European Medicines Agency
Evaluation of Medicines for Human Use

London, 20 January 2010
Doc. Ref No.: EMA/49762/2010

ASSESSMENT REPORT FOR ERBITUX

International non-proprietary name/Common name: cetuximab

Procedure No. EMEA/H/C/558/II/0029

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 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

I. SCIENTIFIC DISCUSSION

1.1 Introduction

Cetuximab is a chimeric monoclonal IgG1 antibody directed against the epidermal growth factor receptor (EGFR). EGFR signalling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis. Cetuximab binds to the EGFR with an affinity higher than that of endogenous ligands. Cetuximab blocks binding of endogenous EGFR ligands resulting in inhibition of the function of the receptor and induces the internalization of EGFR, which can lead to down-regulation of EGFR. Cetuximab also targets cytotoxic immune effector cells towards EGFR-expressing tumour cells (antibody dependent cell-mediated cytotoxicity, ADCC).
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.

For the indication squamous cell cancer of the head and neck (SCCHN) approval was granted initially in September 2006 followed by an indication enlargement in November 2008:
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.

Erbitux is administered intravenously weekly.

This is an application for an indication in NSCLC originally proposed as: Erbitux is indicated for first-line treatment of patients with epidermal growth factor receptor (EGFR)-expressing advanced or metastatic non-small cell lung cancer in combination with platinum-based chemotherapy.

1.2 Clinical aspects

Altogether four randomised studies in chemotherapy naïve patients with NSCLC have been submitted in support of the proposed new indication.

Study Location of report	Comparator	Primary efficacy variable	Randomization stratification factors	Tumor assessment	
				Interval	Criteria
EMR 62 202-046 *5.3.5.1.1-LC1*	Cisplatin+ vinorelbine	Overall survival time	ECOG PS (0 or 1 vs 2) Tumor stage (IIIB with pleural effusion vs IV)	6 weeks until PD	Modified WHO
CA225099 *5.3.5.1.2-LC1*	Carboplatin + taxane	Progression-free survival time [a]	ECOG PS (0 vs 1) Study center Intended taxane (docetaxel or paclitaxel) [b]	6 weeks until PD	Modified WHO
CA225100 *5.3.5.1.3-LC1*	Platinum agent + gemcitabine	Objective response rate	ECOG PS (0 vs 1) Study center Intended platinum agent (cisplatin or carboplatin) [b]	6 weeks until PD	Modified WHO
EMR 62 202-011 *5.3.5.1.4-LC1*	Cisplatin+ vinorelbine	Objective response rate	Not stratified	6 weeks until PD	RECIST

ECOG PS=Eastern Cooperative Oncology Group performance status, PD=progressive disease, PFS=progression-free survival, RECIST=Response Evaluation Criteria in Solid Tumors, WHO=World Health Organization

[a] In study CA225099, primary analyses of PFS and tumor response endpoints were based on the assessments of an Independent Radiology Review Committee.

[b] The intended taxane (CA225099) or platinum agent (CA225100) for a given subject was chosen by the investigator prior to randomization.

1.2.1 Clinical efficacy

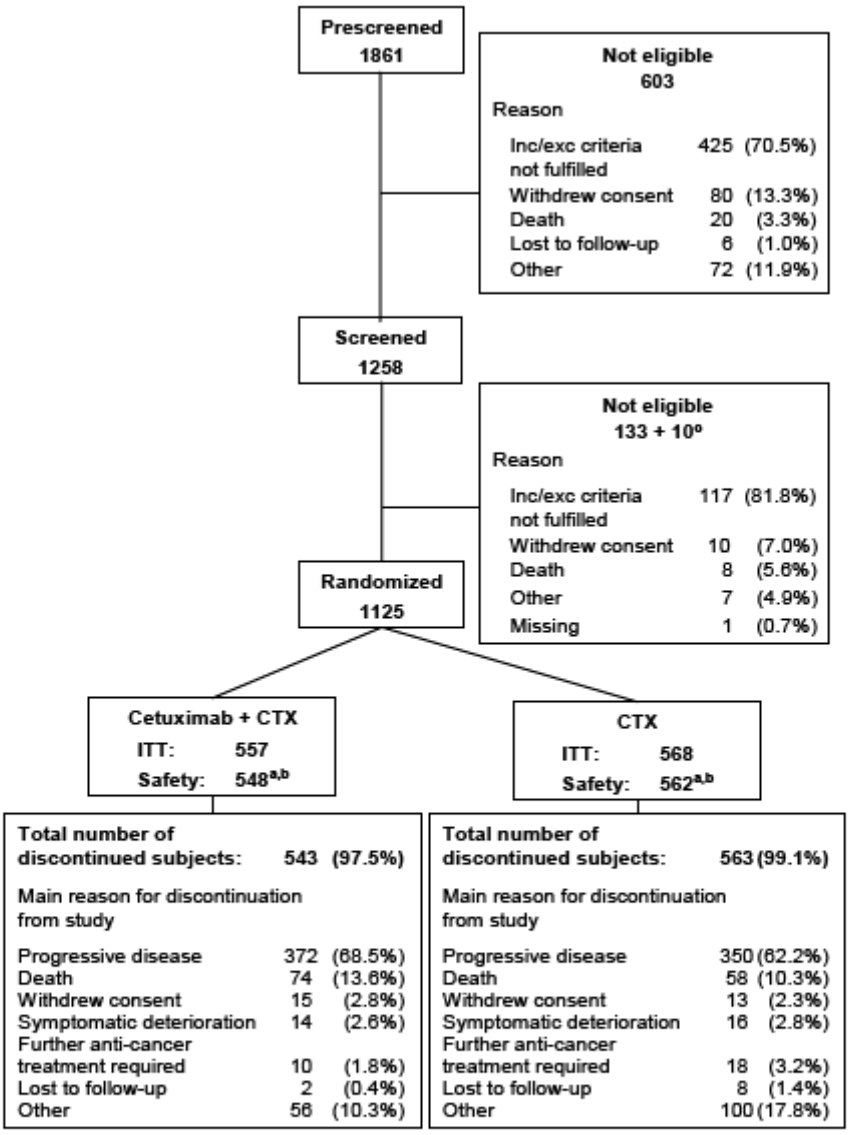
Main studies

EMR 62 202-046
Open, randomized, multicenter phase III study comparing cisplatin + vinorelbine plus cetuximab vs. cisplatin + vinorelbine as first-line treatment for subjects with EGFR-expressing, advanced non-small-cell lung cancer (NSCLC).

Main Inclusion Criteria:
• Histologically or cytologically confirmed NSCLC: stage IIIb with documented malignant pleural effusion, or stage IV.
• Immunohistochemical evidence of EGFR expression on tumour tissue.
• At least 1 bidimensionally measurable index lesion (not in previously irradiated area).
• ECOG PS of ≤2 at study entry.
• Adequate renal, liver and bone marrow function.

Study Treatment and Duration:
• Cetuximab (initial dose 400 mg/m²; subsequent weekly doses 250 mg/m²)
3-weekly cycles of CTX: cisplatin (80 mg/m² on Day 1) + vinorelbine (25 mg/m² on Days 1 and 8).
or
• Cisplatin + vinorelbine alone at the same dosages.

CTX was given for a maximum of 6 cycles in case of at least stable disease with discretionary continuation of cetuximab as monotherapy in subjects who had received cetuximab.
The randomization was stratified by ECOG PS of 0–1, versus 2, and disease stage IIIb with pleural effusion versus IV.
Tumour response and progression was assessed at study sites.
There were three amendments, the most important being that the starting vinorelbine dose was decreased from 30 mg/m² to 25 mg/m² due to the high incidence of neutropenia and neutropenic fever of any grade (49% and 21%, respectively, pooled analysis of 365 subjects for the DSMB). At that point in time 747 subjects had signed the second informed consent. Subjects who had already started with 30 mg/m² before the amendment remained on 30 mg/m² if the investigator considered that the subject benefited from and tolerated this dose.



[a] 6 subjects in the cetuximab + CTX group and 9 in the CTX group were randomized but not treated

[b] 3 subjects randomized to cetuximab + CTX never received cetuximab. They were assigned to the cetuximab + CTX group for the ITT analysis and to the CTX group for the safety analysis

[c] Medical review revealed that 10 subjects who were actually not eligible for treatment were randomized

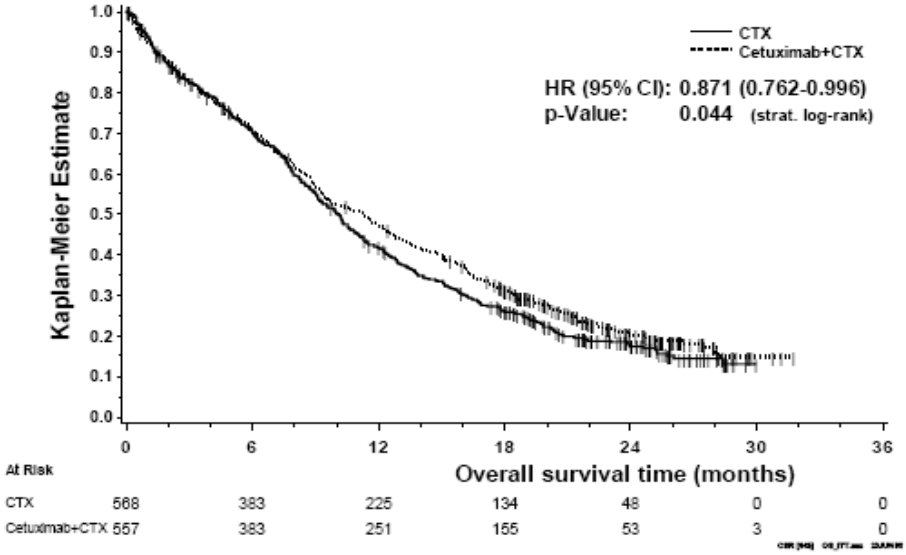
Baseline Characteristics

Characteristic		Cetuximab + CTX N=557	CTX N=568
Ethnic origin			
Caucasian/white		466 (83.7)	480 (84.5)
Black		8 (1.4)	6 (1.1)
Asian		62 (11.1)	59 (10.4)
Hispanic		21 (3.8)	22 (3.9)
Other		0	1 (0.2)
Gender, N (%)	Male	385 (69.1)	405 (71.3)
	Female	172 (30.9)	163 (28.7)
Age, years	Median	59	60
	Range	18–78	20–83
Age categories, years			
<65		385 (69.1)	389 (68.5)
≥65		172 (30.9)	179 (31.5)
Smoking status, N (%)			
Never smoker		121 (21.7)	123 (21.7)
Former smoker		135 (24.2)	168 (29.6)
Current smoker		300 (53.9)	276 (48.6)
ECOG PS, N (%)			
0: Fully active		132 (23.7)	121 (21.3)
1: Restricted in physically strenuous activity		333 (59.8)	343 (60.4)
2: Ambulatory and capable of all self care		92 (16.5)	104 (18.3)

Characteristic	Cetuximab + CTX N=557	CTX N=568
Duration of NSCLC, months, median (range) From diagnosis of stage IIIb/IV to first IC[a] N=556, 568)	0.4 (0–121)	0.4 (0–25)
Histology, N (%)		
Adenocarcinoma	255 (45.8)	277 (48.8)
Squamous cell carcinoma	190 (34.1)	187 (32.9)
Undifferentiated carcinoma	40 (7.2)	40 (7.0)
Large cell carcinoma	34 (6.1)	28 (4.9)
Adenosquamous carcinoma	4 (0.7)	11 (1.9)
Other	33 (5.9)	25 (4.4)
Stage at study entry, N (%)		
Stage IIIb	35 (6.3)	33 (5.8)
Without pleural effusion	7 (1.3)	2 (0.4)
With pleural effusion	28 (5.0)	31 (5.5)
Stage IV	522 (93.7)	535 (94.2)
Location of distant metastases, N (%)		
Lung	324 (58.2)	318 (56.0)
Bone	144 (25.9)	151 (26.6)
Liver	110 (19.7)	104 (18.3)
Adrenal glands	105 (18.9)	90 (15.8)
Brain	3 (0.5)	1 (0.2)
Other	153 (27.5)	164 (28.9)
Number of metastatic sites, N (%)		
0	7 (1.3)	8 (1.4)
1	272 (48.8)	285 (50.2)
2	163 (29.3)	172 (30.3)
≥3	80 (14.4)	70 (12.3)

[a] Duration from date of first diagnosis of stage IIIb/IV to date of first informed consent (IC); only year of diagnosis was given for 1 subject in the cetuximab + CTX group.

Primary Endpoint: Overall Survival



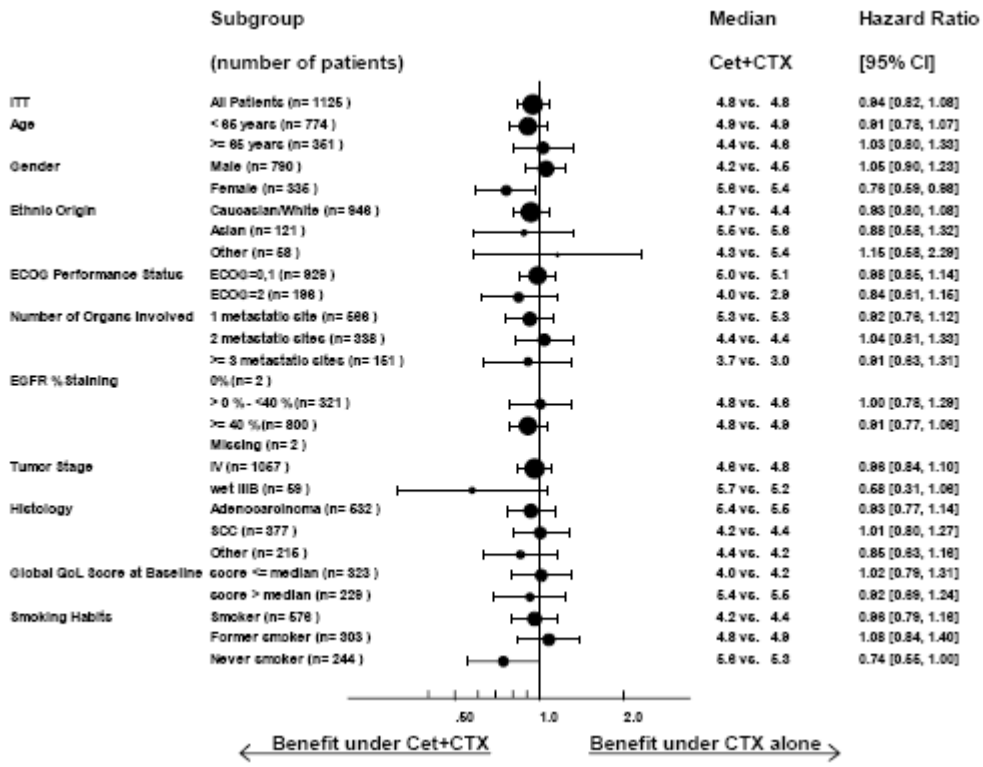
Summary statistics[a]	Cetuximab + CTX N=557	CTX N=568
Number of deaths, %	421 (75.6)	447 (78.7)
Log rank p value (stratified)[b]	0.0441	
Hazard ratio (stratified) [95% CI] [b, c]	0.871 [0.762, 0.996]	
Overall survival time, *months, median [95% CI]* [d]	11.3 [9.4, 12.4]	10.1 [9.1, 10.9]
Number of subjects at risk/survival rates up to [95% CI] [d]		
3 months	448 83% [79, 86]	457 82% [79, 86]
6 months	383 71% [67, 75]	383 70% [66, 74]
12 months	251 47% [43, 51]	225 42% [38, 46]
18 months	155 31% [27, 35]	134 26% [22, 30]
24 months	53 20% [17, 24]	48 17% [14, 21]

[a] Analysis based on 4 September 2007 snapshot.
[b] Stratification based on ECOG PS and tumor stage as per IVRS.
[c] Hazard ratio of cetuximab + CTX over CTX.
[d] Product-limit (Kaplan-Meier) estimates.

Progression-free survival

Summary statistics	Cetuximab + CTX N=557	CTX N=568
Number of PDs and deaths, %	457 (82.0)	431 (75.9)
Log rank p value (stratified)[a]	0.3869	
Hazard ratio (stratified) [95% CI][a, b]	0.943 [0.825, 1.077]	
Progression-free survival time, *months, median [95% CI]* [c]	4.8 [4.2, 5.3]	4.8 [4.4, 5.4]

[a] Stratification based on ECOG PS and tumor stage as per IVRS.
[b] Hazard ratio of cetuximab + CTX over CTX.
[c] Product-limit (Kaplan-Meier) estimates.



More subjects in the CTX group went off study without image-based PD and were therefore censored (cetuximab + CTX: 18%; CTX: 24%). The time to treatment failure was therefore calculated as a post hoc sensitivity analysis, also taking into account events which were considered signs of clinical progression (non-image-proven PD and start of any new anticancer treatment).

