EUROPEAN MEDICINES AGENCY
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Human Medicines Development and Evaluation

Withdrawal Assessment report

Erbitux

cetuximab

Procedure No.: EMEA/H/C/000558/II/0043

This withdrawal Assessment Report is based on the latest assessment report adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Questions and Answers" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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1. Recommendation

Based on the review of the data on safety and efficacy, the CHMP considers that the variation application EMEA/H/C/000558/II/0043 for Erbitux (cetuximab) in the treatment of epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer and squamous cell cancer of the head and neck, for the following proposed change:

Extension of indication in combination with platinum-based chemotherapy for the first line treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) with high Epidermal Growth Factor Receptor (EGFR) expression,

is not approvable since a 'major objection' remains, which precludes a recommendation for marketing authorisation at the present time.

2. Scientific Discussion

2.1. Introduction

Lung cancer is the leading cause of death due to cancer worldwide and is responsible for 1.3 million deaths annually (WHO, 2007). It is the most common cancer of men, with global incidence rates of 35.5 per 100,000 men. The highest rates are observed in North America and Europe, especially Eastern Europe. In women, global incidence rates are lower (12.1 per 100,000 women), with the highest rates seen in North America and Northern Europe (Parkin D et al, 2005). In 2008 in Europe, an estimated 390,900 incident cases of lung cancer were diagnosed and 342,100 patients died from this disease (Ferlay J et al, 2010).

The overall 5-year survival rate for patients with NSCLC is less than 15%. Surgical results in earlier stages are poor compared to other tumour types (recurrence rate of about 40% in stages I and II). Results of chemotherapy in advanced stage disease (IIIb with pleural effusion and IV) are also poor (1-year survival rate of 40%) (Bastin KT and Curley R, 1995; Carney DN, 1995). In NSCLC, OS is considered to be the clinically most important endpoint in clinical trials. The 5-year survival rate for advanced NSCLC is less than 5% (Wang et al, 2010).

NSCLC is a heterogeneous disease that comprises several histologic subtypes, including Squamous Cell Carcinoma (SCC, 30% of all lung cancers), large cell carcinoma (10% of all lung cancers), and adenocarcinoma/adenocarcinoma in situ (formerly known as bronchoalveolar carcinoma, 40% of all lung cancers). Approximately 30% of patients with NSCLC present with locally advanced disease (stage III) and approximately 40% with metastatic disease (stage IV) (Pfister DG et al, 2004).

Platinum-based chemotherapy constitutes the standard first-line treatment for patients with stage IIIB and IV disease and good performance status (PS) (Pfister DG et al, 2004). For a number of years, 4 platinum-based doublets have been in common use in this setting: cisplatin + vinorelbine, cisplatin + gemcitabine, cisplatin + docetaxel, and carboplatin + paclitaxel. In randomised phase III studies, these regimens revealed remission rates of 17–44% and median OS times of 7–11 months (see Fossela et al, 2003; Hotta et al, 2004; Schiller et al, 2002). An Eastern Cooperative Oncology Group (ECOG) phase III study randomised 1,207 patients among 4 platinum-based chemotherapy regimens (see Schiller et al, 2002). None of the regimens offered a significant survival advantage over the others. Furthermore, in a Southwest Oncology Group phase III study, patients were randomised between carboplatin + paclitaxel and cisplatin + vinorelbine with no difference in efficacy (see Kelly et al, 2001).

Four medicinal products (bevacizumab, pemetrexed, gefitinib and erlotinib) have recently been approved for the first-line treatment of advanced NSCLC, each of them in a specific subgroup. Bevacizumab, a monoclonal antibody directed against the vascular endothelial growth factor (VEGF), was approved in 2007 for the first-line treatment of nonsquamous cell NSCLC in combination with chemotherapy. In 2008, the European Commission (EC) approved the cytotoxic drug pemetrexed in combination with cisplatin as a first-line treatment for NSCLC patients with other than predominantly squamous cell histology. In 2009, gefitinib, an EGFR tyrosine kinase inhibitor (TKI) was approved by the EC for the treatment of adult patients who have locally advanced or metastatic NSCLC with activating mutations of EGFR and in 2011, erlotinib, another EGFR TKI, was also approved in the same first line indication as gefitinib.

