0;82.7%
Fisher's exact test p value	0.649	
Difference between response rates 95% CI	2.1% –6.0;10.2%	
Cochran-Mantel-Haenszel p value	0.434	
Adjusted odds ratio 95% CI	0.825 0.510;1.335	

Table 8. Summary of best response by investigator (ITT population)

Response variable	**Number (%) of patients**	
	Radiotherapy alone	**Radiotherapy + cetuximab**
Complete response	111 (52.1)	119 (56.4)
Partial response	26 (12.2)	36 (17.1)
Stable disease	47 (22.1)	38 (18.0)
Progressive disease	12 (5.6)	2 (0.9)
Not evaluable	17 (8.0)	16 (7.6)
Overall response (CR+PR)	137 (64.3)	155 (73.5)
95% CI	57.5; 70.7%	67.0; 79.3%
Fisher's exact test p value	0.047	
Difference RR (95% CI)	9.1% (0.4; 17.9%)	
Cochran-Mantel-Haenszel p value	0.016	
Adjusted odds ratio (95% CI)	0.57 (0.36; 0.90)	

Exploratory analyses

In the following tables (9-11) subgroup analyses of primary endpoints according to baseline characteristics are presented:

Table 9 **Subgroup analyses of duration of locoregional control (ICRC) according to baseline demographic and disease characteristics (ITT population)**

Subgroup	Median number of months				Hazard ratio
	N	Radiotherapy alone	N	Radiotherapy + cetuximab	
All subjects	213	14.9	211	24.4	0.68 (0.52; 0.89)
Gender					
Male	169	14.2	171	30.1	0.68 (0.51; 0.91)
Female	44	16.2	40	24.4	0.85 (0.49; 1.47)
Age					
<65 years	148	17.3	166	44.9	0.68 (0.50; 0.93)
≥65 years	65	14.2	45	14.3	0.87 (0.56; 1.37)
Baseline KPS					
90–100%	142	23.2	147	49.0	0.62 (0.44; 0.86)
50–80%	71	8.7	64	9.5	1.00 (0.68; 1.47)
Site of primary tumor					
Oropharynx	135	23.0	118	49.0	0.61 (0.43; 0.88)
Larynx	51	11.9	57	12.9	0.69 (0.43; 1.10)
Hypopharynx	27	10.3	36	12.5	0.92 (0.52; 1.62)
Tumor stage					
AJCC T1–3	148	17.3	149	44.9	0.67 (0.49; 0.93)
AJCC T4	65	11.3	62	11.9	0.81 (0.54; 1.22)
Nodal stage					
AJCC N0	38	15.5	42	14.6	0.83 (0.47; 1.47)
AJCC N1–3	175	14.9	169	30.1	0.69 (0.52; 0.91)
Overall stage					
AJCC II or III	52	16.2	55	38.9	0.69 (0.42; 1.14)
AJCC IV	161	13.5	156	20.9	0.73 (0.54; 0.98)
EGFR positive cells					
≤50%	92	16.2	91	45.1	0.58 (0.39; 0.86)
>50%	81	13.2	75	14.8	0.83 (0.56; 1.23)
Unknown	40	16.9	45	29.3	0.79 (0.43; 1.46)

Source tables: *EMR 62 202-006 see 5.3.5.1.1, p. 233 (Table 4.2), p. 249 (Table 5.1)*

Table 10 **Subgroup analyses of overall survival based on baseline demographic and disease characteristics (ITT population)**

Subgroup	Median number of months[a]				Hazard ratio
	N	Radiotherapy alone	N	Radiotherapy + cetuximab	
All subjects	213	29.3	211	49.0	0.74 (0.56; 0.97)
Gender					
Male	169	28.3	171	56.7	0.71 (0.53; 0.96)
Female	44	36.3	40	45.5	1.01 (0.57; 1.79)
Age					
<65 years	148	31.0	166	62.6+	0.68 (0.49; 0.94)
≥65 years	65	24.8	45	18.6	1.15 (0.72; 1.84)
Baseline KPS					
90–100%	142	42.9	147	62.6+	0.59 (0.41; 0.85)
50–80%	71	15.1	64	12.2	1.15 (0.78; 1.70)
Site of primary tumor					
Oropharynx	135	30.3	118	62.6+	0.62 (0.43; 0.90)
Larynx	51	31.6	57	32.8	0.85 (0.51; 1.42)
Hypopharynx	27	13.5	36	13.7	0.88 (0.49; 1.55)
Tumor stage					
T1–3	148	42.9	149	62.6+	0.70 (0.50; 0.99)
T4	65	18.1	62	17.5	0.91 (0.60; 1.39)
Nodal stage					
N0	38	50.4	42	62.6+	0.91 (0.48; 1.73)
N1–3	175	26.9	169	48.0	0.73 (0.55; 0.98)
Overall stage					
AJCC II or III	52	42.9	55	55.2	0.80 (0.46; 1.39)
AJCC IV	161	24.2	156	47.4	0.75 (0.56; 1.02)
EGFR positive cells					
≤50%	92	26.0	91	53.0	0.68 (0.45; 1.02)
>50%	81	29.3	75	44.9	0.88 (0.58; 1.34)
Unknown	40	30.9	45	59.5+	0.76 (0.41; 1.41)

Source tables: *EMR 62 202-006 see 5.3.5.1.1,* p. 242 (*Table 4.5), p. 253 (Table 5.3)*

[a] '+' denotes that the median had not been reached at cut-off.