Time to treatment failure

Event	Number (%) of subjects	
	Cetuximab + CTX N=557	CTX N=568
Number of subjects with treatment failure (%)[a]	524 (94.1)	539 (94.9)
Progressive disease assessed by investigator	366 (65.7)	349 (61.4)
Discontinuation of treatment due to adverse event	90 (16.2)	99 (17.4)
Withdrawal of consent	54 (9.7)	51 (9.0)
Start of any new anticancer treatment	14 (2.5)	40 (7.0)

[a] In case of two events with the same date, the following order was applied: PD assessed by the investigator; discontinuation of treatment due to an adverse event; start of any new anticancer therapy; withdrawal of consent.

Summary statistics	ITT Population	
	Cetuximab + CTX N=557	CTX N=568
Number of events, %[a]	524 (94.1%)	539 (94.9)
Log rank p value (stratified)[b]	0.0151	
Hazard ratio (stratified) [95% CI][b, c]	0.860 [0.761, 0.971]	
Time to treatment failure, Months, median (range)[d]	4.2 (0–30)	3.7 (0–22)
[95% CI]	[3.9, 4.4]	[3.1, 4.2]

Response rate

Response variable/Summary statistics	Cetuximab + CTX N=557	CTX N=568
Best overall response		
Complete response	9 (1.6)	6 (1.1)
Partial response	194 (34.8)	160 (28.2)
Stable disease	201 (36.1)	240 (42.3)
Progressive disease	53 (9.5)	62 (10.9)
Not evaluable	100 (18.0)	100 (17.6)
Best overall response rate, % [95% CI][a]	36.4 [32.4, 40.6]	29.2 [25.5, 33.2]
CMH test[b]		
p value	0.0101	
Odds ratio [95% CI][b]	1.389 [1.081, 1.785]	
Disease control rate, % [95% CI] [a]	72.5 [68.6, 76.2]	71.5 [67.6, 75.2]
CMH test[b]		
p value	0.6801	
Odds ratio [95% CI][b]	1.056 [0.814, 1.372]	

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

[b] Stratification based on ECOG PS an tumor stage as per IVRS.

Study CA225099

A randomized, open label, multicenter phase III study of taxane + carboplatin + cetuximab vs. taxane + carboplatin as first-line treatment for subjects with advanced metastatic non-small cell lung cancer.

Main Inclusion Criteria:

• Men and women, age ≥ 18 years.
• Histologically or cytologically confirmed NSCLC, stage IV or stage IIIb with documented malignant pleural effusion, or recurrent disease following radiotherapy or surgical resection.
• Bidimensionally measurable disease; if the only measurable tumor was in previously irradiated area, it had to be regarded as new after completion of radiotherapy.
• ECOG PS of 0 or 1 at study entry.
• Adequate renal, liver and bone marrow function.

Study Treatment and Duration:

• Cetuximab (initial dose 400 mg/m²; subsequent weekly doses 250 mg/m²)
+ 3-weekly cycles of CTX, i.e. paclitaxel (225 mg/m² on Day 1) or docetaxel (75 mg/m² on Day 1)
+ carboplatin (AUC 6).
or
• Paclitaxel or docetaxel + carboplatin alone at the same dosages.

CTX was given for a maximum of 6 cycles in case of at least stable disease with discretionary continuation of cetuximab as monotherapy in subjects who had received cetuximab.

Subjects who met eligibility criteria were randomized (phone) in a 1:1 ratio to either C/T/C or T/C. The investigator specified which taxane the subject would receive, either paclitaxel or docetaxel. Randomization was stratified by PS (0 or 1), investigational site, and intended on-study taxane (paclitaxel or docetaxel) and was carried out using the Pocock and Simon dynamic balancing algorithm.

The primary analyses of PFS and tumour response endpoints were based on IRRC assessments.

There were four protocol amendments. Amendment 3 (11-Nov-2005) changed the primary endpoint from response rate to PFS and increased the sample size from 300 to 660.

Baseline characteristics

	Number of Subjects (%)	
	Cetuximab+Taxane+Carboplatin N = 338	Taxane+Carboplatin N = 338
Gender (%)		
Male	192 (56.8)	204 (60.4)
Female	146 (43.2)	134 (39.6)
Race (%)		
White	296 (87.6)	300 (88.8)
Black	25 (7.4)	24 (7.1)
Asian	6 (1.8)	10 (3.0)
Other (1)	11 (3.3)	4 (1.2)
Age (years)		
N	338	338
Mean (SD)	64.0 (10.0)	63.9 (10.3)
Median	64.0	65.0
Min - Max	37.0 - 87.0	34.0 - 85.0
Age Categorization (years) (%)		
< 65	171 (50.6)	165 (48.8)
>= 65	167 (49.4)	173 (51.2)
Female < 50	18 (5.3)	17 (5.0)
Female >= 50	128 (37.9)	117 (34.6)

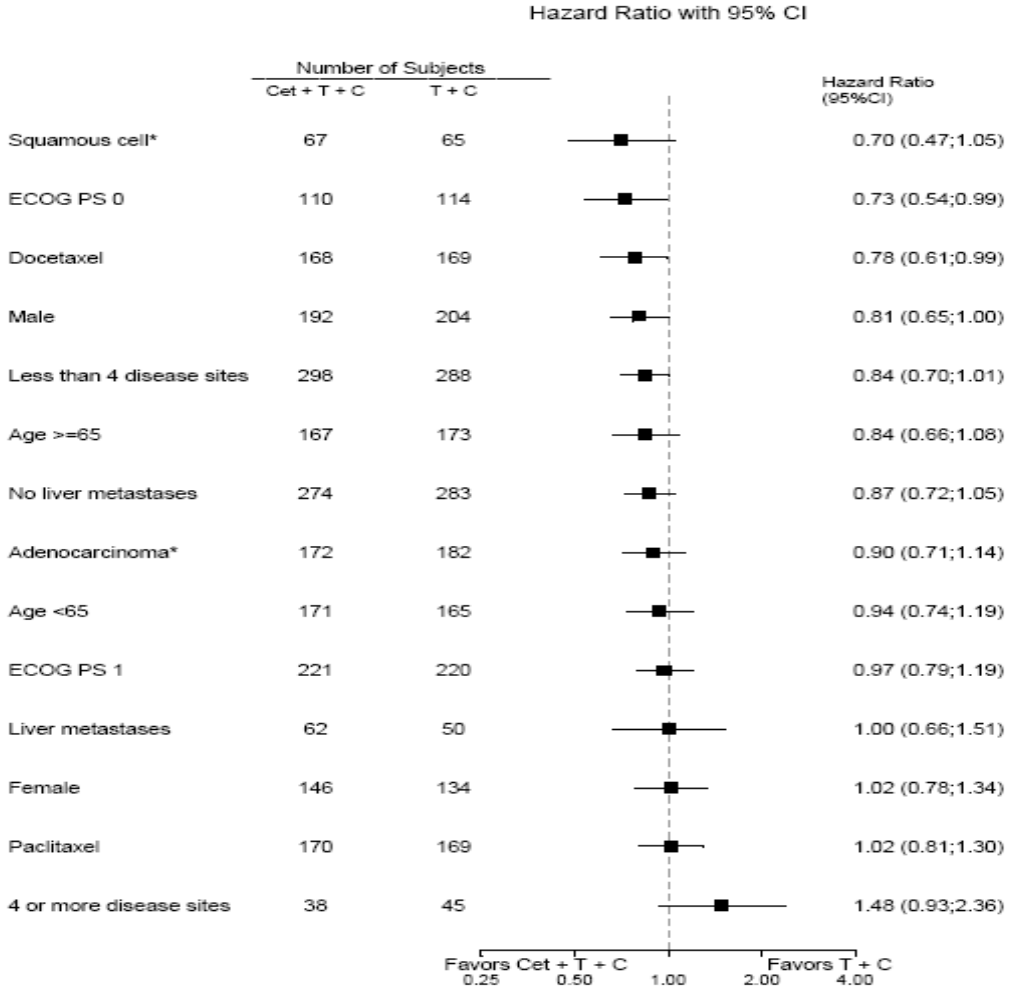
	Number of Subjects (%)	
	Cetuximab+Taxane+Carboplatin N = 338	Taxane+Carboplatin N = 338
Weight (kg)		
N	335	337
Mean (SD)	75.0 (17.1)	75.3 (18.1)
Median	74.0	75.0
Min - Max	41.0 - 142.0	34.0 - 140.0
ECOG Performance Status at Baseline (%) (2)		
0	110 (32.5)	114 (33.7)
1	221 (65.4)	220 (65.1)
2	4 (1.2)	2 (0.6)
3	0	1 (0.3)
Missing	3 (0.9)	1 (0.3)

	Cetuximab+Taxane+Carboplatin N = 338	Taxane+Carboplatin N = 338
Stage of disease at study entry, n(%)		
III B	24 (7.1)	35 (10.4)
IV	296 (87.6)	291 (86.1)
Recurrent Disease	18 (5.3)	12 (3.6)
Months from first pathological diagnosis to randomization		
N	338	338
Median	0.9	0.9
Min - Max	0.2 - 101.4	0.1 - 149.4
Cell type, n(%)		
ADENOCARCINOMA	172 (50.9)	182 (53.8)
BRONCHO-ALVEOLAR CARCINOMA	2 (0.6)	1 (0.3)
LARGE CELL	25 (7.4)	23 (6.8)
OTHER	14 (4.1)	14 (4.1)
SQUAMOUS CELL	67 (19.8)	65 (19.2)
UNKNOWN	58 (17.2)	53 (15.7)

Progression-free survival

	Cetuximab+ Taxane+Carboplatin N=338	Taxane+Carboplatin N=338
Number of events/Number of subjects (%)	284/338 (84.0)	263/338 (77.8)
Median (months) (95% CI) (1)	4.40 (4.11, 5.06)	4.24 (3.94, 4.63)
Log-rank p-value (2)	0.2358	
Hazard ratio (95% CI) (3) (4)	0.902 (0.761,1.069)	

(1) Confidence interval computed using the Brookmeyer and Crowley method
(2) Stratified by ECOG PS (0 vs. 1) and intended on-study taxane (paclitaxel vs. docetaxel) at randomization
(3) Ratio of cetuximab+taxane+carboplatin to taxane+carboplatin
(4) Estimated using a Cox regression model stratified by ECOG PS (0 vs. 1) and intended on-study taxane (paclitaxel vs. docetaxel) at randomization and with treatment as the only covariate



Investigator assessed PFS

	Cetuximab+ Taxane+Carboplatin N=338	Taxane+Carboplatin N=338
Number of events/Number of subjects (%)	294/338 (87.0)	293/338 (86.7)
Median (months) (95% CI) (1)	4.30 (4.07, 5.06)	3.78 (3.15, 4.14)
Log-rank p-value (2)	0.0015	
Hazard ratio (95% CI) (3) (4)	0.766 (0.649,0.903)	

(1) Confidence interval computed using the Brookmeyer and Crowley method
(2) Stratified by ECOG PS (0 vs. 1) and intended on-study taxane (paclitaxel vs. docetaxel) at randomization
(3) Ratio of cetuximab+taxane+carboplatin to taxane+carboplatin
(4) Estimated using a Cox regression model stratified by ECOG PS (0 vs. 1) and intended on-study taxane (paclitaxel vs. docetaxel) at randomization and with treatment as the only covariate

Response rate

	Cetuximab+Taxane+ Carboplatin N = 338	Taxane+Carboplatin N = 338
Best response, number of subjects (%)		
Complete response	0	1 (0.3)
Partial response	87 (25.7)	57 (16.9)
Stable disease	143 (42.3)	154 (45.6)
Progressive disease	54 (16.0)	56 (16.6)
Unable to determine	54 (16.0)	70 (20.7)
Response rate[a]	87/338 (25.7)	58/338 (17.2)
(95% CI)[b]	(21.2, 30.7)	(13.3, 21.6)
Odds ratio[c,d] (95% CI)	1.675 (1.152, 2.436)	
CMH p-value for difference in response[d]	0.0066	

[a] Number of responders (complete response + partial response) / Number of subjects
[b] Confidence interval using the Clopper and Pearson method
[c] Ratio of C/T/C to T/C
[d] Stratified by PS (0 vs 1) and intended on-study taxane (paclitaxel vs docetaxel) at randomization

<u>Supportive studies</u>

Study CA225100

A randomized multicenter phase II study of gemcitabine/platinum/cetuximab vs. chemotherapy alone as first-line treatment for subjects with advanced/metastatic non-small cell lung cancer.

Main Inclusion Criteria:

• Men and women, age ≥ 18 years.
• Histologically or cytologically confirmed NSCLC, stage IV or stage IIIb with documented malignant pleural effusion, or recurrent disease following radiotherapy or surgical resection.

• Bidimensionally measurable disease; if the only measurable tumour was in previously irradiated area, it had to be regarded as new after completion of radiotherapy.
• ECOG PS of 0 or 1 at study entry.
• Adequate renal, liver and bone marrow function.

Study Treatment and Duration:
• Cetuximab (initial dose 400 mg/m²; subsequent weekly doses 250 mg/m²)
3-weekly cycles of CTX, i.e. gemcitabine (1250 mg/m² on Days 1 and 8) + cisplatin (75 mg/m² on Day 1) or gemcitabine (1000 mg/m² on Days 1 and 8) + carboplatin (AUC 5).
or
• Gemcitabine + cisplatin or carboplatin alone at the same dosages.

CTX was given for a maximum of 6 cycles in case of at least stable disease with discretionary continuation of cetuximab as monotherapy in subjects who had received cetuximab.

Efficacy

Response variable	Cetuximab + CTX N=65		CTX alone N=66	
		95% CI		95% CI
Primary variable				
Objective response rate, % subjects	27.7	[17.3, 40.2]	18.2	[9.8, 29.6]
Odds ratio	1.72 [0.75, 3.92]			
Secondary variables				
Progression-free survival time, median (months)	5.1	[4.2, 6.0]	4.2	[3.8, 5.5]
Hazard ratio	0.80 [0.55, 1.16]			
Overall survival time, median (months)	12.0	[8.8, 15.2]	9.3	[7.4, 11.8]
Hazard ratio	0.84 [0.55, 1.27]			

CI=confidence interval, CTX=chemotherapy

Study EMR 62 202-011
Open, randomized phase II pilot study of cetuximab in combination with cisplatin and vinorelbine or cisplatin and vinorelbine alone, to evaluate their efficacy, safety and pharmacokinetics in subjects with advanced epidermal growth factor receptor (EGFR) positive non small cell lung cancer (NSCLC).

Main Inclusion Criteria:
• Men and women, age ≥ 18 years.
• Histologically confirmed NSCLC, stage IV or stage IIIb with documented malignant pleural effusion.
• At least one unidimensionally measurable lesion; if the index lesion was in an irradiated area, progression of that lesion had to be demonstrated before study entry.
• Immunohistochemical evidence of EGFR expression before study entry in primary tumor and/or at least one metastasis.
• Karnofsky performance status (KPS) ≥70 at study entry.
• Adequate renal, liver and bone marrow function.

Study Treatment and Duration:
• Cetuximab (initial dose 400 mg/m²; subsequent weekly doses 250 mg/m²)
3-weekly cycles of CTX, i.e. cisplatin (80 mg/m² on Day 1) + vinorelbine (25 mg/m² on Days 1 and 8)
Or • Cisplatin + vinorelbine alone at the same dosages.

CTX was given for a maximum of 8 cycles in case of at least stable disease with discretionary continuation of cetuximab as monotherapy in subjects who had received cetuximab.