Despite these advances, advanced or metastatic NSCLC remains difficult to treat. Improvements have been achieved in a series of small steps by identifying subpopulations that benefit from new treatment modalities. Nevertheless, there is still a high need for improved first-line therapeutic options for patients with this disease.

Cetuximab is a chimeric monoclonal Immunoglobulin G1 (IgG1) antibody directed against the Epidermal Growth Factor Receptor (EGFR). EGFR signaling 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 the receptor. 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 EGFR-expressing, KRAS (Kirsten rat sarcoma viral oncogene homologue) wild-type metastatic colorectal cancer:

– in combination with irinotecan-based chemotherapy,

- in first-line in combination with FOLFOX,

– as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy, and who are intolerant to irinotecan.

Erbitux is also 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.

In all indications, Erbitux is administered once a week as intravenous infusion at a maximum rate of 10 mg/min. The initial dose is 400 mg/m^2, and all subsequent weekly doses are 250 mg/m^2.

With this variation application the Marketing Authorisation Holder (MAH) proposed to extend the authorised indication with the addition of the following new indication:

Erbitux in combination with platinum-based chemotherapy is indicated for the first line treatment of patients with advanced or metastatic non-small cell lung cancer with high EGFR expression.

In response to the second CHMP Request for Supplementary Information the MAH modified the proposed indication as follows:

Erbitux in combination with platinum-based chemotherapy is indicated for the first-line treatment of patients with advanced or metastatic non-small cell lung cancer with high EGFR expression and without activating EGFR-TK mutations.

The MAH had previously applied for an extension of indication in non-small cell lung cancer (NSCLC) which was not based on levels of EGFR expression or any other biomarker and which received a final negative Opinion by majority vote after re-examination by the CHMP (variation EMEA/H/C/000558/II/0029, EC Decision 20 January 2010). In the course of this procedure the MAH had attempted to identify potential biomarkers which might allow the identification of a population of NSCLC patients in which the benefit-risk balance of cetuximab may be positive. The current application is based on further prospective analyses of the previously submitted (with II/29) clinical trial data based on a proposed biomarker of EGFR expression level.