Table 11 **Subgroup analyses of progression-free survival (ICRC) based on baseline demographic and disease characteristics (ITT population)**

Subgroup	Median number of months				Hazard ratio
	N	Radiotherapy alone	N	Radiotherapy + cetuximab	
All subjects	213	12.4	211	17.1	0.70 (0.54; 0.90)
Gender					
Male	169	12.4	171	16.5	0.71 (0.54; 0.93)
Female	44	14.9	40	20.7	0.83 (0.48; 1.44)
Age					
<65 years	148	13.5	166	29.3	0.68 (0.51; 0.92)
≥65 years	65	12.2	45	12.3	0.97 (0.63; 1.50)
Baseline KPS					
90–100%	142	17.7	147	45.1	0.65 (0.47; 0.89)
50–80%	71	8.0	64	8.5	0.98 (0.67; 1.43)
Site of primary tumor					
Oropharynx	135	17.7	118	45.1	0.65 (0.46; 0.92)
Larynx	51	10.3	57	12.9	0.65 (0.41; 1.03)
Hypopharynx	27	8.0	36	11.5	0.99 (0.57; 1.72)
Tumor stage					
T1–3	148	15.5	149	31.0	0.69 (0.51; 0.94)
T4	65	8.5	62	11.6	0.82 (0.55; 1.23)
Nodal stage					
N0	38	14.8	42	13.4	0.89 (0.51; 1.54)
N1–3	175	12.4	169	19.0	0.70 (0.53; 0.92)
Overall stage					
AJCC II or III	52	14.9	55	29.3	0.73 (0.45; 1.19)
AJCC IV	161	11.9	156	16.5	0.74 (0.56; 0.99)
EGFR positive cells					
≤50%	92	14.8	91	41.6	0.60 (0.41; 0.88)
>50%	81	11.4	75	14.3	0.79 (0.54; 1.15)
Unknown	40	16.9	45	20.9	1.01 (0.56; 1.82)

Source tables: EMR 62 202-006 *see 5.3.5.1.1, p. 238 (Table 4.4), p. 251, (Table 5.2)*

Table 12. Subgroup analysis of duration of locoregional control (ICRC), overall survival and progression-free survival (ICRC) according to radiotherapy regimen (ITT population)

Subgroup	Median number of months[a]				Hazard ratio
	N	Radiotherapy alone	N	Radiotherapy + cetuximab	
Locoregional control					
All subjects	213	14.9	211	24.4	0.68 (0.52; 0.89)
Radiotherapy regimen					
Once daily	55	8.5	50	11.9	0.73 (0.47; 1.15)
Twice daily	37	19.9	38	54.1+	0.82 (0.41; 1.62)
Concomitant boost	120	17.7	117	45.1+	0.62 (0.44; 0.88)
No radiotherapy	1	0.0+	6	5.7	–
Overall survival					
All subjects	213	29.3	211	49.0	0.74 (0.56; 0.97)
Radiotherapy regimen					
Once daily	**55**	**15.3**	**50**	**18.9**	**0.98 (0.61; 1.57)**
Twice daily	37	60.3+	38	58.4+	0.72 (0.35; 1.46)
Concomitant boost	120	31.0	117	62.6+	0.65 (0.45; 0.93)
No radiotherapy	1	0.3+	6	17.8	–
Progression-free survival					
All subjects	213	12.4	211	17.1	0.70 (0.54; 0.90)
Radiotherapy regimen					
Once daily	55	8.3	50	11.5	0.69 (0.45; 1.07)
Twice daily	37	19.9	38	54.1+	0.89 (0.45; 1.74)
Concomitant boost	120	15.9	117	31.0	0.65 (0.47; 0.91)
No radiotherapy	1	0.0+	6	5.7	

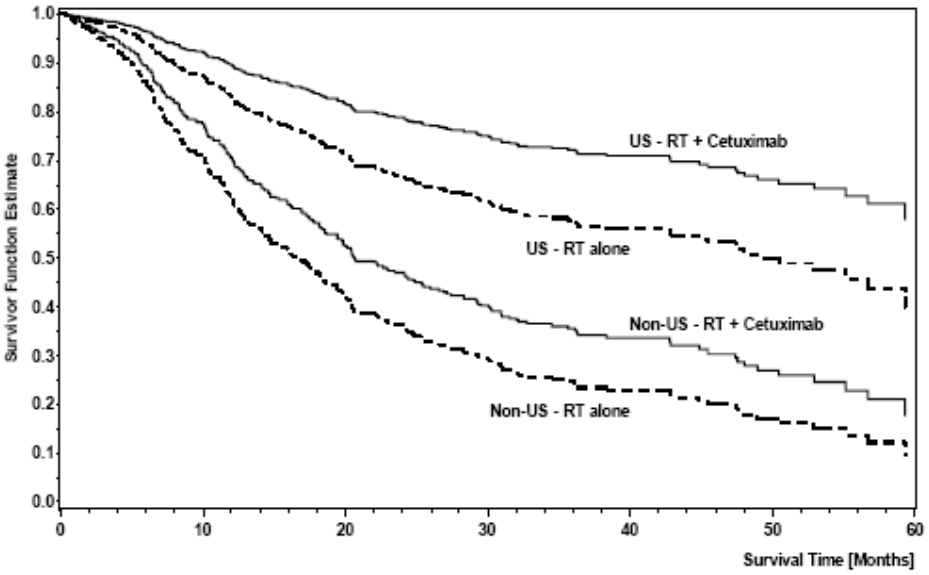
[a] '+' denotes that the upper bound limit had not been reached at cut-off