Response variable	Cetuximab + CTX N=43		CTX alone N=43	
		95% CI		95% CI
Primary variable				
Objective response rate, % subjects	34.9	[21.0, 50.9]	27.9	[15.3, 43.7]
Odds ratio	1.38 [0.55, 3.46]			
Secondary variables				
Progression-free survival time, median (months)	5.0	[4.5, 5.8]	4.6	[2.5, 6.0]
Hazard ratio	0.71 [0.4, 1.2]			
Time to treatment failure, median (months)	3.4	[2.9, 5.0]	2.9	[1.8, 4.5]
Hazard ratio	0.68 [0.4, 1.1]			
Overall survival time, median (months)	8.3	[6.1, 9.9]	7.3	[5.6, 9.5]
Hazard ratio	0.71 [0.5, 1.1]			

CI=confidence interval, CTX=chemotherapy

Hazard Ratios for Overall Survival Time and Progression-free Survival Time, and Objective Response Rates in Studies EMR 62 202-046 and CA225099 (ITT and KRAS-evaluable populations)

Population	N		Hazard ratio			Objective response rate (%)			
			OS time	PFS time		EMR 62 202-046		CA225099	
	EMR 62-202-046	CA 225099	EMR 62-202-046	EMR 62-202-046	CA 225099	Cet + CTX	CTX	Cet + CTX	CTX
ITT	1125	676	0.87	0.94	0.90	36.4	29.2	25.7	17.2
KRAS									
Evaluable	379	202	0.94	0.92	0.97	36.8	26.3	32.7	22.1
Wild-type	307	167	0.92	0.95	1.07	37.2	27.2	32.9	25.6
Mutant	72	35	1.04	0.88	0.64	35.1	22.9	30.8	9.1

Analysis performed across trials

Characteristic	Number (%) of subjects							
	EMR 62 202-046		CA225099		CA225100		EMR 62 202-011	
	Cet + CTX N=557	CTX N=568	Cet + CTX N=338	CTX N=338	Cet + CTX N=65	CTX N=66	Cet + CTX N=43	CTX N=43
Stage[a]								
Stage IV	522 (93.7)	535 (94.2)	314 (92.9)	303 (89.6)	60 (92.3)	58 (87.9)	40 (93.0)	38 (88.4)
Stage IIIb	35 (6.3)	33 (5.8)	24 (7.1)	35 (10.4)	5 (7.7)	8 (12.1)	3 (7.0)	5 (11.6)
Histology								
Adenocarcinoma	255 (45.8)	277 (48.8)	172 (50.9)	182 (53.8)	31 (47.7)	30 (45.5)	20 (46.5)	17 (39.5)
Squamous cell	190 (34.1)	187 (32.9)	67 (19.8)	65 (19.2)	15 (23.1)	13 (19.7)	17 (39.5)	19 (44.2)
Other	112 (20.1)	104 (18.3)	99 (29.3)	91 (26.9)	19 (29.2)	23 (34.8)	6 (14.0)	7 (16.3)
KRAS evaluable[b]	193 (34.6)	186 (32.7)	98 (30.0)	104 (30.8)				
KRAS status[c]								
Evaluable	193 (100)	186 (100)	98 (100)	104 (100)	ND		ND	
Wild-type	156 (80.8)	151 (81.2)	85 (86.7)	82 (78.8)				
Mutant	37 (19.2)	35 (18.8)	13 (13.3)	22 (21.2)				

[a] The category 'Recurrent disease' was included in studies CA225099 (cetuximab + CTX: 18 [5.3%]; CTX: 12 [3.6%]) and CA225100 (cetuximab + CTX: 5 [5.7%]; CTX: 3 [4.5%]). For the purposes of the Summary of Clinical Efficacy, this has been included with Stage IV.

[b] All subjects for whom tumor specimens were available containing NSCLC cells confirmed by histopathological review.

[c] Percentage based on KRAS-evaluable subjects.

Cet=cetuximab, CTX=chemotherapy, ITT=intent-to-treat, ND=not done.

Statistic	EMR 62 202-046		CA225099[a]		CA225100		EMR 62 202-011	
	Cet + CTX N=557	CTX N=568	Cet + CTX N=338	CTX N=338	Cet + CTX N=65	CTX N=66	Cet + CTX N=43	CTX N=43
Median OS time (months) 95% CI	11.3 [9.4, 12.4]	10.1 [9.1, 10.9]	9.5 [8.3, 11.2]	8.4 [7.5, 9.9]	12.0 [8.8, 15.2]	9.3 [7.4, 11.8]	8.3 [6.1, 9.9]	7.3 [5.6, 9.5]
Hazard ratio[b] 95% CI	0.87 [0.76, 1.00]		0.93 [0.77, 1.13]		0.84 [0.55, 1.27]		0.71 [0.45, 1.12]	
Log-rank p-value (stratifie	0.044		0.464		NC		NC	

[a] Findings are based on an interim analysis after 429 events (deaths). A final analysis of survival will be performed after 558 deaths have occurred. No adjustment for multiple testing as this was an interim analysis.

[b] Hazard ratio of cetuximab + CTX over CTX alone.

Note: hazard ratio and log-rank test stratified according to ECOG PS (0 or 1 vs. 2) and disease stage (IIIb vs. IV) for study EMR 62 202-046, and according to ECOG PS (0 vs. 1) and intended-on-study taxane for study CA225099. Analysis was unstratified in studies CA225100 or EMR 62 202-011.

Cet=cetuximab, CI=confidence interval, CTX=chemotherapy, ITT=intent-to-treat, NC=not calculated, OS=overall survival

Statistic	EMR 62 202-046		CA225099[a]		CA225100		EMR 62 202-011	
	Cet + CTX N=557	CTX N=568	Cet + CTX N=338	CTX N=338	Cet + CTX N=65	CTX N=66	Cet + CTX N=43	CTX N=43
Median PFS time (months) 95% CI	4.8 [4.2, 5.3]	4.8 [4.4, 5.4]	4.4 [4.1, 5.1]	4.2 [3.9, 4.6]	5.1 [4.2, 6.0]	4.2 [3.8, 5.5]	5.0 [4.5, 5.8]	4.6 [2.5, 6.0]
Hazard ratio[b] 95% CI	0.94 [0.82, 1.08]		0.90 [0.76, 1.07]		0.80 [0.55, 1.16]		0.71 [0.41, 1.21]	
Stratified log-rank p value	0.387		0.236		NC		NC	

[a] Findings are based on assessment by independent radiology review committee

[b] Hazard ratio of cetuximab + CTX over CTX alone

Note: hazard ratio and log-rank test stratified according to ECOG PS (0 or 1 vs. 2) and disease stage (IIIb vs. IV) for study EMR 62 202-046, and according to ECOG PS (0 vs. 1) and intended-on-study taxane for study CA225099. Analysis was unstratified in studies CA225100 or EMR 62 202-011.

Cet=cetuximab, CI=confidence interval, CTX=chemotherapy, ITT=intent-to-treat, NC=not calculated, PFS=progression-free survival

The efficacy results in terms of OS and PFS in the pooled ITT population (all four trials) are presented in the table below:

Efficacy variable / statistic	ITT	
	Cet + CTX N=1003	CTX N=1015
OS time		
Hazard ratio	0.878	
95 % CI	0.795-0.969	
p-value	0.010	
PFS time		
Hazard ratio	0.899	
95 % CI	0.814-0.993	
p-value	0.036	

1.2.2 Clinical safety

Patient exposure

Characteristic	Statistic	EMR 62 202-046 N=548	EMR 62 202-011 N=42	CA225099 N=325	CA225100 N=64
Duration, weeks	Median	17.7	13.6	12.1	13.6
	Range	1 – 135	1 – 47	1 – 115	1 – 69
Cumulative dose [a],	Median	3761	3395	3143	3188
mg/m²	Range	5 – 33272	186 – 10826	13 – 23020	17 – 16684
Dose intensity [a,b],	Median	236	240	242	241
mg/m²/week	Range	41 – 399	172 – 251	0 – 288	14 – 290
Subjects with ≥80% of planned dose intensity [a,b]	% subjects	78.7	92.5	83.3	84
Cetuximab monotherapy					
No. subjects		241	11	125	22
No. monotherapy infusions	Median	9	6	10	11
	Range	1 – 110	1 – 23	1 – 73	2 – 48

[a] Data for study CA225100 are for the 56 subjects who received carboplatin.

[b] Data for dose intensity are for subjects who received at least 2 doses of cetuximab.

Duration of chemotherapy treatment was limited to 6 cycles in studies EMR 62 202-046, CA225099, and CA225100, and to 8 cycles in study EMR 62 202-011. In each of the 4 randomized, controlled studies the dose intensity of chemotherapy was reasonably comparable between the cetuximab + CTX group and the CTX alone group, but a tendency towards more dose-reductions was seen in the add-on arms in study CA225009 as illustrated below.

Characteristic	Paclitaxel		Docetaxel	
	Cet + CTX	CTX	Cet + CTX	CTX
Cumulative dose, mg/m²	N=166	N=161	N=159	N=159
Median	900.9	897.0	304.8	279.9
Range	122.8–1375.0	0.0–1368.7	70.7–505.7	73.3–603.3
Dose intensity, mg/m²/week	N=166	N=161	N=159	N=159
Median	73.0	74.0	24.4	24.8
Range	36.5–390.5	0.0–174.9	15.3–42.3	14.0–132.0
Relative dose intensity, % subjects	N=166	N=161	N=159	N=159
<60%	3.0	2.5	0	0.6
60 to <80%	14.5	15.5	20.1	10.1
80 to <90%	18.7	13.7	15.7	12.6
≥90%	63.9	68.3	64.2	76.7

N=number of subjects

Subjects in the cetuximab + CTX groups who discontinued chemotherapy could continue on cetuximab monotherapy if they did not have progressive disease. A total of 399/979 (40.8%) subjects received cetuximab monotherapy. The median numbers of cetuximab monotherapy infusions in the individual studies ranged from 6 to 11.

Adverse events

The AE profile of cetuximab is considered well-known:

• **Infusion-related Reactions (IRRs).** Mild or moderate IRRs are very common and occur in a close temporal relationship mainly to the first cetuximab infusion. Severe IRRs may occur, in rare cases with fatal outcome. They usually develop during and up to 1 hour after the end of the initial cetuximab infusion, but may occur after several hours or with subsequent infusions. Some of these reactions may be anaphylactoid/anaphylactic in nature.

• **Skin reactions** may develop in more than 80% of patients and mainly present as acnelike rash and/or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis, or nail disorders. Approximately 15% of skin reactions are severe, including single cases of skin necrosis. The majority of skin reactions develop within the first 3 weeks of therapy.

• **Very common side effects (≥10% patients):** hypomagnesemia, increase in liver enzyme levels, mucositis (mild to moderate that may lead to epistaxis).

• **Common side effects (≥1% to <10% patients):** headache, conjunctivitis, diarrhoea, dehydration, hypocalcemia, nausea, vomiting, fatigue, anorexia that may lead to weight decrease.

• **Uncommon side effects (≥0.1% to <1% patients):** blepharitis, keratitis, pulmonary embolism, deep vein thrombosis.

Grade 3 or 4 AEs
As expected, CTX-related events dominated in the add-on studies. This is illustrated by data on grade 3 or 4 AEs occurring in ≥5% of subjects or grade 4 AEs occurring in ≥1% of subjects in either treatment group in **Study EMR 62 202-046** (add-on to cisplatin + vinorelbine)

MedDRA preferred term	Number (%) of subjects			
	Grade 3 or 4 events		Grade 4 events	
	Cet + CTX N=548	CTX N=562	Cet + CTX N=548	CTX N=562
Any AE	**499 (91.1)**	**485 (86.3)**	**342 (62.4)**	**294 (52.3)**
Neutropenia	289 (52.7)	289 (51.4)	210 (38.3)	212 (37.7)
Leukopenia	139 (25.4)	109 (19.4)	57 (10.4)	28 (5.0)
Febrile neutropenia	119 (21.7)	87 (15.5)	34 (6.2)	25 (4.4)
Anemia	76 (13.9)	94 (16.7)	8 (1.5)	5 (0.9)
Dyspnea	47 (8.6)	51 (9.1)	13 (2.4)	8 (1.4)
Fatigue	40 (7.3)	37 (6.6)	5 (0.9)	3 (0.5)
Rash	36 (6.6)	0 –	0 –	0 –
Vomiting	34 (6.2)	38 (6.8)	1 (0.2)	1 (0.2)
Hypokalemia	34 (6.2)	20 (3.6)	2 (0.4)	3 (0.5)
WBC decreased	29 (5.3)	18 (3.2)	14 (2.6)	4 (0.7)
Pulmonary embolism	23 (4.2)	16 (2.8)	23 (4.2)	11 (2.0)
Pneumonia	18 (3.3)	9 (1.6)	7 (1.3)	2 (0.4)
Hypocalcemia	15 (2.7)	4 (0.7)	7 (1.3)	2 (0.4)
Respiratory failure	15 (2.7)	8 (1.4)	11 (2.0)	8 (1.4)
Sepsis	10 (1.8)	3 (0.5)	10 (1.8)	1 (0.2)
Neutrophil count decreased	10 (1.8)	10 (1.8)	3 (0.5)	6 (1.1)
Septic shock	6 (1.1)	0 –	6 (1.1)	0 –

AEs Occurring in ≥10% of Subjects in Either Treatment Group in Study CA225099

MedDRA preferred term	% of subjects	
	Cetuximab + CTX N=325	CTX N=320
Any AE	99.7	99.7
Fatigue	74.8	70.9
Nausea	60.3	50.6
Rash	56.9	14.7
Diarrhea	47.7	32.8
Constipation	45.2	31.3
Anorexia	40.3	30.3
Alopecia	36.3	43.8
Dyspnea	32.9	34.4
Vomiting	32.9	30.0
Cough	30.8	25.3
Dehydration	27.4	16.3
Insomnia	26.5	22.2
Stomatitis	22.2	12.8
Dry skin	20.9	3.4
Weight decreased	20.6	10.0
Dizziness	20.3	14.7
Dysgeusia	18.5	14.4
Dermatitis acneiform	17.5	0.6
Edema peripheral	16.9	14.4
Arthralgia	15.4	15.9
Back pain	15.4	12.8
Mucosal inflammation	15.4	5.9
Dyspepsia	14.8	9.4
Musculoskeletal pain	14.5	9.7
Pruritus	13.8	5.3
Pain in extremity	13.2	10.6
Pyrexia	13.2	9.7
Peripheral sensory neuropathy	12.9	15.9
Abdominal pain	12.9	8.8
Epistaxis	11.7	5.6
Depression	11.4	8.8
Headache	11.1	10.3
Neuropathy	11.1	10.3
Asthenia	11.1	6.9
Hypotension	11.1	5.9
Myalgia	10.2	11.3
Neutropenia	10.2	6.9
Anxiety	9.5	10.3
Neuropathy peripheral	8.6	11.3

Deaths up to 30 Days after Last Dose of Study Treatment or Chemotherapy in the 4 Randomized, Controlled Studies

Study / Primary reason for death	No. (%) of subjects who died					
	Up to 30 days after last dose of study treatment				Up to 30 days after last dose of CTX	
	Cetuximab + CTX		CTX		Cetuximab + CTX	
EMR 62 202-046	N=548		N=562		N=548	
All reasons	103	(18.8)	76	(13.5)	85	(15.5)
Disease progression	33	(6.0)	30	(5.3)	22	(4.0)
Disease-related complications	28	(5.1)	18	(3.2)	25	(4.6)
Intercurrent or unrelated illness or event	17	(3.1)	8	(1.4)	15	(2.7)
Events related to chemotherapy	14	(2.6)	10	(1.8)	14	(2.6)
Events related to cetuximab	1 [a]	(0.2)	NA	NA	0	–
Unknown	10	(1.8)	10	(1.8)	9	(1.6)
EMR 62 202-011	N=42		N=43		N=42	
All reasons	6	(14.3)	4	(9.3)	4	(9.5)
Disease progression	2	(4.8)	1	(2.3)	0	–
Disease-related complications	3	(7.1)	1	(2.3)	3	(7.1)
Intercurrent or unrelated event	0	–	1	(2.3)	0	–
Unknown	1	(2.4)	1	(2.3)	1	(2.4)
CA225099	N=325		N=320		N=325	
All reasons	37	(11.4)	27	(8.4)	30	(9.2)
Tumor-related disease	31	(9.5)	19	(5.9)	24	(7.4)
Other	6	(1.8)	6	(1.9)	6	(1.8)
Study drug toxicity	0	–	2	(0.6)	0	–
CA225100	N=64		N=66		N=64	
All reasons	8	(12.5)	8	(12.1)	7	(10.9)
Tumor-related disease	7	(10.9)	7	(10.6)	6	(9.4)
Other or unknown	1	(1.6)	1	(1.5)	1	(1.6)
Study drug toxicity	0	–	0	–	0	–

[a] Subject died after first dose of cetuximab and did not receive CTX.

The overall incidences of **deep vein thrombosis and pulmonary embolism** in the 4 randomized, controlled studies were higher in the cetuximab + CTX groups compared to the CTX groups: deep vein thrombosis 3.1% (30/979) vs 1.6% (16/991) subjects and pulmonary embolism 3.8% (37/979) vs 2.4% (24/991) subjects. Deep vein thrombosis and pulmonary embolism are labelled side effects of cetuximab.