2.2. Non-clinical aspects

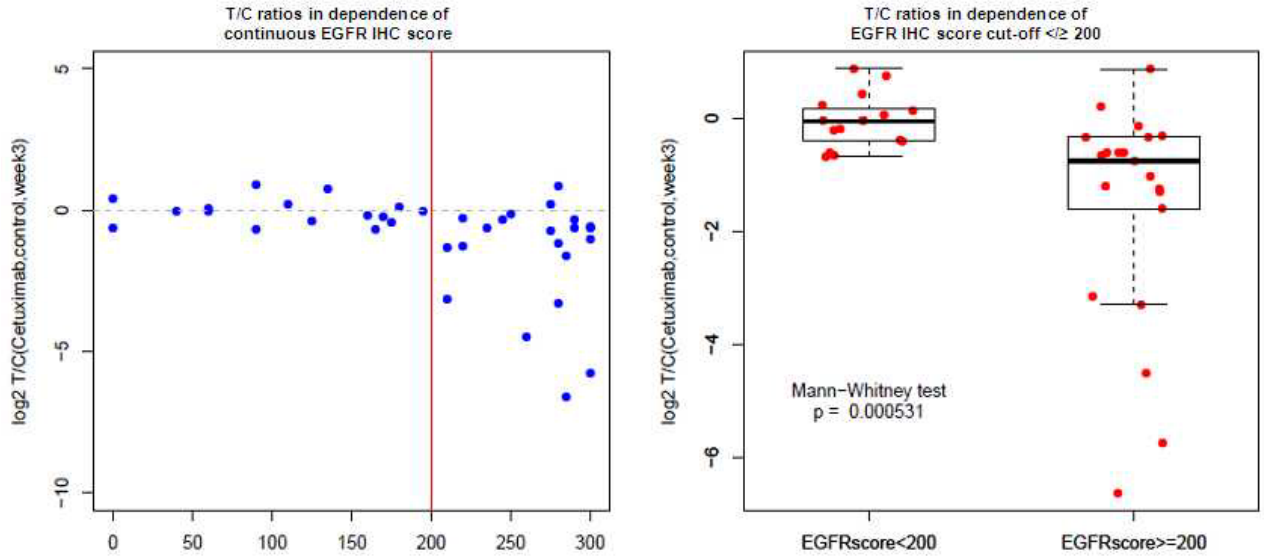
2.2.1. Pharmacology

An *in vivo* study with primary NSCLC explants was submitted in support of the biological rationale of cetuximab activity associated with high EGFR expression. Tumour explants from 47 NSCLC cases were implanted into 50 mice (NMRI nu/nu or HSD athymic) each. The mice were divided into 5 groups comprising 10 mice each (untreated control, cetuximab monotherapy, cisplatin monotherapy, cetuximab in combination with cisplatin and biomarker group). Five mice from the biomarker group of each tumour were used for EGFR immunohistochemistry (IHC) analysis which was performed and scored as described under Clinical aspects below. More specifically, the score was measured in a scale from 0 (absence of any staining anywhere in the tumour) to 300 (strong staining throughout the tumour).

Efficacy endpoints were response according to treatment/control (T/C) ratios or response according to modified RECIST. T/C values describe the ratio of the volumes of tumours treated with a therapy under investigation to the volumes of control tumours (untreated or receiving control treatment) at a defined point in time. T/C ratios < 1 (or log2 (T/C) < 0) indicate tumour growth inhibition of treated tumours relative to controls.

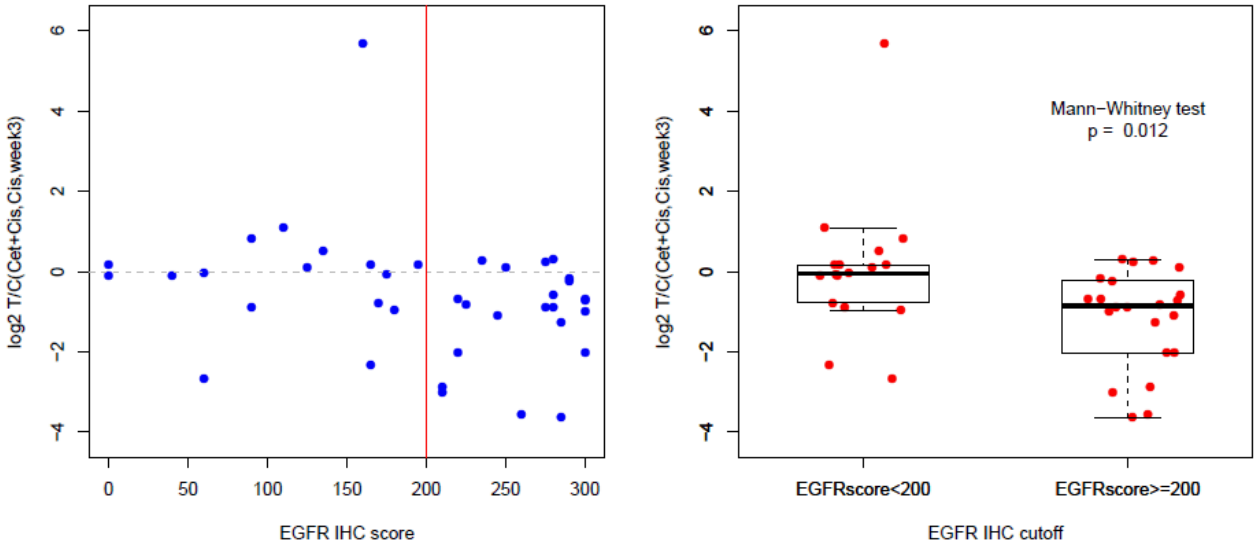
Results are shown in the following figures. These are presented by EGFR IHC score in two categories (<200 and ≥200) based on the EGFR IHC score cut-off of 200. The computation of this score and the determination of the cut-off of 200 is described under Clinical aspects below. The following figures present T/C ratios for the comparisons of cetuximab monotherapy vs no treatment (Figure 1) and of cetuximab/cisplatin combination vs cisplatin monotherapy (Figure 2). Figure 3 shows the response rates (based on RECIST) for the cetuximab monotherapy and for the cetuximab/cisplatin combination vs cisplatin monotherapy, respectively.