Multivariate analyses

The following prognostic factors (ignoring region) were identified as potentially relevant: age, Hb, KPS, neck dissection, RT regimen, quality of RT, tumour stage, site of primary tumour. These factors were fitted together in a model leading to removal of "neck dissection" and "tumour site". Nodal stage, however, was found informative and was added to the model.
The following interactions were identified: age by tumour stage, Hb by KPS, RT by nodal stage.
Treatment was found to interact with age and KPS. Adding "region" did not significantly improve the model, p=0.18.
In the final model, the estimates including the treatment-by-factor interactions were used to calculate survivor function estimates based on equal distribution of the factors included with each region, i.e. for each region, the distribution across both treatment groups was used for both treatments separately. The figure below illustrates the results based on the model including the interaction of treatment with KPS and age.

Table 13, fig 4. Distribution of subjects by age group and KPS by region

Factor	Number (%) of subjects			
	Non-USA		USA	
	RT alone	RT + C	RT alone	RT + C
Age group				
<65 years	70 (76.9)	60 (80.0)	78 (63.9)	106 (77.9)
≥65 years	21 (23.1)	15 (20.0)	44 (36.1)	30 (22.1)
KPS				
≤80%	40 (44.0)	39 (52.0)	31 (25.4)	25 (18.4)
>80%	51 (56.0)	36 (48.0)	91 (74.6)	111 (81.6)



Subgroup analyses according to worst grade of acne-like rash.

A relation between rash and anti-tumour activity has been observed previously for cetuximab and other compounds targeting EGFR signalling. This analysis was predefined in the SAP

Table 14. Subgroup analysis of duration of locoregional control (ICRC), overall survival and progression free survival (ICRC) according to worst grade of acne-like rash (As-treated population)

Subgroup	Median number of months[a]			
	N	Radiotherapy alone	N	Radiotherapy + cetuximab
Locoregional control				
All subjects	213	14.9	211	**24.4**
Grade 0	198	15.5	36	**10.9**
Grade 1	9	36.3	47	**20.9**
Grade 2	2	7.8	92	**43.5**
Grades 3 and 4	3	5.8	33	**12.3**
Overall survival				
All subjects	213	29.3	211	**49.0**
Grade 0	198	29.3	36	**20.7**
Grade 1	9	36.3	47	**29.2**
Grade 2	2	18.2	92	**55.2**

Grades 3 and 4	3	12.8	33	**62.6+**
Progression-free survival				
All subjects	213	12.4	211	**17.1**
Grade 0	198	12.8	36	**10.1**
Grade 1	9	19.8	47	**16.2**
Grade 2	2	7.8	92	**38.9**
Grades 3 and 4	3	5.8	33	**11.9**

[a] '+' denotes that the upper bound limit had not been reached at cut-off

Patients with recurrent/metastatic SCCHN on or after platinum-based therapy

A monotherapy indication for Patients with recurrent/metastatic SCCHN on or after platinum-based therapy was based on three non-controlled studies and one retrospective study providing a basis for a historical comparison.

Open European multicenter study EMR 62 202-016 is regarded as "pivotal".

Diagnosis and main criteria for inclusion were:

- Karnofsky performance status (KPS) of at least 60 %
- Histologically confirmed diagnosis of AJCC Stage III/IV SCCHN, metastatic or recurrent
- Progressive disease (PD) documented by CT or MRI on platinum based therapy (2 cycles and not more than 6 cycles of cisplatin ≥60 mg/m2/cycle or carboplatin ≥300 mg/m2/cycle or AUC ≥4) in the 30 days before cetuximab single-agent therapy
- Presence of at least 1 lesion measurable bidimensionally by computed tomography or magnetic resonance imaging
- Tumour tissue available for determination of epidermal growth factor receptor expression

Subjects received cetuximab as a single agent for at least 6 weeks until PD, clinical deterioration or unacceptable AEs occurred. In case of PD or clinical deterioration, patients were offered combination therapy with cisplatin + cetuximab. Altogether 103 subjects were enrolled. All received at least 1 dose of cetuximab as single-agent therapy; 53 subjects entered the combination therapy phase after progression under monotherapy.