Number (%) of Subjects with (Febrile) Neutropenia, Septic Events, or Pneumonia in the Randomized Controlled Studies

Parameter / grade	EMR 62 202-046		EMR 62 202-011		CA225099		CA225100	
	Cet + CTX N=648	CTX N=682	Cet + CTX N=42	CTX N=43	Cet + CTX N=326	CTX N=320	Cet + CTX N=84	CTX N=88
Neutropenia (lab. value)	N=531	N=545	N=42	N=43	N=316	N=315	N=64	N=65
Any grade	474 (89.3)	467 (85.7)	42 (100)	43 (100)	250 (79.1)	220 (69.8)	54 (84.4)	55 (84.6)
Grade 3 or 4	420 (79.1)	380 (69.7)	35 (83)	23 (54)	198 (62.7)	176 (55.9)	31 (48.4)	32 (49.2)
Grade 4	320 (60.3)	281 (51.6)	21 (50)	16 (37)	135 (42.7)	102 (32.4)	15 (23.4)	7 (10.8)
Neutropenia (PT) [a]								
Any grade	315 (57.5)	330 (58.7)	26 (61.9)	25 (58.1)	33 (10.2)	22 (6.9)	5 (7.8)	7 (10.6)
Grade 3 or 4	289 (52.7)	289 (51.4)	21 (50.0)	22 (51.2)	28 (8.6)	19 (5.9)	5 (7.8)	7 (10.6)
Grade 4	210 (38.3)	212 (37.7)	13 (31.0)	14 (32.6)	19 (5.8)	12 (3.8)	3 (4.7)	3 (4.5)
Febrile neutropenia (PT)								
Any grade	124 (22.6)	92 (16.4)	3 (7.1)	3 (7.0)	15 (4.6)	12 (3.8)	3 (4.7)	1 (1.5)
Grade 3 or 4	119 (21.7)	87 (15.5)	NA [b]	NA	15 (4.6)	11 (3.4)	3 (4.7)	1 (1.5)
Grade 4	34 (6.2)	25 (4.4)	NA	NA	2 (0.6)	2 (0.6)	1 (1.6)	0 –
Septic events (AE category)								
Any grade	28 (5.1)	10 (1.8)	2 (4.8)	0 –	9 (2.8)	4 (1.3)	4 (6.3)	0 –
Grade 3 or 4	25 (4.6)	9 (1.6)	2 (4.8)	0 –	9 (2.8)	3 (0.9)	4 (6.3)	0 –
Sepsis (PT)								
Any grade	10 (1.8)	4 (0.7)	2 (4.8)	0 –	7 (2.2)	3 (0.9)	1 (1.6)	0 –
Grade 3 or 4	10 (1.8)	3 (0.5)	2 (4.8)	0 –	7 (2.2)	2 (0.6)	1 (1.6)	0 –
Neutropenic sepsis (PT)								
Any grade	10 (1.8)	5 (0.9)	0 –	0 –	0 –	0 –	0 –	0 –
Grade 3 or 4	8 (1.5)	5 (0.9)	0 –	0 –	0 –	0 –	0 –	0 –
Septic shock (PT)								
Any grade	6 (1.1)	0 –	0 –	0 –	0 –	0 –	0 –	0 –
Grade 3 or 4	6 (1.1)	0 –	0 –	0 –	0 –	0 –	0 –	0 –
Pneumonia (PT)								
Any grade	30 (5.5)	25 (4.4)	1 (2.4)	2 (4.7)	23 (7.1)	19 (5.9)	6 (9.4)	4 (6.1)
Grade 3 or 4	18 (3.3)	9 (1.6)	1 (2.4)	1 (2.3)	18 (5.5)	14 (4.4)	5 (7.8)	3 (4.5)
Grade 4	7 (1.3)	2 (0.4)	0 –	1 (2.3)	4 (1.2)	1 (0.3)	1 (1.6)	2 (3.0)

[a] Number and percent of subjects for study EMR 62 202-011 are for the COSTART preferred term leukopenia.

[b] Febrile neutropenia cases in study EMR 62 202-011 were coded in COSTART as separate events of neutropenia and fever. Therefore no NCI-CTC grading is available for febrile neutropenia cases in this study.

Note: Other AEs belonging to the special AE category "septic events" were as follows (cetuximab + CTX vs CTX group): EMR 62 202-046: bacteremia any grade 1 (0.2%) vs 1 (0.2%), grade 3 or 4 1 (0.2%) vs 0; bacterial sepsis any grade 0 vs 1 (0.2%), grade 3 or 4 0 vs 1 (0.2%); staphylococcal sepsis any grade 1 (0.2%) vs 0, grade 3 or 4 0 vs 0. EMR 62 202-011: no other AEs. CA225099: bacteremia any grade 1 (0.3%) vs 0, grade 3 or 4 1 (0.3%) vs 0; staphylococcal sepsis any grade 0 vs 1 (0.3%), grade 3 or 4 0 vs 0; urosepsis any grade 1 (0.3%) vs 1 (0.3%), grade 3 or 4 1 (0.3%) vs 1 (0.3%). CA225100: bacteremia any grade 1 (1.6%) vs 0, grade 3 or 4 1 (1.6%) vs 0; bacterial sepsis any grade 1 (1.6%) vs 0, grade 3 or 4 1 (1.6%) vs 0; staphylococcal sepsis any grade 1 (1.6%) vs 0, grade 3 or 4 1 (1.6%) vs 0.

AE=adverse event, NA=not available, PT=MedDRA preferred term

Frequencies of neutropenia reported by the investigator as AEs were similar between treatment groups, but neutropenia findings based on laboratory values differed. Frequencies of laboratory assessments of neutropenia were higher than those based on AEs, and grade 3 or 4 / grade 4 laboratory values were generally more common in the cetuximab + CTX groups than in the CTX control groups.

The frequency of grade 4 neutropenia was higher in studies EMR 62 202-046 and -011 than in studies CA225099 and CA225100. However, laboratory evaluations were performed more frequently in studies EMR 62 202-046 and -011.

Number (%) of Subjects with Septic Events and Predisposing Factors in Randomized, Controlled Studies

Parameter	EMR 62 202-046		EMR 62 202-011		CA225099		CA225100	
	Cet + CTX N=648	CTX N=682	Cet + CTX N=42	CTX N=43	Cet + CTX N=325	CTX N=320	Cet + CTX N=84	CTX N=88
Subjects with septic events	28 (5.1)	10 (1.8)	2 (4.8)	0	9 (2.8)	4 (1.3)	4 (6.3)	0
Without severe neutropenia [a]	5	2	0	0	7	3	3	0
With severe neutropenia								
Total	23	8	2	0	2	1	1	0
Associated with diarrhea (grade 3/4), mucositis or skin events	17	3	2	0	1	1	1	0

[a] Severe neutropenia is defined as a laboratory value for neutrophils low grade 3 or 4 or AEs of febrile neutropenia , agranulocytosis, neutropenic sepsis, neutropenic infection, neutropenic colitis (any grade) or granulocytopenia, granulocyte count decreased, neutropenia, or neutrophil count decreased grade 3 or 4.

1.3 Pharmacovigilance/Risk management plan

A new version of the RMP was submitted with this application taking into account the results of the submitted studies.

1.4 Overall Discussion and SAG- Oncology outcome

Platinum-based doublets have for long been considered standard therapy in patients with advanced NSCLC. Recently, however, bevacizumab was licensed as add-on therapy in patients with non-squamous NSCLC. Bevacizumab is the only targeted therapy that has been approved in combination with CTX for the first-line treatment of non-squamous cell NSCLC. At the time of approval (end of 2007) a statistically significant prolongation of the most relevant endpoint OS time for NSCLC was reported for the combination of 15 mg/kg bevacizumab with carboplatin + paclitaxel (HR 0.79, difference in median OS of 2 months).
It is agreed that progress in the treatment of NSCLC is slow. In non-squamous NSCLC the HR for ciplatin + pemetrexed vs. cisplatin + gemcitabine was 0.84, for example. Similarly the HR for the comparison cisplatin + docetaxel vs. cisplatin + vinorelbine was 0.85 and only borderline statistically significant.
Recently, data presented at the ESMO meeting in September 2008 showed that the addition of 7.5 or 15 mg/kg bevacizumab to cisplatin + gemcitabine did not result in a statistically significant survival benefit (HR 0.93 for 7.5 mg/kg and 1.03 for 15 mg/kg bevacizumab, differences in median 0.5 and 0.3 months, respectively).
Large confirmatory studies have been conducted with erlotinib and gefitinib (EGFR tyrosine kinase inhibitors) as add-on to platinum based regimens without any discernable add-on activity.

Cetuximab as add-on to standard chemotherapies in the treatment of advanced NSCLC has demonstrated to increase tumour response rates. This increase appears unrelated to KRAS mutation status, even though data are limited. This implies that the activity may be unrelated to EGFR signalling and could be due to e.g. ADCC. Seemingly higher activity in squamous cell carcinoma in the two main studies would also indicate that EGFR signalling may not be the main target for activity. EGFR expression, as estimated by IHC or FISH, may not be of importance for the activity of cetuximab.

In the largest study a statistically borderline add-on activity in terms of survival was shown. The add-on benefit, however, is modest (HR 0.87, corresponding to about 5 weeks median difference), but it is acknowledged that next-line therapies, including use of TK inhibitors, might dilute the apparent treatment effect. Comparable HR:s for OS have been reported in the other studies submitted in support of the application. Pooled analyses using different methodologies indicate that the HR is about 0.88 corresponding to a median difference of slightly more than 1 month at a p-value of 0.01.

Add-on activity in terms of prolonged PFS has been less convincingly demonstrated from a statistical perspective. The HR of 0.9 corresponds to an estimated median difference of 0.5 months.

The tolerability/toxicity profile of cetuximab is considered relatively well characterised also as add-on to various chemotherapy regimens. Very common and common adverse reactions of importance for the tolerability encompass skin reactions, diarrhoea, mucositis, nausea, fatigue, etc. Less common, but severe and serious reactions include neutropenic fever, thromboembolic complications, dehydration and severe infusion related reactions.
In all 4 studies, the combined frequencies of subjects with SAEs and grade 4 AEs in all 4 randomized controlled studies were 56.8% (556/979) and 48.6% (476/979) for cetuximab + CTX and 41.3% (409/991) and 40.6% (402/991) for CTX alone resulting in a difference of 15.5% and 8.0%, respectively.

In the presented trials the estimated benefit of add-on cetuximab to standard chemotherapy in terms of survival is considered modest (HR 0.88) and statistically non-compelling in the light of non-convincing effects in terms of PFS. Documented benefits are not considered to outweigh the

tolerability and safety concerns, including an increased risk for grade 4 AE:s and SAE:s in studies CA225099 and EMR 62202-046. Benefit – risk is thus considered unfavourable.

The CHMP decided to consult the SAG- Oncology group on the following questions.

1. **Cetuximab shows a modest add-on activity to platinum-based therapies in the treatment of NSCLC. This activity appears not to be affected by KRAS mutation status and the activity profile also differs from what has been seen with small molecule EGFR-TK inhibitors. This could imply that blockage of EGFR-signalling is not of major importance for the activity of cetuximab in this setting. Antibody mediated cytotoxicity would be a possible mechanistic explanation. Does the SAG foresee ways forward to identify patients with increased likelihood of response to cetuximab?**

   The SAG acknowledged that a substantial effort has been made to identify important clinical and biological markers to select likely responders to treatment with cetuximab+chemotherapy. Despite such effort, no reliable markers could be found. Adequate samples were only available in a variable subset of patients, less than 30% for certain analyses, and the outcome in terms of overall survival (OS) for such subsets was not always comparable to the overall population. Thus, selection bias in the analysis presented may have contributed to this. The SAG agreed that further analyses of the available samples, if possible, as well as additional studies are strongly recommended. Ideally samples should prospectively be saved for broader drug target screens; e.g. gene expression profiling with repeated sampling for intrapatient analysis. With modern standards cytological samples should give sufficient material. The rapid development of (c)DNA based sequencing strategies may also give important more global insights into the genetic alterations, including those pathways already examined.

   The SAG also agreed that based on the exploratory analyses presented, histology did not seem to be a convincing predictor for selecting responders.

2. **The add-on activity in terms of PFS and OS is modest. Is the benefit considered to outweigh the tolerability and toxicity profile of add-on cetuximab?**

   The SAG agreed that OS, progression-free survival (PFS) health-related quality of life (HRQL) and toxicity are important clinical endpoints, and that favourable effects need to be balanced against the unfavourable ones, particularly grade 3-4 toxicity, treatment-related deaths, and need for hospitalisation.

   Concerning OS, a statistically significant effect was observed in the larger pivotal trial EMR 62 202-046 ("FLEX") where OS was the primary endpoint and in the pooled analyses of all included studies, but not in exploratory analyses of trial CA225099 ("099") where this was studied as a secondary endpoint. Concerning the clinical significance of the effect on OS, the SAG acknowledged that the statistical significance might primarily be due to the high number of patients enrolled (> 2000) and followed until death, that the improvement in median OS was about 1 month (+/- 12 vs 11 months), that it was consistent across studies, but transient and that the magnitude of the effect was at best of very modest clinical significance.

   Concerning PFS, no statistically significant effect was observed in study 099 (where this was studied as a primary endpoint) and no convincing effect was shown in exploratory analyses of the FLEX study, but PFS was statistically significant in the pooled analyses of all included studies. Based on conventional estimates, the effect, if any, was considered clinically very marginal.

   Concerning HRQL, a summary of the main results was verbally presented by the holder of the marketing authorisation. It was claimed that HRQL analyses were importantly hampered by missing data but that no clinically relevant detriment in HRQL was associated with cetuximab+chemotherapy compared to chemotherapy alone in longitudinal analyses. Some worsening in the HRQL for certain domains, such as the social functioning around cycle 3, was claimed to be associated with skin toxicity. As always, the major problem is the lack of predefined domains being the primary end-point, making any conclusions questionable based on HRQL.

   Concerning toxicity, the SAG agreed that cetuximab+chemotherapy was associated with an increase in toxicity compared to chemotherapy alone, particularly about 10% increase in grade 3

skin toxicity (skin toxicity grade 1 or more, however, may be associated with a better outcome-retrospective observation), and about 6% increase in febrile neutropenia in the FLEX study, or a 4.2% and 1.1% in grade 3/4 and grade 4 febrile neutropenia, respectively, increase in the pooled safety population analysis presented. The marketing authorisation holder claimed that the number of hospitalisations due to febrile neutropenia was similar between treatment arms. There was an about 11% increase in serious adverse events in the pooled population. No data were presented about need for hospitalisation regardless of cause.

Concerning the balance of benefits and risks, the SAG members were split into two slightly different views:

a. According to one view, the very modest benefit observed did not outweigh the risks due to the observed toxicity profile. From a clinical perspective, the tradeoffs in terms of the risks observed should be at least in the order of 2-3 months improvement in median OS, and this should be based on convincing clinical data, including supportive data on PFS and other clinically relevant endpoints. According to this view, the lack of a clearly consistent effect in PFS was difficult to explain and may suggest that the effect on OS could be due to treatment given after progression.

b. According to another view, although very modest in absolute terms, the effect on OS cannot be ignored, it is a very relevant effect in relative terms due to the short survival, and is similar to incremental improvement achieved with other agents in NSCLC. The added toxicity was of some concern but it was considered manageable and in the overall balance did not outweigh the benefits in a condition where there are only few treatments with an effect on OS. The lack of convincing supportive data in terms of PFS was considered not to be critical because the overall pattern was generally consistent with OS in terms of a favourable treatment effect.

2. Possibility to identify patients with increased likelihood of response to cetuximab

As requested by the CHMP, the MAH made efforts to identify retrospectively subgroups of patients where the benefit of cetuximab treatment would be more pronounced.

2.1. Biomarker analyses

Following the CHMP request and the presentation to the SAG, the MAH submitted results form biomarker analyses. With the exception of EGFR staining in study EMR 62 202-046, neither phase III study had other biomarker analyses prospectively planned in the original protocol. However, for exploratory analyses, substantial efforts were made to collect, retrospectively, as much archived tumour tissue as possible from patients in the two studies.

Summary of Biomarker Analyses in EMR 62 202-046 and CA225099

Biomarker	**EMR 62 202-046 (ITT = 1125 (100 %))**		**CA225099 (ITT = 676 (100 %))**	
	Analyzed samples N (% of ITT)	**Frequency (n) of marker within analyzed samples (% of N)**	**Analyzed samples N (% of ITT)**	**Frequency (n) of marker within analyzed samples (% of N)**
KRAS mutation	395 (35 %)	75 (19 %)	202 (29 %)	35 (17 %)
EGFR FISH (FISH positive tumors)	279 (25 %)	102 (37 %)	104 (15 %)	54 (52 %)
EGFR kinase domain mutation	436 (39 %)	64 (15 %)	167 (25 %)	17 (10 %)

The results of the analyses were discussed at the SAG meeting. The rationale governing the selection of biomarkers was acknowledged, but the problems associated with low percentages of samples for analyses were also emphasized. Due to this and the overall low add-on activity of cetuximab only major differential activity would be detected. The lead hypotheses based on external but not NSCLC related data, i.e. that KRAS mutation status would be of importance, however, can reasonably be regarded as refuted. With respect to KRAS, similar results have also been reported for erlotinib administered after chemotherapy first line NSCLC, i.e. that KRAS mutations seem not to be associated with major loss in efficacy (study SATURN).

Available biomarker data have been presented and analysed and that there is agreement that these analyses provide no basis for selecting patients for treatment with cetuximab. In case of a positive opinion, the company's plans to address this issue should be further detailed. It is obvious, however, that additional clinical studies are needed.

2. 2. Further subgroup analyses of Study EMR 62 202-046 ("FLEX").