Figure 1: T/C ratios at week 3 dependent on EGFR score: cetuximab vs untreated controls



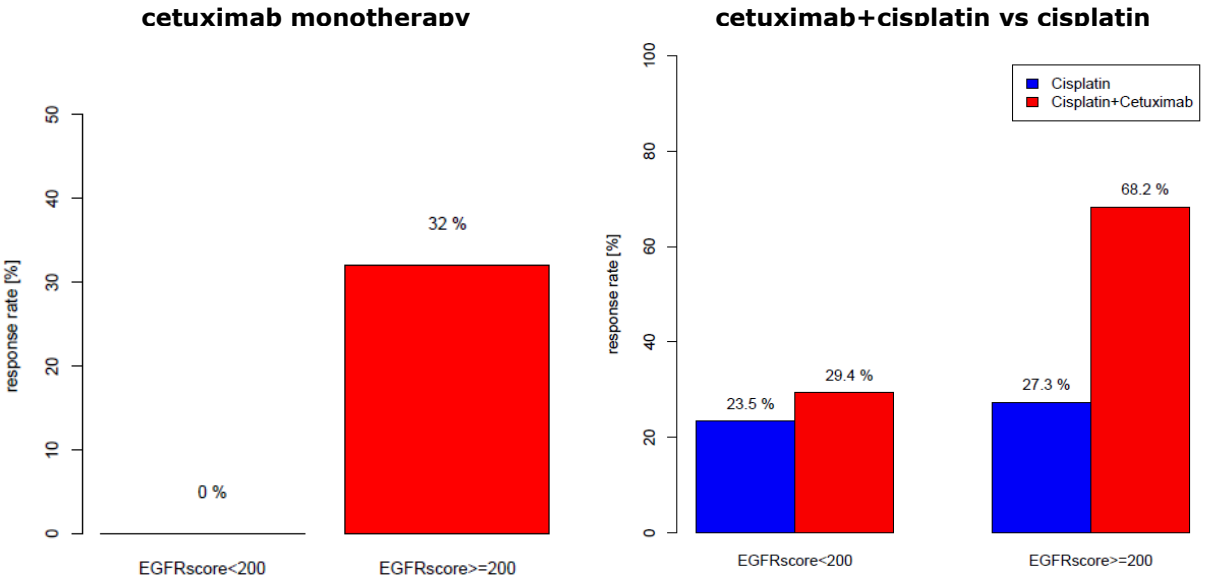
Left panel: The log2-transformed T/C ratio (cetuximab monotherapy/untreated control) at week 3 is plotted against the EGFR histoscore. Right panel: The same T/C data are visualized in a combined stripchart/boxplot with tumours stratified according to an EGFR IHC cut-off of 200. T/C: Relative tumour volume (ratio) of treated vs. control group

Figure 2: T/C ratios at week 3 dependent on EGFR score: cetuximab+cisplatin vs cisplatin



Left panel: Scatter plot of log2-transformed T/C (T = cetuximab + cisplatin, C = cisplatin) ratios at week 3. Lower tumour volumes for combination treatment compared to cisplatin control result in a log2(T/C)<0. Right panel: A combined stripchart/boxplot for log2(T/C) ratios as stratified by the EGFR IHC cut-off 200. T/C: Relative tumour volume (ratio) of treated (here: cetuximab + cisplatin) vs. control (here: cisplatin) group

Figure 3: Objective Response (OR, RECIST) at week 3 dependent on the EGFR IHC Score



2.2.2. Discussion on non-clinical aspects

The CHMP agrees with the MAH conclusions from this NSCLC in vivo explant study as supporting the IHC score cut-off selected (≥200 vs <200).