Open European multicenter study in 98 subjects **EMR 62 202-001** is regarded as "supportive" by the sponsor. Diagnosis and main criteria for inclusion were: KPS of at least 60 %, histologically confirmed, diagnosis of AJCC Stage III/IV SCCHN, metastatic or recurrent, documented PD after at least 2 cycles but not more than 4 cycles of cisplatin ≥60 mg/m2/cycle or carboplatin ≥250 mg/m2/cycle, Presence of at least 1 lesion measurable bidimensionally by computed tomography or magnetic resonance imaging, or in two diameters by calliper, tumour tissue available for determination of epidermal growth factor receptor, expression

Subjects were treated for at least 2 and up to 12 cycles with cetuximab plus cisplatin or carboplatin at the same dosage on which they had failed. Treatment was continued until progressive disease (PD), clinical deterioration or unacceptable adverse events (AEs) occurred.

IMCL CP02-9816 is regarded as "supportive" by the sponsor.

Diagnosis and Main Criteria for Study Entry: Patients at least 18 years of age with pathologically confirmed and bidimensionally measurable recurrent or metastatic SCCHN who have failed a cisplatin-containing regimen within 3 months of study entry.

Methodology: This multicenter, open-label, non-randomized, phase II US study was originally designed to enrol 210 patients with metastatic or recurrent SCCHN (Versions 1.0 through 3.0). Patients received two 3-week courses of either cisplatin/paclitaxel or cisplatin/5-FU and were evaluated for response.

Patients with a complete or partial response were not eligible for further treatment on this study; if these patients subsequently relapsed (recurrent or metastatic), they were then eligible to receive weekly infusions of cetuximab on CP02-9816C. Concurrent carboplatin was permitted. Patients with stable disease (treatment group 1) or progressive disease (treatment group 2) following treatment with either cisplatin/paclitaxel or cisplatin/5-FU were eligible to continue on the study and receive cetuximab in combination with cisplatin. Nota bene in this assessment report, only the results from treatment group 2 (n=79, progressive disease on cisplatin) are presented. Response assessments by

investigator. Number of patients enrolled: 187. Number of patients who entered cetuximab/cisplatin combination therapy: 131

Table 15. Best response, objective response rate, disease control rate and retrospective analysis

Characteristic	Monotherapy	Combination therapy (N=175)	
	EMR 62 202-016 (N=103) ITT/safety IRC assessment	EMR 62 202-001 (N=96) ITT/safety IRC assessment	IMCL CP02-9816 (N=79) PD cohort Investigator
Best response No. (%) patients			
CR	0 (–)	0 (–)	0 (–)
PR	13 (12.6)	10 (10.4)	8 (10.1)
SD	34 (33.0)	41 (42.7)	36 (45.6)
PD	38 (36.9)	27 (28.1)	23 (29.1)
Image not assessable	16 (15.5)	14 (14.6)	12 (15.2)
No image available	2 (1.9)	4 (4.2)	-
Objective response rate (%)[a]	12.6	10.4	10.1
95% CI	6.9, 20.6	5.1, 18.3	4.5, 19.0
Disease control rate (%)[b]	45.6	53.1	55.7
95% CI	35.8, 55.7	42.7, 63.4	44.1, 66.9

[a] (CR+PR)/N*100
[b] (CR+PR+SD)/N*100

Table 16. Overall survival

Variable	Monotherapy	Combination therapy (N=175)	
	EMR 62 202-016* (N=103) ITT/safety IRC assessment	**EMR 62 202-001 (N=96) ITT/safety IRC assessment**	**IMCL CP02-9816 (N=79) PD cohort Investigator**
Survival time			
Median (days)	178	183	158
95% CI	149;217	148;213	93;181
Survival rate (% patients) at			Not available
3 months	79	82	-
6 months	47	51	-
9 months	32	23	-
12 months	12	15	-

Time to response (about 7 weeks), duration of response (about 5 months) and time to progression (about 10 weeks) were also similar comparing mono with combination therapy.

Discussion on clinical efficacy

The design of the study EMR 62 202 006 was subject to CPMP advice in 1999. At that time, the sponsor proposed an add-on design; cetuximab to concomitantly administered chemoradiotherapy (CRT). An exploratory CRT+cetuximab study (IMCL CP02-9813) was terminated early due to safety concerns. Therefore the add-on activity to RT alone was investigated, but not in comparison with concomitant CRT. Excluding patients with low-volume, favourable stage III/IV SCCHN, CRT is today (but less commonly 1999) the favoured therapeutic option. CRT, however, is associated with considerable toxicity. Locoregional control (LRC) was accepted as primary measure of efficacy. This is still a valid measure of patients benefit, but as CRT has been shown to improve OS, favourable effects on OS should be documented.
With respect to gender, age, KPS, nodal stage, etc. the study appears reasonably similar to published confirmatory studies conducted in patients with locally advanced SCCHN and there are no important imbalances, but patients in the test arm tended to be slightly younger.

An add-on effect of cetuximab to definitive radiotherapy has been demonstrated as regards locoregional control, PFS and OS and altogether efficacy data are considered sufficiently robust to support regulatory conclusions. The difference in OS survival at three years is about 10% absolute and this is considered clinically relevant.
A statistically significant difference between treatment arms was observed also if timing of event was neglected (event rate 63% vs. 52%), 95% CI for difference 1 to 20% (no adjustment for stratification factors). The results are therefore considered non- sensitive to "timing of event bias" and the results are considered reasonably convincing also for a "single pivotal trial". The difference in two year recurrence rates, about 10% absolute, is found clinically meaningful.
The long term, relapse-free rate is expected to be >30%. The survival analysis was conducted at an event rate about 50% and is therefore considered mature and stable.