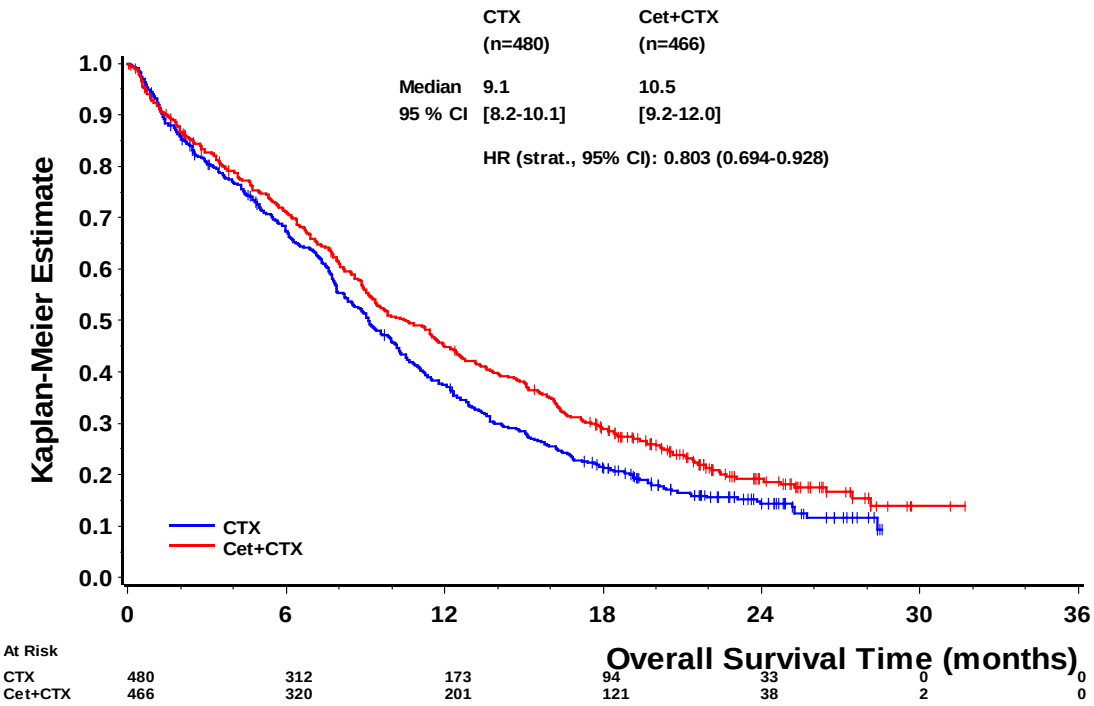
Study EMR 62 202-046 ("FLEX") was conducted worldwide. As today Asians are known to present with NSCLC biologically different from NSCLC in Caucasian, this study was further analysed.

	Asian (n=121)	**Caucasian (n=946)**
Adenocarcinoma	72%	44%
Female	46%	27%
Never-smoker	52%	17%
Post study EGFR TKI	61%	17%
Median survival (95% CI) months	19.5 (16.4; 23.3)	9.6 (9.0; 10.4)

The table above well illustrates the expected differences between "Asian" (Japan, China, Korea) and Caucasian patients. In Asian patients enrolled in this study, EGFR TK mutations are expected in about 40% of the patients vs. about 10% in Caucasians. EGFR tyrosine kinase inhibitors (EGFR TKI) were also more frequently used in Asians (61 vs. 17%).
In Asians PFS was 0.88 in favour of cetuximab, while OS favoured the chemotherapy (CTX) only arm (1.18). This may relate to more frequent use of TKI in the CTX only arm (73% vs. 50%).

Based on these findings it is considered reasonable to further analyse study outcome in Caucasians only.

Kaplan-Meier Plot of OS time, Caucasian, Study EMR 62 202-046



As PFS data also in Caucasians were unconvincing (HR 0.93), differential use of next line therapies was raised as a concern at the SAG meeting.

Summary of Most Important Efficacy Results in Studies EMR 62 202-046 (Caucasian)

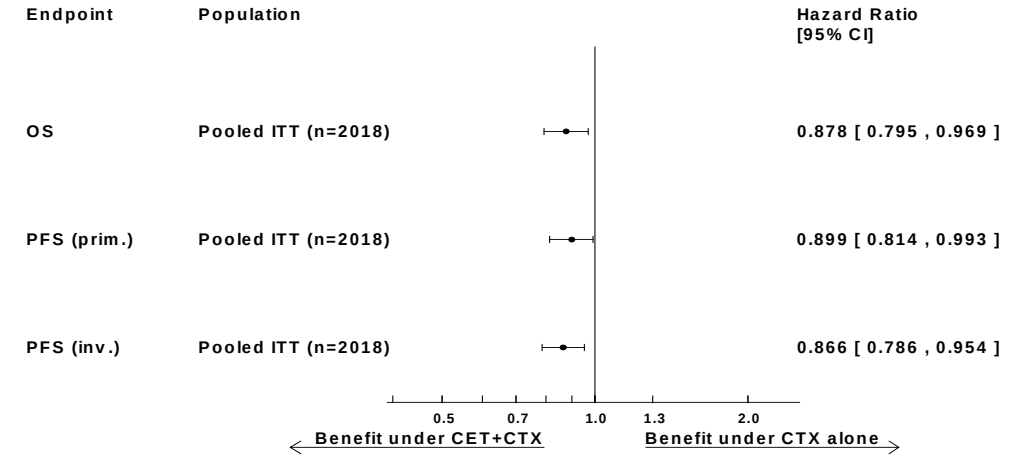
Efficacy variable / statistic	EMR 62 202-046			
	ITT Population		Caucasian	
	Cet + CTX N=557	CTX N=568	Cet + CTX N=466	CTX N=480
Median OS time, months [a]	11.3	10.1	10.5	9.1
p-value (stratified log-rank test)	0.044		0.003	
Hazard ratio	0.87		0.80	
Median PFS time, months	4.8	4.8	4.7	4.4
p-value (stratified log-rank test)	0.387		0.345	
Hazard ratio	0.94		0.93	
Median TTF, months	4.2	3.7	4.2	3.3
p-value (stratified log-rank test)	0.015		0.010	
Hazard ratio	0.86		0.84	
ORR, % patients	36.4	29.2	34.8	26.3
p-value (CMH test)	0.010		0.004	
Odds ratio	1.39		1.51	

While being reasonable, the outcome in Caucasians still refers to an analysis for which no alpha spending was foreseen. The difference at the median tends to underestimate the treatment effect. Post study anti-cancer therapy is considered unlikely to contribute to observed difference in OS.

Pooled efficacy analysis

In order to further confirm the robustness of the add-on efficacy and to receive a more precise estimate of the overall treatment effect of cetuximab to standard CTX a pooled efficacy analysis on raw data was performed based on the 4 randomized clinical studies with comparable study populations and treatment regimens.

Forest Plot of Results for OS time and PFS time



prim. = primary definition

inv. = investigator assessment

P-values <0.05 were obtained for all endpoints: OS p=0.010, PFS p=0.036, and ORR p<0.001.

A high unmet medical need remains in the treatment of advanced or metastatic NSCLC, because only limited improvements in OS were achieved with new treatments, in particular in patients with NSCLC other than predominantly adenocarcinoma. Therefore, the MAH has analyzed the efficacy of cetuximab treatment in the subgroups of NSCLC patients with adenocarcinoma and with non-adenocarcinoma.

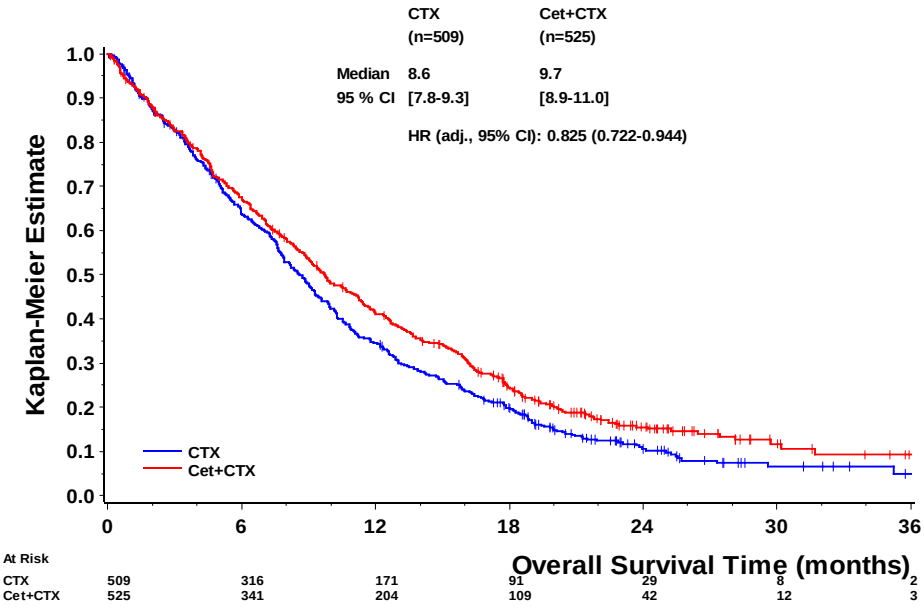
Pooled Efficacy Analysis by Histological Subgroup

Efficacy variable / statistic	ITT		Adenocarcinoma		Non-adenocarcinoma[a]	
	Cet + CTX N=1003	CTX N=1015	Cet + CTX N=478	CTX N=506	Cet + CTX N=525	CTX N=509
OS time						
Hazard ratio	0.878		0.935		0.825	
95 % CI	0.795-0.969		0.808-1.082		0.722-0.944	
p-value	0.010		0.366		0.005	
PFS time						
Hazard ratio	0.899		0.900		0.891	
95 % CI	0.814-0.993		0.780-1.039		0.776-1.023	
p-value	0.036		0.150		0.101	
ORR						
Odds ratio	1.463		1.583		1.368	
95 % CI	1.201-1.783		1.186-2.113		1.042-1.794	
p-value	<0.001		0.002		0.023	

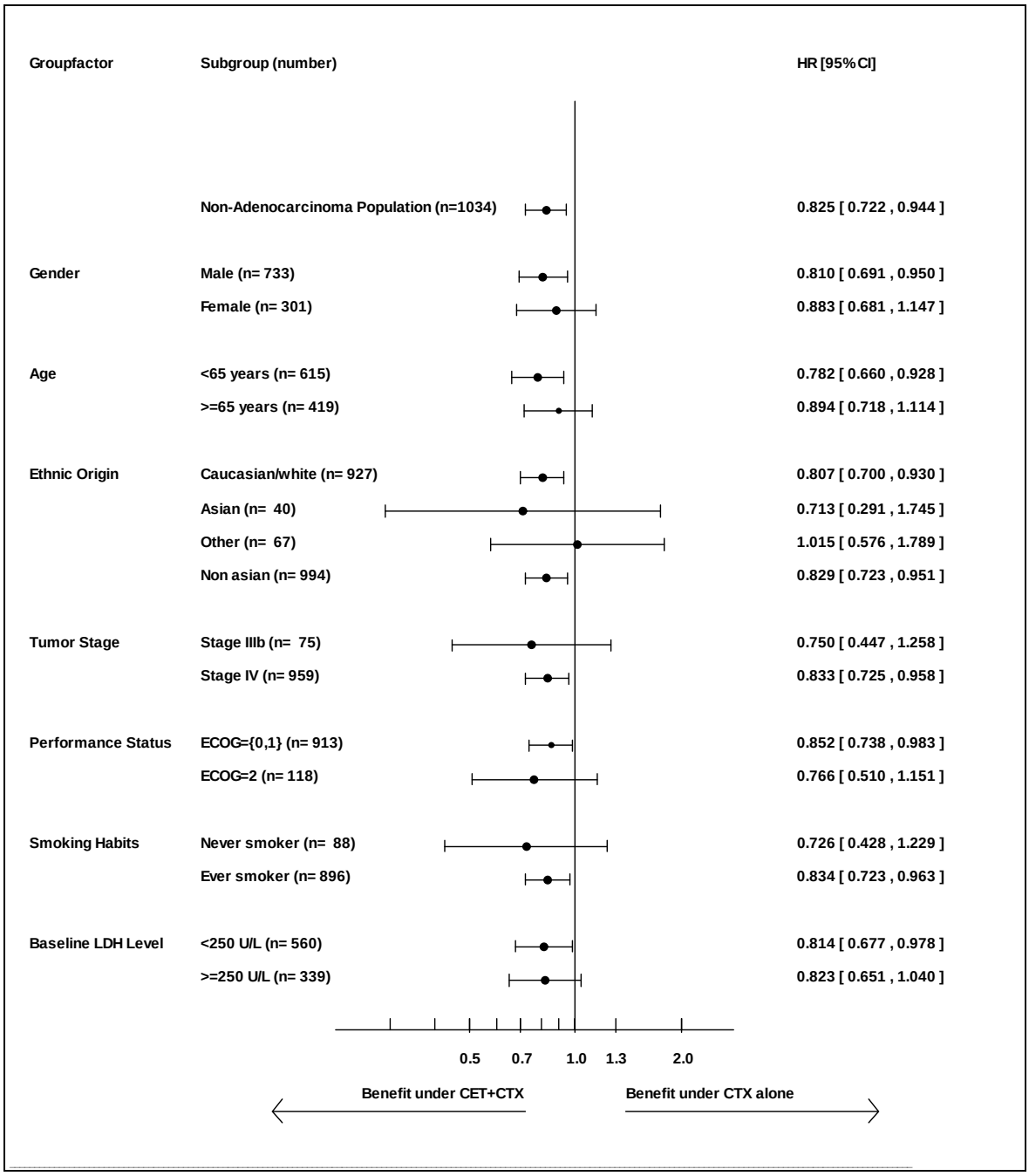
[a] Non-adenocarcinoma includes squamous cell carcinoma, adenosquamous carcinoma and other histologies

Cet=cetuximab, CTX=platinum-based chemotherapy, ITT=intent to treat, CI=confidence interval, OS=overall survival, PFS=progression-free survival, ORR=objective response rate

Kaplan-Meier Plot for OS time, Pooled Non-Adenocarcinoma Population



Forest Plot of OS Results by Subgroups in Patients with Non-Adenocarcinoma



2.3. Safety Reanalysis

In order to evaluate the risk-benefit of cetuximab in patients with non-adenocarcinoma, safety data were compared between the non-adenocarcinoma population (N=1012) and the safety population (N=1970). The safety analyses presented here focus on a comparison of all AEs, grade 3/4 AEs, grade 4 AEs, SAEs, AEs of particular relevance (special AE categories, infectious complications), and deaths, in patients with non-adenocarcinoma and the safety population.
Overall the safety profile of cetuximab in the non-adenocarcinoma population was comparable to the safety profile in the safety population.

Comparison of AE frequencies (any grade, grade 3 and 4, grade 4 and serious AEs)

An overview of frequencies of AEs, grade 3 and grade 4 AEs, grade 4 AEs, and SAEs, in the safety population compared to the non-adenocarcinoma population by treatment group is shown in the following table.

Overview of Adverse Event Frequencies by Treatment Group and Histological Subgroup

Nature of adverse event	Safety population (% patients)		Non adenocarcinoma population (% patients)	
	Cetuximab + CTX (N=979)	CTX (N=991)	Cetuximab + CTX (N=513)	CTX (N=499)
Any adverse event	974 (99.5)	975 (98.4)	510 (99.4)	489 (98.0)
Grade 3 or 4 adverse events	837 (85.5)	749 (75.6)	437 (85.2)	375 (75.2)
Grade 4 adverse events	476 (48.6)	402 (40.6)	241 (47.0)	194 (38.9)
Any serious adverse event	556 (56.8)	409 (41.3)	288 (56.1)	203 (40.7)

Key safety parameters remain unchanged in the non-adenocarcinoma histological subgroup compared to the overall safety population.
The difference between treatment groups in terms of SAEs (approx. 15 %), grade 3/4 AEs (approx. 10 %), and grade 4 AEs (approx. 8 %) that was observed in the safety population remained unchanged in the non-adenocarcinoma population. These increases are attributable to side effects that are in line with the well-characterized safety profile of cetuximab and are manageable and did not result in more treatment-related deaths.
It is agreed that the overall safety profile is unaffected by the underlying NSCLC histology. This is not too surprising. The difference between CTX and CTX+ cetuximab with respect to grade 4 events and SAEs is clearly non-trivial.

Differences in SAEs and grade 4 AEs

In all 4 studies, AEs were routinely analyzed from the first day of any study treatment administration until 30 days (42 days for EMR 62202-011) after the last infusion of any study treatment. As a consequence the average observation period was longer for cetuximab + CTX compared to CTX alone due to subjects who continued on cetuximab therapy (median of 6 to11 weeks) after the end of CTX.
Previous analysis on any SAEs and grade 4 AEs did not take into account the different observation periods. The combined frequencies of subjects with SAEs and grade 4 AEs in all 4 randomized controlled studies were 56.8% (556/979) and 48.6% (476/979) for cetuximab + CTX and 41.3% (409/991) and 40.6% (402/991) for CTX alone resulting in a difference of 15.5% and 8.0%, respectively.

Adverse Events During the CTX Phase[1] (all 4 Studies)

	Number of subjects		
	Cet + CTX	**CTX**	**Difference**
	N=975[2] (100%)	N=991 (100%)	
SAEs	487 (49.9%)	386 (39.0%)	10.9%
grade 4 AEs	427 (43.8%)	379 (38.2%)	5.6%

[1] The CTX phase lasts from the first administration of any study treatment until the end of CTX. The latter is defined as EMR 62202-046 + EMR 62202-011: max {date of last dose of cisplatin + 20, date of last dose of vinorelbine + 13},CA225099: max {date of last dose of taxane + 20, date of last dose of carboplatin + 20},CA225100: max {date of last dose of platinum + 20, date of first dose of gemcitabine in last cycle + 20}

[2] subjectx in the cetuximab who have only received cetuximab and no CTX are not included (4 subjects in EMR 62202-046)

Cet=cetuximab, CTX=platinum-based chemotherapy

Assessing comparable observation periods reduced the difference between treatment arms from 15.5% to 10.9% in SAEs and form 8.0% to 5.6% in grade 4 AEs.