The data seem to indicate that the major mode of action of cetuximab in NSCLC must be direct inhibition of central EGFR-mediated cellular functions, since (a) cetuximab monotherapy is also active and associated with EGFR expression levels, which suggests independence of an interaction with chemotherapy (resensitisation due to lowering of apoptotic threshold) and (b) since the beneficial effects of cetuximab +/- chemotherapy were observed in a NOD-SCID model which is independent of ADCC. Results obtained from this study are in accordance with information provided in the current SmPC.

Furthermore, it was shown that addition of cetuximab to cisplatin did not increase ORR in tumours with EGFR IHC score <200 and that this observed response rate (= 29.4%) is approximately as high as that obtained when only cisplatin was applied to tumours with either IHC score, i.e. ≥200 (=27.3%) or <200 (=23.5%), as one would expect.

2.3. Clinical aspects

2.3.1. Introduction

The previous extension of indication application for Erbitux in NSCLC (II/29) was based primarily on the following studies:

Table 1: Overview of cetuximab NSCLC studies

Study ID	Treatment	No patients ITT	No patients EGFR eval	Stratification factors	Primary efficacy endpoint	phase
EMR 62 202-046 (FLEX)	Cetuximab+cisplatin+vinorelbine vs cisplatin+vinorelbine	557 568	555 566	ECOG PS (0 vs 1 vs 2) Tumour stage (IIB with pleural effusion vs IV)	OS	III
CA225099	Cetuximab+carboplatin+taxane vs carboplatin+taxane (taxane=paclitaxel or docetaxel)	338 338	74 62	ECOG PS (0 vs 1) Study centre Intended taxane[II]	PFS[I]	III
CA225100	Cetuximab+platinum+gemcitabine vs platinum+gemcitabine (platinum=cisplatin or carboplatin)	43 43	42 39	ECOG PS (0 vs 1) Study centre Intended platinum[II]	ORR	II
EMR 62 202-011	Cetuximab+cisplatin+vinorelbine vs cisplatin+vinorelbine	65 65	- -	Not stratified	ORR	II

ECOG PS+ Easter Cooperative Oncology Group performance status
[I]In study CA225099, primary analyses of progression-free survival and tumour response endpoints were based on the assessments of an Independent Radiology Review Committee
[II]The intended taxane (CA225099) or platinum agent (CA225100) for a given patient was chosen by the investigator prior to randomisation.

EGFR expression was an inclusion criterion (≥ 1 EGFR-positive tumor cell) in studies EMR 62 202-046 and EMR 62 202-011.

Design, results and previous CHMP assessment of these studies have been previously described (refer to variation II/29 for detailed description) and the design and results are summarised within the updated analyses based on EGFR expression in the clinical efficacy and clinical safety sections below.

2.3.2. Pharmacodynamics

EGFR testing of tumour specimens for the clinical studies was prospectively performed by immunohistochemistry (IHC) in designated, experienced central laboratories that were trained and synchronised under the supervision of a central pathology laboratory. EGFR assessment was performed using the CE-labelled, standardized DAKO PharmDx kit according to the kit instruction manual.

For each patient, the following staining parameters were documented:

- Intensity of EGFR membrane staining: absent (0), weak (1+), moderate (2+), strong (3+)
- Proportion (%) of EGFR-positive cells with the respective staining intensities

The EGFR expression level for each patient was determined by generating an IHC score that took into account both the intensity of EGFR membrane staining and the proportion (%) of EGFR-positive cells with the respective staining intensity. The EGFR IHC score was calculated according to the following formula: EGFR IHC score = (% weak [1+] x 1) + (% moderate [2+] x 2) + (% strong [3+] x 3). The EGFR IHC score thus ranges from 0 (no staining at all) to 300 (100% of cells with strong staining).