The overall impression of all subgroup analyses is that the add-on effect of cetuximab tends to be small or absent irrespective of outcome measure in patients with poor prognosis (estimated from median OS), the exceptions being female and nodal stage N0 and here mainly for survival. These two exceptions are likely to represent spurious findings. Nevertheless, the sponsor will be asked to further analyse the apparent gender-related difference in add-on activity of cetuximab not at least as similar but also rather weak trends were seen in the CRC study (favouring men).
"Poor" performance status was consistently linked to a poor add-on effect. This observation has some face validity and is considered credible.
As discussed already in the scientific advice 1999, the choice of radiotherapy regimen is likely to be partly governed by certain patient factors so that more fragile patients with consequently less favourable prognosis in the long run are more likely to be treated with once daily RT. This might explain the apparent lack of add-on activity in terms of survival while logoregional control appears improved.

The difference in survival (test and control) comparing patients from US sites with non-US sites is to a meaningfully large extent explained by differences in baseline prognostic factors. At the same time, the apparent baseline differences in baseline covariates overall favouring the experimental arm have been addressed. There was also an imbalance within regions so that patients within the experimental arm in the non-US sites had a less favourable prognosis compared with the control (and vice versa for the US sites). In this context it should be noticed that dynamic allocation was used and that region was not an allocation factor. In the final model and based on the figure above, the relative add-on treatment effect in the non-US sites appears to be similar to the effect in the US sites. This is somewhat in conflict with the impression based on the univariate analyses where poor survival (irrespective of prognostic factor) appeared to be associated with a poor add-on effect of cetuximab. In conclusion, while this assessor accepts that "region" is not a major prognostic factor of relevance for the activity of cetuximab, low KPS (and high age) constitutes a concern.

The magnitude of the treatment effect for PFS appears similar to effects on OS (HR about 0.7), while the level of statistical significance is more robust. The open label nature of the trial might introduce bias, but also here the event rate (irrespective of timing) is significantly higher in the control group,

66.2 vs. 56.4%, 95% CI for difference +0.5; 19% (non-adjusted). This is reassuring and PFS (and locoregional control) data provide support for the observed difference in OS.
No effects on distant metastases (2-year rate 16.5 vs 17.3%) were observed, but a seemingly higher event rate was noted in the cetuximab arm as regards "second primaries" (2-year rate 7.8 vs. 4.7%).
No consistent improvement in terms of OS in time-related measures of activity was seen for grade 3 and 4 rash. The low number of patients should be noted as well as the rather flat survival curves around the median. The overall impression is, however, that there is a relationship between rash and anti-tumour activity, similar to what is observed in colorectal cancer. The sponsor, however, will be asked to discuss "grade 3 and 4" data further.

Another issue of major putative clinical relevance is the relationship between EGFR genotype and activity of cetuximab. As availability of tumour tissue for EGFR staining was an inclusion criterion it is assumed that tumour tissue will be investigated for EGFR amplification, mutations and polymorphism. As population PK data are available, this opens for putatively meaningful exploratory PK/PD analyses. The MAH has committed to further analyse tumour samples for EGFR gene amplifications for EMR 62202-006 / IMCL-CP02-9815 as a post-approval follow-up measure.

Patients with advanced SCCHN refractory to platinum based chemotherapies constitute a patient group where there is no evidence-based therapy available. In the draft NfG under revision it is stated:
"If, for a specific target population, there is no regimen with an evidence-based favourable benefit - risk relationship available, a regimen used in clinical practice with a well-documented and benign safety profile is acceptable as comparator. Alternatively, "investigator's best choice" among a few selected regimens with these characteristics (may include BSC) is acceptable. In these cases, superior efficacy has to be shown versus the pooled results in the reference arm.
In many cases, the absence of evidence-based therapies refers to patients who have failed several lines of therapy. In this situation, it might be easier to obtain the data needed for marketing authorisation based on a properly conducted randomised study in less advanced patients, supported by "salvage" studies, compared with conducting a last line, randomised BSC/investigator's best choice comparative study."

The design of these exploratory studies for the monotherapy was in principle similar to the design of the phase II studies conducted in patients with colorectal cancer (CRC) failing irinotecan therapy, where add-on of cetuximab to the failing irinotecan regimen appeared to provide better tumour control than cetuximab monotherapy. This was regarded as highly interesting, indicating that inhibiting the binding of a growth factor might render a tumour responsive to chemotherapy where baseline chemotherapy resistance had been clinically documented.
However, there are no indications that adding cetuximab to platinum in patients with platinum refractory tumours reverses platinum resistance. One difference of putative interest comparing studies conducted in patients with CRC and patients with SCCHN was noticed, however. In the SCCHN studies, the vast majority of patients probably showed primary resistance to chemotherapy while most patients in the CRC studies were pretreated with two or more lines of chemotherapy. This increases the likelihood of secondary resistance (resistance after a period of tumour response). The MAH undertook a retrospective review (EMR 62 202-005) of the outcome for SCCHN patients refractory to first-line cisplatin-based chemotherapy at 7 centres. This is in line with the advice given in 1999. In this historical cohort the prognosis appears worse, e.g. with respect to survival, median about 100 days. This apparent difference, however, is too small to be convincing. Similarly, the response rate in the current cetuximab studies, although higher than reported in the sparse literature, cannot be regarded as sufficiently high to be convincing. Altogether currently available data do not support an indication covering platinum resistant SCCHN, but data are sufficiently relevant to be mentioned in section 5.1 of the Summary of Product Characteristiccs (SPC).