The increase in serious adverse events in the cetuximab arms is considered non-trivial. In study 62 202-046 at least one SAE was reported by 56% vs. 42% of the patients.

Febrile neutropenia	18%	12%
Gastrointestinal SAEs	7%	5%
General physical health deterioration	3.5%	0.7%
"Metabolism and nutrition" (mainly dehydration)	5%	2%

In terms of deaths (up to 30 days after the end of therapy) a higher rate was reported for the cetuximab + CTX group which can be explained by the longer observation period. When standardizing for similar observation periods the number of deaths was comparable (12.9% vs 11.6%). Moreover treatment-related deaths were low and comparable between cetuximab + CTX and CTX alone (1.4% and 1.2%, respectively). As expected the SAEs and grade 4 AEs were in line with the well established safety profile. The SAEs and grade 4 AEs were manageable and did not result in more treatment-related deaths.

Overview of the Primary Reasons for Death: CTX phase

Primary reason for death	**No. (%) of patients who died**			
	Safety population		**Non-adenocarcinoma population**	
	Up to 30 days after last dose of CTX			
	Cetuximab + CTX	**CTX**	**Cetuximab + CTX**	**CTX**
	N=979	N=991	N=513	N=499
All reasons	126 (12.9)	115 (11.6)	76 (14.8)	64 (12.8)
Tumor-related [a]	80 (8.2)	76 (7.7)	47 (9.2)	40 (8.0)
Other [b]	32 (3.3)	27 (2.7)	21 (4.1)	14 (2.8)
CTX-related	14 (1.4)	12 (1.2)	8 (1.6)	10 (2.0)
Cetuximab-related [c]	-	-	-	-

[a] EMR 62 202-046 + EMR 62202-011: Disease progression or disease-related complications;

CA225099 + CA225100: tumor-related disease

[b] EMR 62 202-046 + EMR 62202-011: Intercurrent or unrelated illness or event or unknown;

CA225099 + CA225100: other or unknown

Adverse events of special interest in NSCLC Patients

Infectious complications with focus on grade 3 and 4 and serious AEs

In the 4 randomized controlled studies 224 subjects in the cetuximab + CTX groups experienced at least one severe infectious complication (defined as febrile neutropenia, pneumonia or septic event)

compared to 163 subjects in the CTX group. 22/224 (9.8%) subjects in the cetuximab + CTX group and 13/163 (8.0%) subjects in the CTX group have a reported outcome of death, respectively.

Subjects with Severe Infectious Complications and Reported Outcome Death up to 30 days After last Study Treatment – Classification by Primary Reason for Death

Number of subjects based on combined safety population (Cet + CTX: 979, CTX: 991)							
Death within 30 days after last treatment							
Any primary reason		**Primary reason: treatment related** [a]		**Primary reason: tumor related** [b]		**Primary reason: other** [c]	
Cet+CTX	**CTX**	**Cet+CTX**	**CTX**	**Cet+CTX**	**CTX**	**Cet+CTX**	**CTX**
22	**13**	**11**	**9**	**9**	**2**	**2**	**2**

[a] EMR 62202-046 + EMR 62202-011: Events related to chemotherapy or to cetuximab, CA225099: Study drug toxicity.

[b] EMR 62202-046 + EMR 62202-011: Disease progression or Disease-related complications, CA225099: Tumor-related disease

[c] EMR 62202-046 + EMR 62202-011: Intercurrent or unrelated illness or event or Unknown, CA225099: Other or Unknown.

Cet=cetuximab, CTX=platinum-based chemotherapy

Thromboembolic complications

The combined analysis of all 4 studies revealed a higher frequency of grade 3 and 4 events for cetuximab + CTX (6.8%; 67/979) compared to CTX alone (4.8%; 48/991). The most frequent events were pulmonary embolism (3.4%; 33/979 for cetuximab + CTX and 2.3%; 23/991 for CTX alone); and deep vein thrombosis (2.2%; 22/979 in the cetuximab + CTX group and 1.5%; 15/991 for the CTX alone group).

Thromboembolic events are listed, but a 2% absolute increase is of clinical relevance.

Incidence of cardiac events in patients with cardiac history and patients of over 65 years of age

In an additional safety analysis a higher Incidence of cardiac events in elderly patients with cardiac history was observed. No differences by age seen in acne like rash, infusion related reactions, mucositis, hemorrhage, thromboembolic events and septic events

Cardiac events	**< 65 years**		**≥ 65 years**	
	Grade 3/4	Grade 4	Grade 3/4	Grade 4
Without Cardiac history	3.0% vs. 3.3%	1.6% vs. 1.5%	7.1% vs. 4.5%	3.5% vs. 3.4%
Difference	-0.3%	0.1%	2.6%	0.1%
With Cardiac history	3.2% vs. 4.8%	1.6% vs. 2.4%	11.7% vs. 4.8%	9.2% vs. 2.7%
Difference	-1.6%	-0.8%	6.9%	6.5%

2.4. Overall benefit risk and grounds for refusal of the variation.

Platinum-based doublets have for long been considered standard therapy in patients with advanced NSCLC. Recently, however, bevacizumab was licensed as add-on therapy in patients with non-squamous NSCLC.

Large confirmatory studies have been conducted with erlotinib and gefitinib (EGFR tyrosine kinase inhibitors) as add-on to platinum based regimens without any discernable add-on activity in an unselected population.

This submission refers to the use of cetuximab as add-on to standard platinum based doublets. In the largest trial (FLEX) designed to demonstrate a survival benefit of cetuximab add-on, a small (HR 0.87) but borderline significant (p=0.044) effect was shown. Post hoc, an analysis excluding Asians due to their today well known and well characterised different tumour biology on a group level resulted in a p-value of 0.003. In a pooled analysis of all studies and including all patients the p-value was 0.010.

Study CA225099 was designed to show a Progression-free survival (PFS) benefit and was the only study with independent verification of tumour progression. Based on independent review this study failed to meet its objectives (p=0.24), but results were statistically significant based on investigator data and in a post hoc time to treatment failure analysis. None of the other studies showed a statistically significant effect. In a pooled analysis the results were borderline significant (0.036).

An increased response rate has been convincingly demonstrated in the individual studies, including CA225099, i.e. the study with independent verification.

The documented patient benefit in terms of survival is small, HR 0.88 corresponding to a median benefit of 1+ months (pooled analysis). The most favourable results were those in Caucasians in the FLEX study (HR 0.80 corresponding to 2 months median benefit, estimated from the HR). Due to the uncertainties with respect to PFS as discussed above, PFS benefit is hard to estimate.

A proposed restriction to patients with NSCLC with non-adenocarcinoma histology was discussed. In this subgroup, survival results are borderline better (HR 0.83 vs. 0.94) while PFS is very similar (HR 0.89 vs. 0.90), i.e. non-convincing with respect to differential activity. However, there is no licensed product which has shown an add-on survival benefit to standard therapy in this group of patients.

The tolerability/toxicity profile of cetuximab is considered relatively well characterised also as add-on to various chemotherapy regimens. Very common and common adverse reactions of importance for tolerability encompass skin reactions, diarrhoea, mucositis, nausea, fatigue, etc. Less common, but severe and serious reactions include neutropenic fever and other infectious complications, thromboembolic complications, cardiac events, dehydration and severe infusion related reactions which may be fatal.

Despite a large and comprehensive studies programme investigating the add-on use of cetuximab to standard platinum-based doublets in the first-line treatment of patients with NSCLC, the documented benefit is considered borderline and appears not to outweigh the risk.

During the SAG oncology meeting, there was a split view among oncologists as to the magnitude of the clinical benefit. The field of treatment of NSCLC is characterised by small steps towards improved efficacy and moreover cetuximab exhibited add-on effects on survival in patients with tumours of non-adenocarcinoma histology. The documented survival benefit is undoubtedly small, but the risk associated with the add-on use of cetuximab is well characterised, i.e. can and should influence the decision whether to treat or not an individual patient with cetuximab. Unfortunately biomarkers or clinical characteristics (other than those generally applicable) cannot be used to guide this decision.

Rash (and probably diarrhoea) is a very common and often disturbing side effect of cetuximab, but associated with a favourable outcome. As it is an on-treatment effect, it cannot be stated that it is predictive of benefit of therapy, but it is a good prognostic sign. This is of some importance for the individual patient on therapy experiencing these side effects.

Incidence of grade 3/4 cardiac events on cetuximab treatment is increased in patients $\geq$ 65 years with cardiac history in NSCLC patients. The issue should be further investigated across indications.

In conclusion, in the presented trials the estimated benefit of add-on cetuximab to standard chemotherapy in terms of survival is considered modest (HR 0.88) and statistically non-compelling in the light of non-convincing effects in terms of PFS. Documented benefits are not considered to

outweigh the tolerability and safety concerns, including an increased risk for grade 4 AE:s and SAE:s in studies CA225099 and EMR 62202-046.

Despite a large and comprehensive studies programme investigating the add-on use of cetuximab to standard platinum-based doublets in the first-line treatment of patients with NSCLC, the documented benefit is borderline statistically and clinically and does not outweigh the risks.

Therefore, the Benefit – risk ratio of Erbitux in the indication of:

> "first-line treatment of patients with epidermal growth factor receptor (EGFR)-expressing advanced or metastatic non-small cell lung cancer in combination with platinum-based chemotherapy"

is considered negative.

Some members of the CHMP expressed a divergent position as follows:

> Although very modest in absolute terms, the effect on Overall survival is a very relevant effect in relative terms due to the short survival, and is similar to incremental improvement achieved with other agents in NSCLC.
>
> The lack of convincing supportive data in terms of PFS was considered not to be critical because the overall pattern was generally consistent with OS in terms of a favourable treatment effect.
>
> There is an unmet medical need particularly in patients with tumors of non-adenocarcinoma histology.
>
> The added toxicity was of some concern but it was considered manageable and in the overall balance did not outweigh the benefits in a condition where there are only few treatments with an effect on OS.

3. Re-Examination procedure

The Applicant in response to CHMP negative opinion requested a re-examination on grounds of safety and efficacy as analysed below

3. 1. Grounds for re-examination – Safety aspects

The major concern of the CHMP seemed to be that the modest benefit of erbitux was likely to be outweighed by the non-trivial side-effects of the treatment.

The CHMP regarded the risk associated with the add-on use of cetuximab as well characterized. However, the CHMP considered the documented benefits of adding cetuximab to platinum-based chemotherapy not to outweigh the tolerability and safety concerns, including an increased risk for grade 4 AEs and SAEs. In addition it was noticed that the Kaplan-Meier survival curves, particularly for study EMR 62 202-046, did not separate during the first 6 months of treatment. One possible explanation was that early treatment benefit might be balanced by toxic deaths during the CTX phase.

The MAH presented further analyses to support that the add-on toxicity of cetuximab when added to CTX is clearly reduced in patients <65 years compared to patients ≥65 years and compared to the overall safety population in NSCLC. Importantly, in patients <65 years the addition of cetuximab to CTX increased the rate of grade 4 AEs only by 3.8% compared to 14.7% in patients ≥65 years. This difference is also reflected in the rate of AEs leading to deaths: In patients <65 years with cetuximab + CTX the rate of AEs reported with outcome deaths was only marginally increased compared to CTX (0.4%) whereas in patients ≥65 years this rate was increased by 9.9%. The same trend was also observed for grade 3/4 toxicities and for SAEs (grade 3/4 AEs increase of 7.4% in patients <65 years vs. 13.7% in patients >65 years; SAEs increase of 13.1% in patients <65 years vs. 19.6% in patients

≥65 years). The improved safety profile of cetuximab in combination with CTX in patients <65years is also seen in the histological subgroup of non-adenocarcinoma NSCLC. In the population ≥65 years the most important finding was the increased incidence of cardiac events (grade 3/4, grade 4 and SAE) in the cetuximab + CTX group particularly in patients with cardiac history. Cardiac events accounted for about half of the additional AEs with reported outcome death in the cetuximab + CTX group.

The MAH concluded that the safety profile of cetuximab + CTX in patients <65 years is improved compared to the safety population.

The Applicant has now made a considerable effort to document that the Erbitux has a more favourable safety profile in patients with NSCLC under the age of 65 years which is not surprising. According to the presented data the add-on therapy has been poorly tolerated in the elderly, more frail patients (with more co-morbidities) who have experienced more SAEs, grade 3 and 4 toxicities and deaths in the pooled safety evaluation. It has been documented that the effect of add-on therapy with Erbitux in patients aged ≥ 65 years is diluted by the higher risk of death due to AEs in this subpopulation.

Importantly, an increased incidence of *cardiac events* has been identified in the cetuximab + CTX group in patients aged ≥ 65 year, particularly in high-risk patients with a cardiac history. It is recommended that the Applicant should undertake an investigation of this safety signal in all indications approved or under investigation.

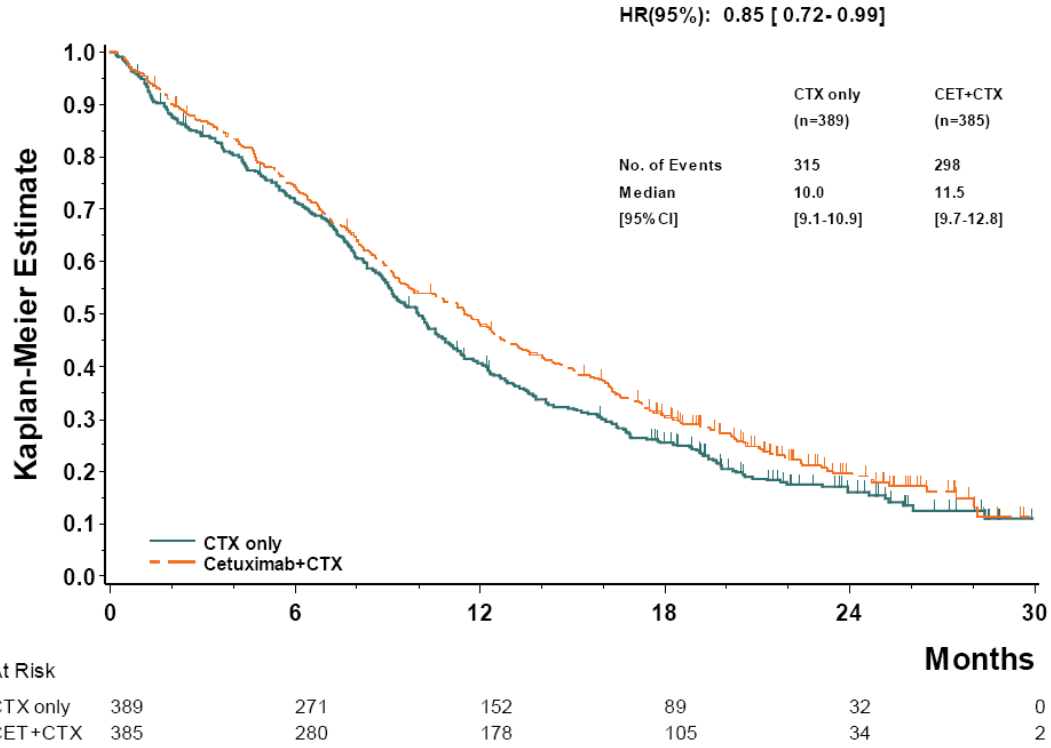
Interestingly, the Applicant has also explored the safety profile of Erbitux in the important subgroup of patients with non-adenocarcinoma, and the safety findings in this subpopulation seems consistent with the safety profile in the overall population and as such independent of the histological tumour subtype.

Although these are post-hoc analyses, the study protocol for Erbitux in NSCLC pre-specified the two subpopulations by age (< or ≥ 65 years). Furthermore, the Applicant has used a Cox proportional hazard model with 3 age levels to support the use of 65 years as the most appropriate age cutpoint.
The difference between the 2 age groups is that for those ≥65 years an increased number of deaths occurred within the first few months of the trial with multiple causes and about half being preceded by a cardiac AE. These early deaths affected the Kaplan-Meier survival curves particularly for study EMR 62 202-046. However, whether this observation was a chance finding or indeed reflects some add-on toxicity from cetuximab, needs to be clarified by the MAH and clarification of this point is central to the validity of the sub-group analysis in support of an improved benefit:risk balance as proposed by the MAH for those <65 years and the need for further safety assessment of cetuximab in licensed indications for those >65 years.

3. 2 Grounds for re-examination – Efficacy aspects

Results in Patients <65 Years
In the pivotal study EMR 62 202-046 the OS benefit (primary endpoint) in the patient population <65 years for cetuximab + CTX vs. CTX is seen early as the Kaplan-Maier curves separate from the start, with a median OS benefit of 1.5 months (*see Figure 10*). This difference in median OS (11.5 vs. 10.0 months) was greater compared to 1.2 months for the ITT population (11.3 vs. 10.1 months). The 1-year survival rate for patients <65 years was also more improved compared to the ITT population (difference of 7% vs. 5.1%). In patients <65 years the HR for OS was 0.85 [95% CI: 0.72-0.99; p=0.043] reflecting improvement in survival by 18% in the cetuximab + CTX group compared to the CTX group, which is also an improvement when compared to the ITT population (HR 0.87).