A recent paper (Moroni et al. Lancet Oncol. 2005) implies that EGFR gene amplification is of importance for the activity of cetuximab (and panitumumab). These limited data indicate that gene amplification is of similar importance for the activity in monotherapy and in combination therapy, but data as regards type of chemotherapy regimen (and prior resistance) were not reported.

In addition, recent data for EGF tyrosine kinase inhibitors (gefetinib, erlotinib) show a similar pattern, i.e. that the survival benefit seems to be confined to patients with gene amplification. Based on data from the CRC (and the SCCHN) studies, it seems feasible to further test these hypotheses, i.e. is there a difference between tumours showing primary and secondary resistance with respect to reversibility in case of cetuximab add-on therapy and how is activity governed by EGFR genotype?

Clinical safety

The evaluation of safety focuses on data from studies in which cetuximab was administered at the target dose (initial 400 mg/m² dose followed by weekly doses of 250 mg/m²)

Patient exposure

Data from 810 patients who received at least 1 dose of study treatment have been included in the integrated analyses: 750 from the SCCHN studies.

Table 16. Most frequent AEs in the locally advanced SCCHN study

COSTART preferred term	% patients with AE	
	RT alone (N=212)	RT + cetuximab (N=208)
Any	100.0	100.0
Mucous membrane disorder	86.3	85.6
Radiation dermatitis	89.6	85.1
Weight loss	**71.7**	**83.7**
Dry mouth	70.8	72.1
Dysphagia	63.2	65.4
Acne	**1.4**	**61.5**
Asthenia	**49.1**	**55.8**
Nausea	**37.3**	**48.6**
Constipation	**30.2**	**34.6**
Fever	**12.7**	**28.8**
Vomiting	**23.1**	**28.8**
Taste perversion	27.8	28.8
Pain	28.3	28.4
Rash	**4.7**	**28.4**
Anorexia	**22.6**	**27.4**
Pharyngitis	**18.9**	**26.0**
Dehydration	**19.3**	**25.5**
Stomatitis	21.7	23.1
Dry skin	**4.7**	**21.6**
Oral moniliasis	21.7	19.7
Cough increased	19.3	19.7
Diarrhea	**13.2**	**19.2**
Voice alteration	22.2	19.2
Headache	**8.0**	**18.8**
Leukopenia	20.3	18.8
Application site reaction	**11.8**	**18.3**
Pruritus	**4.2**	**16.3**
Chills	**4.7**	**15.9**
Insomnia	14.2	14.9
Dyspepsia	**9.4**	**14.4**
Sputum increased	14.6	13.5
Infection	9.4	13.0
Anxiety	9.4	10.6
Anemia	13.2	3.4

Deaths
A number of cases of death are reported (between 5.7% and 21.6% in the integrated database studies), the vast majority assessed as being related to disease progression, disease related complication or intercurrent, non-cetuximab related events. One case of fatal anaphylactic reaction to cetuximab is reported. One case of death in the studies was deemed related to RT. In the completed supportive studies, one death (septic shock) was probably related to chemotherapy (cisplatin and 5-FU) and possibly related to cetuximab.

Hypersensitivity reactions
The frequency of any HSR -AE was within the expected range compared to current labelling.
Five patients were re-exposed to cetuximab after having experienced a grade 3 HSR during previous infusions. In 3 of these patients, rechallenge was positive (same toxicity grade during re-exposure). In 2 patients rechallenge was negative and they continued to receive cetuximab without experiencing any further HSRs.

Acne-like rash and skin reactions
Acne-like rash was similar across the 3 SCCHN patient populations and the incidence of any grade "acne-like rash" was as expected, given the previous data from CRC patients (81% in CRC). In contrast, the incidence of grade 3 or 4 "acne-like rash" was lower than expected.

Mucositis, Diarrhea, Thromboembolism, Asthenia, Fever, Nausea
Overall, the incidence and severity of AEs belonging to these groups were within the expected ranges, given the specific patient populations and treatment and the current labelling for the product.

Respiratory disorders
Dyspnea and increased cough are very commonly seen in this patient population and have also been observed with the administration of other monoclonal antibodies. Furthermore, the risk of interstitial pneumonia with EGFR inhibitors has been raised with gefitinib, which is an agent that inhibits EGFR tyrosine kinase, albeit of a different target and nature from cetuximab.

Heart failure
Overall, the incidence of AEs belonging to the special AE category "heart failure" was low and no grade 3 or 4 heart failure occurred.

Bleeding
Overall, the incidence of bleeding may be attributable to the underlying disease, and may be aggravated by concomitant platinum-based therapy (thrombocytopenia).

Safety in special populations

Table 17. AEs with notable differences by gender.

COSTART preferred term	No. (%) of patients							
	RT alone				RT + cetuximab			
	Male (N=168)		Female (N=44)		Male (N=170)		Female (N=38)	
Any	168	(100.0)	44	(100.0)	170	(100.0)	38	(100.0)
Acne	2	(1.2)	1	(2.3)	**112**	**(65.9)**	**16**	**(42.1)**
Dry skin	5	(3.0)	5	(11.4)	**29**	**(17.1)**	**16**	**(42.1)**
Infection	11	(6.5)	9	(20.5)	24	(14.1)	3	(7.9)
Nausea	56	(33.3)	23	(52.3)	**71**	**(41.8)**	**30**	**(78.9)**
Pharyngitis	31	(18.5)	9	(20.5)	**39**	**(22.9)**	**15**	**(39.5)**
Radiation dermatitis	152	(90.5)	38	(86.4)	141	(82.9)	36	(94.7)
Rash	8	(4.8)	2	(4.5)	41	(24.1)	18	(47.4)
Sputum increased	19	(11.3)	12	(27.3)	23	(13.5)	5	(13.2)
Weight loss	12	(73.2)	29	(65.9)	139	(81.8)	35	(92.1)
	3							

Table 18. Summary of AEs with notable differences in frequencies by race in the locally advanced SCCHN study

COSTART preferred term	No. (%) of patients							
	RT alone				RT + cetuximab			
	Caucasian (N=174)		Non-Caucasian (N=38)		Caucasian (N=174)		Non-Caucasian (N=34)	
Any	174	(100.0)	38	(100.0)	174	(100.0)	34	(100.0)
Acne	1	(0.6)	2	(5.3)	**113**	**(64.9)**	**15**	**(44.1)**
Anemia	17	(9.8)	11	(28.9)	6	(3.4)	1	(2.9)
Anorexia	36	(20.7)	12	(31.6)	**54**	**(31.0)**	**3**	**(8.8)**
Application site reaction	19	(10.9)	6	(15.8)	35	(20.1)	3	(8.8)
Asthenia	83	(47.7)	21	(55.3)	**104**	**(59.8)**	**12**	**(35.3)**
Chills	7	(4.0)	3	(7.9)	31	(17.8)	2	(5.9)
Constipation	50	(28.7)	14	(36.8)	**65**	**(37.4)**	**7**	**(20.6)**
Cough increased	30	(17.2)	11	(28.9)	29	(16.7)	12	(35.3)
Diarrhea	19	(10.9)	9	(23.7)	36	(20.7)	4	(11.8)
Dry mouth	131	(75.3)	19	(50.0)	**133**	**(76.4)**	**17**	**(50.0)**
Fever	19	(10.9)	8	(21.1)	54	(31.0)	6	(17.6)
Leukopenia	39	(22.4)	4	(10.5)	31	(17.8)	8	(23.5)
Lung disorder	4	(2.3)	5	(13.2)	**5**	**(2.9)**	**8**	**(23.5)**
Nausea	66	(37.9)	13	(34.2)	89	(51.1)	12	(35.3)
Pain	44	(25.3)	16	(42.1)	47	(27.0)	12	(35.3)
Pharyngitis	33	(19.0)	7	(18.4)	41	(23.6)	13	(38.2)
Radiation dermatitis	**160**	**(92.0)**	**30**	**(78.9)**	**158**	**(90.8)**	**19**	**(55.9)**
Skin discoloration	3	(1.7)	11	(28.9)	6	(3.4)	4	(11.8)
Stomatitis	31	(17.8)	15	(39.5)	45	(25.9)	3	(8.8)

AEs with notable differences in frequencies by KPS at baseline
The frequency of dry mouth, dysphagia, and voice alteration was higher in patients with KPS ≥80 compared to patients with KPS <80.Given the small number of patients with KPS <80 in both treatment groups, caution is required in the interpretation of the differences.
No subgroup analysis by hepatic or renal status at baseline was performed for any of the studies. The abnormal hepatic status subgroup was too small (i.e. less than 10% of patients).

Use in pregnancy and lactation
Studies in pregnant or lactating women or animals have not been performed to date. It is not known whether and to what extent cetuximab may enter the fetal circulation or is excreted in human milk. It is recommended in current labelling that the time between cessation of cetuximab therapy and start of breast feeding should be extended from 1 month to 2 months.

Overdose
No new information relevant for the labelling has been gathered.

Discussion on clinical safety
Adherence to the planned posology for cetuximab in the RT combination study was high indicating acceptable overall tolerability.
Most of the AEs were either typical of the underlying disease or consistent with the known safety profiles of RT and cetuximab. Skin reactions occurred in a higher frequency in the combination therapy group than in the RT only group. While skin reactions are already labelled as very common for cetuximab it could also reflect an aggravation of a local radiation dermatitis although the similarity in the frequencies of radiation dermatitis may appear to contradicts this. Fever and headache are common findings when treating with cetuximab. Other AEs that occurred more often in the combination group such as anorexia, pharyngitis, dehydration, asthenia, nausea, fever, weight loss and vomiting are typical for the underlying disease and local reactions to the radiotherapy. The data seems to indicate that these problems were aggravated by adding cetuximab to the radiotherapy. While the frequency of stomatitis seems not to differ much between the treatment groups the frequency of pharyngitis does. This may be a reflection of the radiated field which of course determines the extent and localisation of a local reaction. Anaemia was more common in the RT alone group than in the combination group. The reason for this difference is unclear and maybe a chance finding. The frequency of leukopenia is similar in the two groups.
The most frequent AEs causing discontinuation of cetuximab are skin reactions (including acne and radiation dermatitis), asthenia, hypersensitivity reactions/anaphylactiod rections, chills, dyspnea, vomiting. The incidence of any AE causing discontinuation was similar in the RT + cetuximab group and the monotherapy group of the R/M SCCHN studies.