Figure 10 **OS time: EMR 62 202-046, ITT Population <65 years**



The increased OS benefit for cetuximab + CTX is further confirmed in the pooled analysis including all 4 randomized, controlled studies for the ITT population <65 years. The early separation of the Kaplan-Meier curves is also observed for the pooled population. In contrast, in the study CA225099, the improved safety in patients <65 years does not translate in an improvement in median OS (secondary endpoint) and HR in patients <65 years.

Efficacy results are summarized for the ITT population <65 years in *Table 12*.

Table 12 **Efficacy Results in Study EMR 62 202-046, Pooled Analysis and CA225099 (ITT Population, <65 years)**

	OS		PFS		TTF*	
	Median	**HR**	**Median**	**HR**	**Median**	**HR**
EMR 62 202-046 (n=774 of 1125)	11.5 [9.7-12.8] vs. 10.0 [9.1-10.9]	0.85 [0.72, 0.99]	4.9 [4.2- 5.4] vs. 4.9 [4.3- 5.4]	0.91 [0.78, 1.07]	4.3 [4.2- 4.9] vs. 3.7 [3.1- 4.2]	0.83 [0.72-0.97]
Pooled analysis (n=1247 of 2018)	10.8 [9.5-11.8] vs. 9.5 [8.9-10.3]	0.86 [0.76, 0.97]	4.7 [4.3- 5.2] vs. 4.4 [4.2- 5.1]	0.87 [0.77, 0.98]	4.2 [4.1- 4.4] vs. 3.4 [3.0- 3.9]	0.78 [0.69-0.88]
CA225099 (n= 336 of 676)	9.7 [7.7-11.6] vs. 9.2 [7.2-10.9]	0.92 [0.73, 1.17]	4.2 [3.9- 5.0] vs. 4.2 [3.6- 4.9]	0.94 [0.74, 1.19]	4.0 [3.3- 4.2] vs. 2.8 [2.6- 3.4]	0.71 [0.57-0.88]

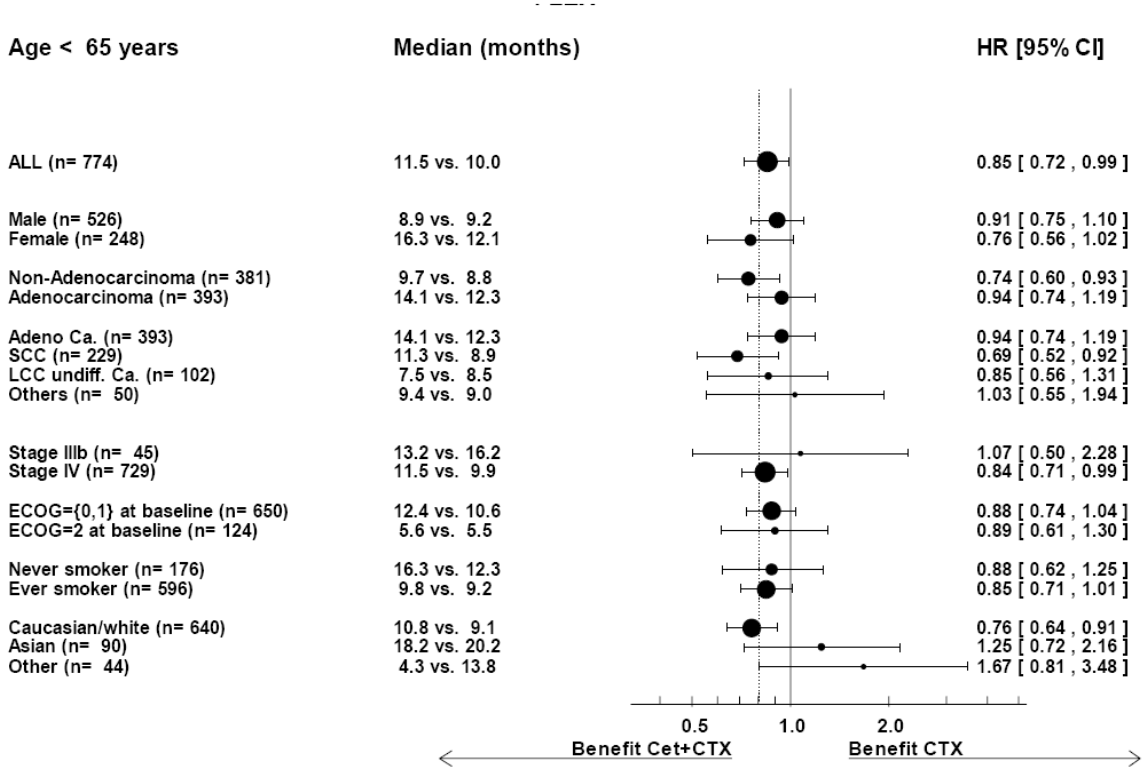
OS=overall survival, PFS=progression-free survival, TTF=time to treatment failure

* For TTF only studies EMR 62 202-046 + CA 225099 were included in the pooled analysis

Time to treatment failure
More patients in the CTX group in study EMR 62 202-046 (ITT population) went off study without image based PD and were therefore censored (18% vs. 24%). The time to treatment failure was therefore calculated as a post-hoc sensitivity analysis, also taking into account events which were considered signs of clinical progression (non-image-proven PD and start of any new anti-cancer treatment). TTF in patients <65 years was significantly prolonged favouring the cetuximab + CTX group (HR 0.83 [95% CI: 0.72-0.97], p=0.02, (*see Table 12*). TTF was also improved in CA225099 and pooled analysis.

Subgroup analyses
The results of subgroup analyses of OS time in the ITT population <65 years (EMR 62 202-046) are summarized in *Figure 11*.

Figure 11 **OS time: EMR 62 202-046, ITT Population, <65 years**



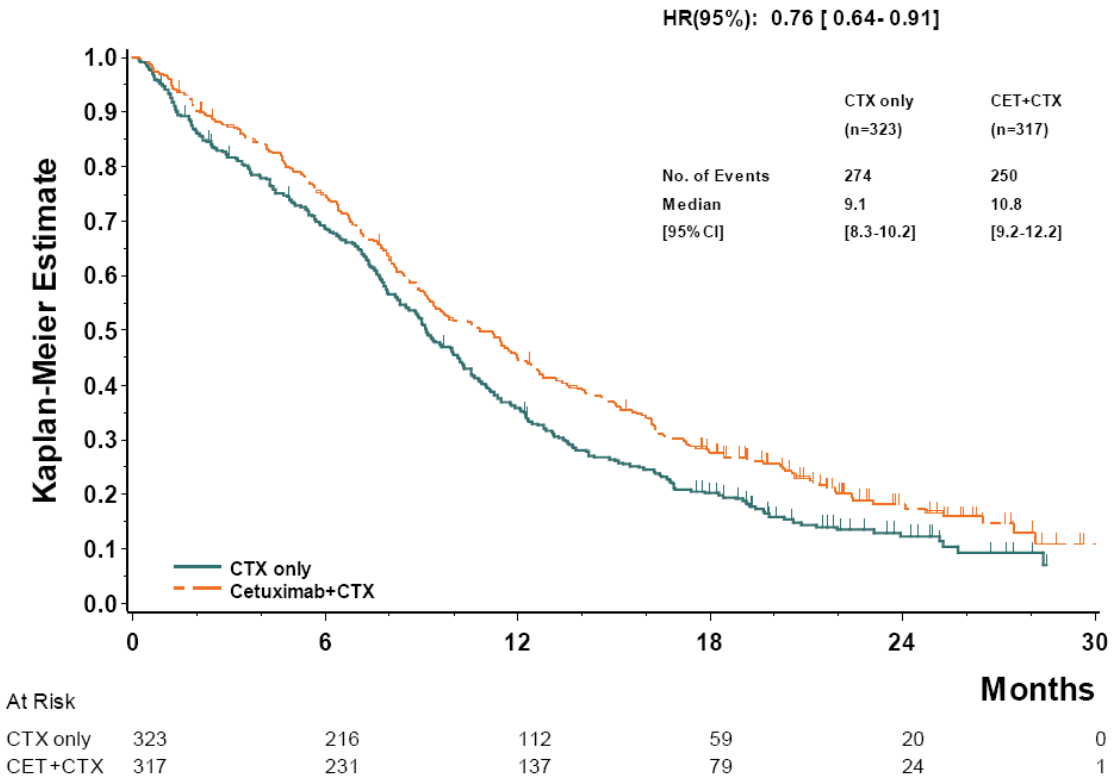
The forest plot demonstrates that the addition of cetuximab to CTX was generally associated with benefit over CTX alone in terms of OS time in the ITT population <65 years but not for the Asian population (*see Figure 11*). This was further supported in the pooled analysis. Subgroup analyses of the treatment effect showed advantages in terms of OS favouring cetuximab + CTX compared to CTX in all histological subtypes.

Caucasian patients <65 years
In the overall ITT population the most favourable results were those for Caucasians in study EMR 62 202-046 with a p-value of 0.003 (HR 0.8 corresponding to 2 months median benefit, calculated from the HR). In this context the CHMP acknowledged that the Asian patients are different due to their today well known and well characterized different tumor biology. Therefore the Caucasian population better reflects the patients treated mainly in Europe than the overall ITT population. For Caucasian patients <65 years the combination of cetuximab+CTX demonstrated a significant median OS benefit of 1.7 months (10.8 vs. 9.1 months, HR 0.76) in the pivotal study EMR 62 202-046. Calculating the

corresponding benefit to the HR of 0.76 [95% CI: 0.64-0.91] in this population the median OS benefit is 2.9 months.

The Kaplan-Meier curve for Caucasian patients < 65 years is shown in *Figure 12.*

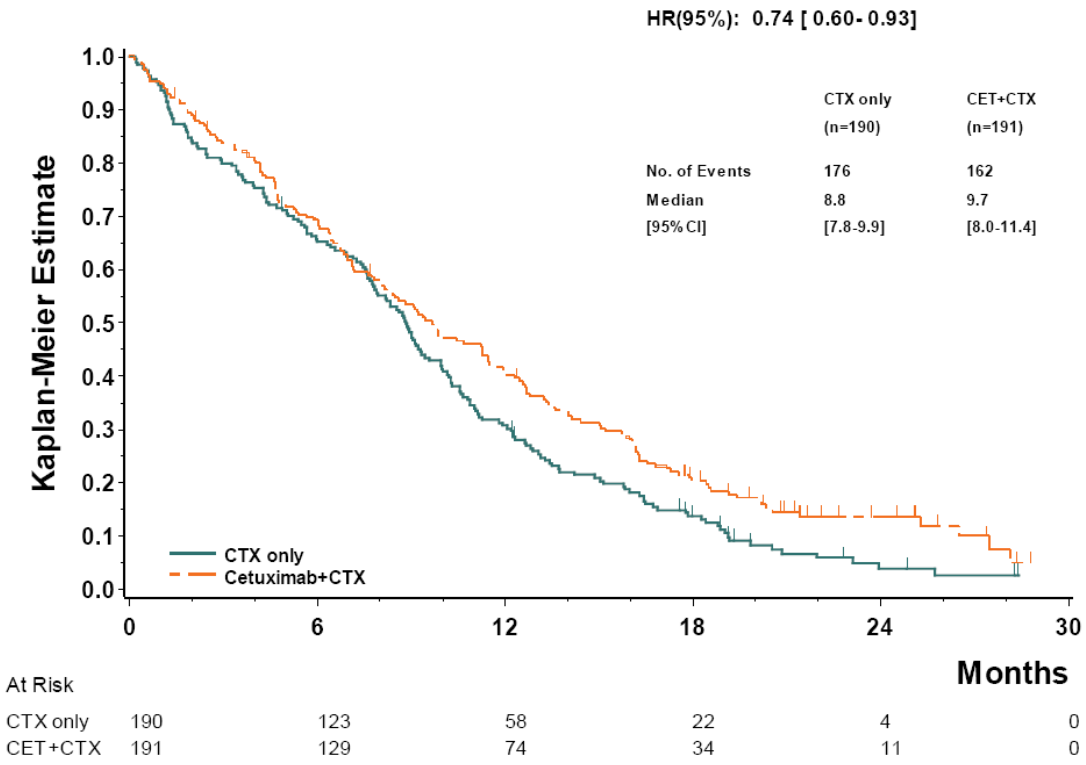
Figure 12 OS time: EMR 62 202-046, Caucasian Population, <65 years



Results for Non-Adenocarcinoma <65 years

Recent progress has been made in particular in adenocarcinoma in the treatment of advanced or metastatic NSCLC, whereas improvements in terms of survival have not been achieved in the last decade for the treatment of non-adenocarcinoma. Therefore a high unmet medical need remains, especially in patients with advanced or metastatic NSCLC other than adenocarcinoma. The increased benefit in NSCLC patients with non-adenocarcinoma histology was acknowledged by the CHMP, and it was pointed out that cetuximab is unique among licensed products as a treatment option for tumors of non-adenocarcinoma histology, with documented add-on effects on survival. Therefore, the sponsor has analyzed the efficacy of cetuximab treatment in the subgroup of NSCLC patients with non-adenocarcinoma. In study EMR 62 202-046 the OS and PFS benefit for patients <65 years in the non-adenocarcinoma histology with cetuximab + CTX was further improved (OS: HR: 0.74 [95% CI: 0.60-0.93], PFS: HR: 0.79 [95% CI: 0.63-0.99]) when compared to the ITT population (*see Figure 13*). Of note, the OS curve separates early indicating an add-on benefit of cetuximab during the CTX phase.

Figure 13 **OS time: EMR 62 202-046, Non-adenocarcinoma population, <65 years**



For the non-adenocarcinoma population <65 years the pooled analysis as well as the other studies support the results observed in study EMR 62 202-046 in terms of OS.

Efficacy results are summarized for the non-adenocarcinoma population <65 years in *Table 13*.

Table 13 **Efficacy Results in Study EMR 62 202-046, Pooled Analysis and CA225099 (Non-Adenocarcinoma Population, <65 years)**

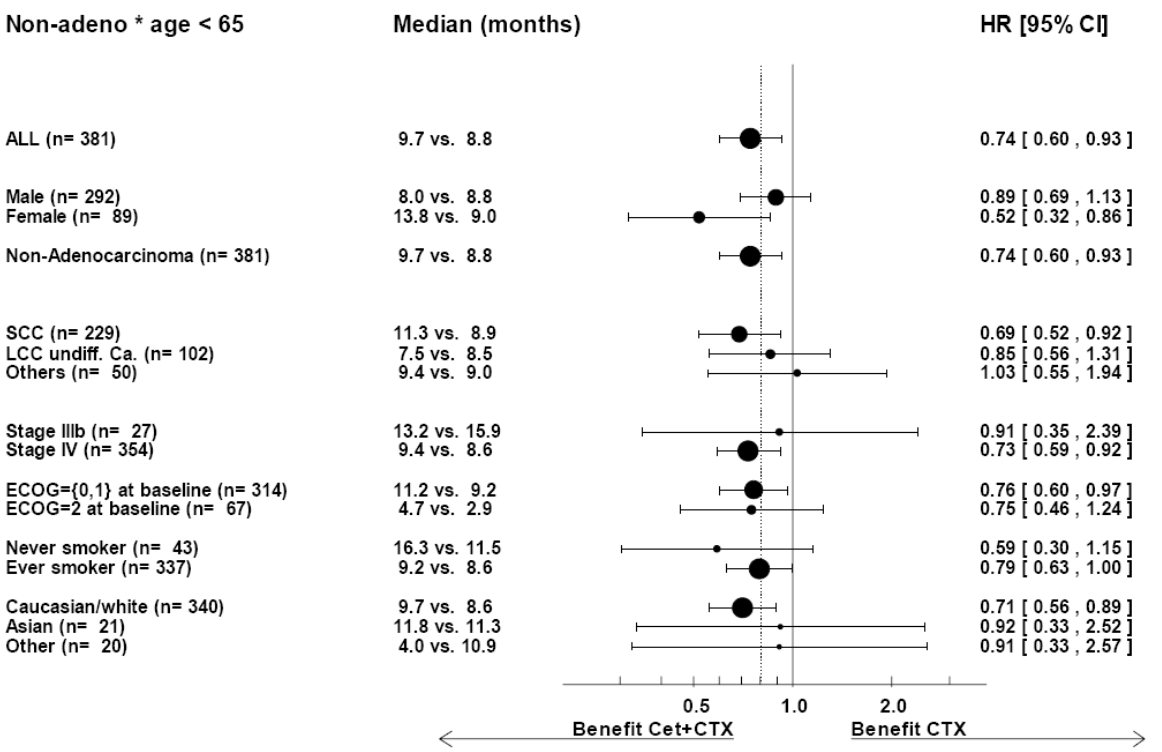
	OS		PFS		TTF*	
	Median	**HR**	**Median**	**HR**	**Median**	**HR**
EMR 62 202-046 (n=381 of 1125)	9.7 [8.0-11.4] vs. 8.8 [7.8- 9.9]	0.74 [0.0.60, 0.93]	4.2 [4.1- 5.2] vs. 4.2 [3.5- 4.4]	0.79 [0.63, 0.99]	4.2 [3.8- 4.4] vs. 3.4 [2.9- 4.1]	0.75 [0.61-0.93]
Pooled analysis (n=615 of 2018)	9.5 [8.4-10.6] vs. 8.8 [7.7- 9.4]	0.78 [0.66, 0.93]	4.4 [4.2- 5.0] vs. 4.1 [3.5- 4.2]	0.78 [0.65, 0.93]	4.1 [3.6- 4.2] vs. 3.2 [2.9- 3.7]	0.74 [0.62-0.88]
CA225099 (n= 158 of 676)	8.7 [7.3-11.2] vs. 8.9 [5.5-11.1]	0.85 [0.61, 1.19]	4.4 [3.2- 5.4] vs. 3.8[2.8- 4.2]	0.76 [0.55, 1.07]	3.5 [2.8- 4.2] vs. 2.8 [1.8- 3.6]	0.67 [0.49-0.93]

OS=overall survival, PFS=progression-free survival, TTF=time to treatment failure

* For TTF only studies EMR 62 202-046 + CA 225099 were included in the pooled analysis

Subgroup analysis
The results of subgroup analyses of OS time in the non-adenocarcinoma population <65 years are summarized in *Figure 14*.