One case of fatal anaphylactic reaction to cetuximab is reported. Cases of fatal anaphylactic reactions to cetuximab should be mentioned in the SPC. No other apparent systematic increase of fatalities due to cetuximab treatment can be detected from this data. Hypomagnesemia (of unknown frequency) has recently been introduced into the European SPC and the patient leaflet of cetuximab. The clinical impact of hypomagnesemia is still under investigation. Overall the incidence of reports of hypomagnesemia was low in studies where cetuximab was given alone, or in combination with RT or carboplatin. Higher incidences of reports of hypomagnesemia were seen in studies where cetuximab was given in combination with cisplatin, known to cause hypomagnesemia. In the ECOG study, the higher incidence of hypomagnesemia in the cetuximab group may be due to the approximately 25% higher cumulative dose of cisplatin. The incidence of hypomagnesemia and relationship to cetuximab treatment is difficult to establish based on these studies.

With regard to hypersensitivity reactions, the fact that in some patients rechallenge was negative could be worth exploring further in order to include in the labelling (e.g methods of overcoming HSRs) in the future since HSR is a common obstacle in the use of the drug.

Respiratory disorder is a labelled side effect of cetuximab. Whether there is a relevantly increased risk of interstitial pneumonitis for EGFR targeting compounds, including cetuximab is debateable, but is labelled. The incidence of interstitial pneumonitis and lung fibrosis in these studies was low (0.3%) with just one case reported. Dyspnea is a labelled very common AE. Cough may, as the applicant

points out be explained by the underlying disease- which is supported by the frequency also being high in the RT only group.

The frequency of anorexia and pain in the RT + cetuximab group was higher in older patients compared to younger patients as well as compared to older patients in the RT alone group. The risk benefit analysis for the drug in the applied indications is not affected by age differences in AEs. As expected, the frequency of nausea was higher in females compared to males in both treatment groups. In the RT + cetuximab group the frequencies of the following AEs were notably higher in females compared to males: dry skin, pharyngitis, and rash. For acne the opposite effect was seen. The risk benefit analysis for the drug in the applied indications is not affected by gender differences in AEs.

Lung disorders could be of interest from a benefit risk perspective, but the difference here is apparent also in the RT alone group. The risk benefit analysis for the drug in the applied indications is not affected by putative race-related differences in AEs.

In conclusion, the AEs observed in the presented studies, mainly reflect the AE pattern of the underlying diseases, of the concomitant treatment regimens and the cetuximab treatment. No unexpected interactions were identified.

- The occurrence of fatal HSRs has been addressed in the SPC.

- Headache, fever, and chills are common side effects of intravenous monoclonal antibody therapy and may be associated with administration of cetuximab. Consequently headache was included in the SPC.

- Data indicate that dry skin and pruritus should be considered as cetuximab-related reactions and described in the SPC.

- Aggravation of local radiation reactions caused by cetuximab can be suspected from the data presented and is mentioned in section 4.8 of the SPC.

- Late radiation toxicity appears from the data to be increased when combining radiotherapy with cetuximab. This is included in section 4.8 of the SPC.

No new safety data that affects the benefit risk analysis for the already approved indications are presented. There are, however, a number of issues in need for clarification as reflected in the list of questions.
Overall the safety profile of cetuximab is considered reasonably satisfactory for an oncology product as add-on to radiotherapy or chemotherapy.

OVERALL CONCLUSION AND Benefit-risk assessment

Benefit-risk is favourable for cetuximab in combination with radiation therapy for the first-line treatment of locally advanced SCCHN. Relevant improvement in survival and locoregional control has been demonstrated and the safety profile of add-on cetuximab constitutes no concern. No study directly comparing RT + cetuximab with concomitant chemoradiotherapy (CRT) has been conducted. Even if the efficacy of cetuximab + radiotherapy were inferior to CRT, the safety profile is relevantly favourable. Therefore this indication is recommended for approval. The add-on effect of cetuximab is small in patients with poor performance status and this is reflected in the SPC. The importance of EGFR gene amplification should also be investigated as a follow-up measure.
A favourable benefit-risk for cetuximab as a single agent for the treatment of patients who have failed chemotherapy for recurrent and/or metastatic SCCHN has not been established. The MAH withdrew the claim for the monotherapy indication in this setting.

IV. CONCLUSION

On 23 February 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments:

Area	Description	Date due
Clinical	To further analyse tumour samples for EGFR gene amplifications for EMR 62202-006 / IMCL-CP02-9815 within the remits of approval of relevant Ethics Committees	Submission of analyses together with study report EMR 62202-002 expected to be submitted by 31 March 2008