Figure 14 **OS time: EMR 62 202-046, Non-adenocarcinoma Population, <65 years**



OS benefits seen in patients with non-adenocarcinoma and age <65 years were consistent across subgroups supporting the main survival findings.

Quality of Life
Quality of life (QoL) was assessed in study EMR 62 202-046 by means of EORTC QLQC30 Global Health Status. The assessment concluded that no significant differences in the QoL score between the treatment groups was observed during the period of the first 6 months after randomization.

In accordance with the safety and efficacy analyses performed in different subgroups, additional QoL analyses were performed for the following subgroups: ITT; age < 65years; age ≥65years; non-adenocarcinoma and age < 65years. It was planned to also carry out an analysis on the subgroup: non-adenocarcinoma and age ≥65 years. However, there were not sufficient subjects with QL data in this subgroup to perform the analysis. The analyses were performed on the multi-item scales from the EORTC QLQ-C30, (i.e. the global health status\QL scale, the functional scales: physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, three symptom scales: fatigue, nausea and vomiting, pain) and the Dyspnoea scale from the EORTC QLQ-LC13.
Overall in patients <65 years the treatment differences were smaller than in the original study, indicating less impact on all 3 scales at cycle 3 by cetuximab + CTX. The subset analyses suggested that the subset ≥65 years showed the largest differences between treatment groups in favour of CTX alone. In patients <65 years with non-adenocarcinoma the results were comparable to the total patient population <65 years.

Efficacy Conclusions

The primary endpoint OS shows a median of 1.5 months improvement. The most favourable results were those seen in the Caucasian patients with an OS HR of 0.76 corresponding to 2.9 months median benefit estimated from the HR in EMR 62 202-046. Due to the differences in Asian patients, the Caucasian population better reflects the patients treated mainly in Europe. While improved safety in patients <65 years does not translate in study CA225099 in an improvement in median OS and HR in patients <65 years the Kaplan-Meier curve for patients <65 years separate early supporting the findings of study EMR 62 202-046. In the non-adenocarcinoma population <65 years the findings of study CA225099 were consistent with those of study EMR 62 202-046. Most importantly the early separation of the Kaplan-Meier curves was consistent for overall survival in the pivotal study EMR 62 202-046 and the supportive study CA225099 demonstrating a benefit for patients <65 years treated with cetuximab + CTX compared to CTX alone from start of treatment onwards supporting the concept of reducing early death in the cetuximab + CTX group.

Post-hoc subgroup analyses were conducted with the aim of improving the benefit-risk profile in an identified sub-population, primarily by reducing the number of early, serious adverse events which it is speculated had a detrimental effect on OS. Post-hoc subgroup analyses should be interpreted with caution; in particular it is difficult to know whether a subgroup has been identified as having improved efficacy / safety because these patients genuinely respond better to treatment, or simply due to chance. In any clinical trial some subgroups will artificially appear to do better than the overall patient population due to chance alone. Key considerations as to whether this type of analysis can be accepted include the biological plausibility of finding an improved response in the subgroup and consistency of the evidence of the improved effect across the different sources of evidence (trials) provided.

Examining the OS data in the two main trials for trial 046, those <65 years have a 1.5 month difference with a slightly lower HR than the ITT. For trial -099 the OS for those <65 years is 0.5 months (compared with 1.3 months for the ITT) with a larger HR than the ITT. The PFS data for the <65 years group in each of the large controlled trails is less convincing than the PFS data for the ITT.

The proposition made by the MAH is that based on the subgroup analysis the benefit: risk is more favourable for patients <65 years due to less early deaths in the trial seen in those ≥65 years. It is agreed that in those <65 years there are less early deaths, but overall the absolute % of SAE are similar between those <65 years and the total population.

On the basis of the above analyses the Applicant proposed during the re-examination to modify the indication as follows:

"Erbitux is indicated in combination with platinum-based chemotherapy for the first-line treatment of patients with epidermal growth factor receptor (EGFR)-expressing advanced or metastatic non-small cell lung cancer. A positive risk-benefit ratio was not demonstrated in patients 65 years of age or older (see section 4.4 and 5.1)",

It is proposed that the SAG-Oncology should be re-consulted on the clinical relevance/need of treatment of Erbitux in patients under the age of 65 years where the safety profile appears more favourable. Given the finding of an increased incidence of cardiac events in patients aged ≥ 65 years of age, the Applicant should undertake an investigation of this safety signal in all indications approved or under investigation.

Finally, the modest increase in OS in those <65 years was not reflected in PFS.

Therefore the proposal that an improved benefit: risk in those <65 years is not supported from the efficacy data. With the exception of early deaths in those >65 years the overall incidence in SAEs was similar in those <65years to that seen in the initial ITT population. Multiple sub-group analyses were performed which raises concern about the validity of conclusions drawn as the results in each trial and in the pooled analysis were not consistent.

Therefore, the CHMP recommends that the **SAG-Oncology** should be re-consulted on the grounds for negative opinion in view of the grounds for re-examination submitted, in particular on the clinical

relevance and need of treatment of Erbitux in patients under the age of 65 years where the safety profile is claimed to be more favourable.

3. 3 Discussion at the SAG-Oncology

The following questions were discussed at the SAG-O convened on the re-examination:

1. What is the view of the SAG on the discordance between the PFS and OS results? Are the data on OS considered reliable in light of the less favourable data on PFS?

It is difficult to speculate on the discordance between PFS and OS, although it is an unexpected finding. Concerning the importance of this poor correlation, this may suggest that the effect on OS could be due to treatment given after progression although this remains a hypothesis. The SAG agreed that in this setting, the most relevant clinical endpoints to balance benefits and risks are OS and toxicity, and some members argued that one should not put too much emphasis on the presence or absence of effect on PFS.

2. What is the view of the SAG on the use of post-hoc subgroup analyses in this setting to substantiate a positive benefit: risk balance in NSCLC in those <65 years?

In general, the conclusions from post-hoc subgroup analyses to substantiate the main claim of a positive benefit-risk profile cannot be considered as reliable to establish clinical efficacy or safety, or to formally establish the existence of interactions with treatment, due to multiplicity and the possibility of introducing bias. In this case, there is no established biological rationale for the chosen cut-off. If this hypothetic finding is considered worthy of further investigation it should be formally confirmed prospectively, using robust methodology. In any case, even in the proposed subset of patients <65 years old, the magnitude of the effect was at best of very modest clinical significance, although it achieved early separation of the survival curves. It should be mentioned that in the subgroup analyses we observed no clinical response in Stage III patients (although few patients have been enrolled.

3. What is the view of the SAG of the adverse event profile in patients <65 years compared to that in the original ITT population, including all patients regardless of age?

The observed adverse event profile in the subgroup appeared to be slightly improved in the analyses presented. According to some SAG members, in lung cancer a survival advantage of about 6 weeks is meaningful, if we compare these data to other studies, and the effect is unlikely to be due to further lines of therapy. Accordingly some SAG members concluded that in the patient group < 65 years, there was a positive benefit/risk balance.
However, most of the SAG members agreed that due to the post-hoc methodology employed to address efficacy, it is difficult to draw formal conclusions about this subgroup. It would be of interest, however, to explore the interaction between age and cetuximab-associated toxicity in other indications. For the time being, even assuming that the slightly improved safety profile in younger patients is real, the toxicity remained significant although manageable and compared unfavourably against the very modest effect in terms of OS.

4. Does the SAG consider that the estimated overall survival benefit of cetuximab as add-on to standard chemotherapy in those <65 years represents adequate and statistically compelling evidence in view of the PFS data?

The claimed OS advantage is now based on a post-hoc analysis. From a methodological point of view, this level of evidence is far from compelling and in any case insufficient to draw any conclusions about the efficacy or the safety in the subgroup. Even accepting the methodological flaws, the magnitude of the effect was at best of very modest clinical significance.
A minority of the members insisted on the fact that although modest, the effect observed with cetuximab was in the same order of magnitude of what has been observed with other active agents for the treatment of advanced NSCLC.

3.4 Issues addressed at the Oral Explanation and discussion on the benefit-risk ratio

Due to progressive reduction of organ function and age-dependent co-morbidities affecting functional status, general health, and tumor symptoms, toxicity to anti-cancer therapy is reported to be aggravated in patients ≥65 years. As per the ICH E7 (studies in support of special populations: geriatrics) guideline and in line with current practice, *the clinical study protocols for cetuximab in NSCLC defined two subpopulations by age, younger than 65 years and 65 years or older.* Therefore, the Applicant performed additional safety analyses by age (younger patients, defined as <65 years and elderly patients, defined as ≥65 years), and consequentially also efficacy analyses by age, in order to re-assess the risk/benefit ratio of cetuximab in NSCLC. These analyses included an evaluation of the appropriateness of the use of 65 years as the cut-point.
The proposition made by the MAH is that based on the subgroup analysis the benefit: risk is more favourable for patients <65 years due to less early deaths early in the trial seen in those ≥65 years.

It is agreed that in those <65 years there are less early deaths, but overall the absolute % of SAE are similar between those <65 years and the total population.

It can be considered biologically plausible that a subgroup of these fragile elderly patients are at higher risk of experiencing fatal toxicities related to treatment containing cetuximab, thereby shifting the B/R-ratio in a negative direction in this subgroup of patients. In general, age is an important prognostic factor that is taken into consideration by medical oncologists and haematologists on a daily basis. It is a well-known fact that intensive treatment regimens are poorly tolerated in elderly populations with numerous co-morbidities and that well-defined age limits play an important role in the selection of treatment options and in the planning of clinical trials for several malignancies, e.g. AML and multiple myeloma (thalidomide indicated in patients ≥ 65 years of age). As such there could be a biological rationale behind an improved B/R-ratio in younger cetuximab-treated patients. Whether the threshold should be set at 65 years, could of course be debatable, but this decision was based on a pre-specified subdivision of the study population in the protocol and a post-hoc analysis of age as a continuous variable vs. outcome showing that the 65 years was the most optimal cut-off point. Based on the results of the trial this cut-off point is merely considered as supportive information for the treating physicians.

It has to be emphasized however that post-hoc subgroup analyses were conducted with the aim of improving the benefit-risk profile in an identified sub-population, primarily by reducing the number of early, serious adverse events which it is speculated had a detrimental effect on OS. Post-hoc subgroup analyses should be interpreted with caution; in particular it is difficult to know whether a subgroup has been identified as having improved efficacy / safety because these patients genuinely respond better to treatment, or simply due to chance. In any clinical trial some subgroups will artificially appear to do better than the overall patient population due to chance alone. Key considerations as to whether this type of analysis can be accepted include the biological plausibility of finding an improved response in the subgroup and consistency of the evidence of the improved effect across the different sources of evidence (trials) provided.

Examining the OS data in the two main trials for trial 046, those <65 years have a 1.5 month difference with a slightly lower HR than the ITT. For trial -099 the OS (secondary endpoint) for those <65 years is 0.5 months (compared with 1.3 months for the ITT) with a larger HR than the ITT. The PFS data for the <65 years group in each of the large controlled trails is less convincing than the PFS data for the ITT.

The MAH during an Oral Explanation at the CHMP focused on the following issues:

The proposed indication is based on a post hoc subgroup analysis that was not intended to be the basis for confirmation of efficacy. The MAH discussed whether this approach is statistically robust considering the biological plausibility of the hypotheses on which the proposal is based and the apparent lack of consistency of effects in this subgroup in the two pivotal trials. The MAH also presented PFS curves for study 046 in Caucasian patients < and > 65 years of age.

It is of particular interest to seek external validation of the hypothesis that age and smoking-related comorbidities were responsible for this toxicity in other indications. Given the similarities in risk factors, life-style and resulting co-morbidities, the comparison between patients with NSCLC and SCCHN (squamous cell cancer of the head and neck) was considered most pertinent for this purpose. The MAH elaborated on these data and submitted an overview of the absolute number of total deaths and the grade 3 and 4 events in patients with SCCHN. The applicant provided survival curves for patients < and > 65 years of age for the two randomised head and neck cancer studies.

The estimated benefit of add-on cetuximab to standard chemotherapy in terms of survival in those <65 years is considered modest (HR 0.86) and statistically non-compelling and is not considered to outweigh the tolerability and safety concerns. According to the subgroup analysis (both in the entire ITT population and in patients < 65 years of age) patients with squamous cell carcinoma (SCC) seem to have the most benefit from add-on treatment with cetuximab. The excess toxicity in those >65 years was considered by the MAH to be related to co-morbidities in these subjects as a result of smoking. The MAH also discussed the benefit-risk ratio of cetuximab in the subgroup of patients with SCC who have a high unmet medical need considering that SCC of the lung is largely a disease of older patients with a history of smoking.

Following the oral explanation, the CHMP concluded that:

- The magnitute of effect in terms of overall survival as estimated from post-hoc subgroup analyses is not consistent across trials and not supported by an improvement in progression-free survival.

- Even in a proposed subset of patients <65 years old, the effect seen is at best of very modest clinical significance and due to methodological concerns, multiplicity and the possibility of introducing bias, it cannot be considered as reliable to establish clinical efficacy or safety.

- The toxicity (rash, diarrhea) remained significant although well known and manageable and compared unfavourably against the very modest effect in terms of OS, therefore the CHMP considers that the benefit-risk profile in the indication:

  Erbitux in combination with platinum -based chemotherapy for the first -line treatment of patients with epidermal-growth factor receptor (EGFR) -expressing advanced or metastatic non small cell lung cancer

is negative and reconfirmed its initial negative opinion.

A minority view acknowledged that study EMR 62 202-046 has demonstrated a significant overall survival benefit of 1.5 months as compared to what is usually seen in this setting, favoring the use of Erbitux as add-on therapy in patients with advanced, EGFR-expressing NSCLC.
In view of the poor prognosis and the slow, but stepwise, improvement in survival benefit related to new therapies in NSCLC, a medium gain of 1.5 months in OS (primary endpoint) in the pivotal trial (-046) in patients < 65 years of age is difficult to disregard. A similar result was found in the pooled analysis of studies whereas no significant gain in OS (secondary endpoint) was found in study -099.
In patients aged < 65 years of age, this benefit is even more evident. This observation is well-known and consistent among indications and due to well-known differences in tumor biology, the benefit was even more pronounced in Caucasians.
In further support, TTF was significantly prolonged and there were indications of less impact on quality of life in patients <65 years favouring the cetuximab + CTX group.
The inconsistencies noted in terms of PFS could be explained and nevertheless the overall survival is a harder and more important endpoint.
The clinical benefit is of more importance in the histological subgroup of squamous cell carcinoma where there have been no recent developments and there is a high unmet medical need.

IV. CONCLUSION

On 19 November 2009 the CHMP considered the re-examination of this Type II variation and agreed that the changes to the terms of the Marketing Authorisation should be refused on the following grounds:

Whereas,

- The estimated magnitude of the treatment effect on overall survival is complicated by methodological concerns relating to retrospective subgroup analyses conducted to identify patients with a more favourable benefit-risk. The effect on progression-free survival does not give strong support to the observed effect on overall survival.

- The effects on overall survival and progression-free survival are of modest clinical significance in the patient population proposed.

- The toxicity, although well known and manageable, is significant. The estimated effect on overall survival is inadequate to offset this toxicity

and therefore the CHMP considers that the benefit-risk profile of Erbitux in the indication

> "in combination with platinum -based chemotherapy for the first-line treatment of patients with epidermal-growth factor receptor (EGFR) -expressing advanced or metastatic non-small cell lung cancer"

is negative, and reconfirmed its initial opinion of 23 July 2009.