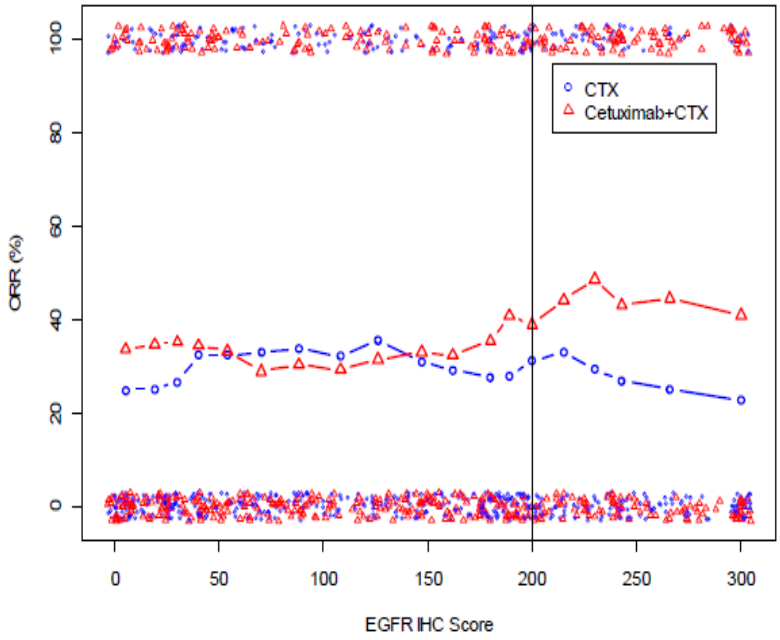
The reproducibility of the EGFR IHC score was evaluated in an international Round Robin Test (RRT). The RRT intended to determine inter-observer variability of the EGFR IHC score for the evaluation of

NSCLC specimens. It was divided into two different parts, a feasibility study (part 1) and a main study (part 2). Although the methodology of the two parts of the study is not described, results of the main study were as follows: The study showed an inter-observer agreement of EGFR IHC scoring in comparison to the reference evaluation with an overall concordance rate of 91% and a mean kappa coefficient of 0.81. Samples with a reference EGFR IHC score < 200 (≥ 200) showed a mean concordance rate of 95% (86%), respectively. Cases with a reference EGFR IHC score clearly below or above the cut-off (score <150 or ≥250), were categorised with a mean concordance rate of 98% each. Samples with a reference EGFR IHC score close to the cut-off (score 150 - <250) showed a mean concordance rate of 74%.

The EGFR IHC score was calculated for 1121 (99.6%) of the 1125 randomised patients from study EMR 62202-046 (EGFR data were incompletely recorded for 4 patients). The EGFR IHC scores were evenly distributed across the range of 0 to 300 in both treatment groups with a median of 150 for the cetuximab + chemotherapy (CTX) group and 144 for the CTX group.

For each x-percentile (x = 5, 10, 15, …, 95) of the distribution of the IHC score, the ORR per treatment arm for the respective IHC score level was calculated based on all patients with an IHC score between (and including) the (x-10)–percentile and the (x+10)–percentile. Thus, each of the sliding windows in Figure 4 contains data from 20% of the patients.

Figure 4: Relationship between EGFR expression (IHC score) and Objective Response Rate (ORR) in study EMR 62 202-046 (FLEX): ITT population



This analysis indicated a difference in ORR in favour of the add-on cetuximab above an IHC score of approximately 150. The pattern seen in the figure above was taken as the basis for defining a discriminating threshold to separate patients with potential benefit from cetuximab treatment from those without such benefit. A cut-off of 200 was selected for the discrimination of a group of patients expected to benefit from cetuximab from a group who should not benefit based upon EGFR expression.

The following 2 groups of patients were therefore defined for the analyses of efficacy in studies EMR 62 202-046, CA225099, and EMR 62 202-011:

- Low EGFR expression group (EGFR IHC score <200)
- High EGFR expression group (EGFR IHC score ≥200)

Based on the above criterion, patients with EGFR evaluable tumours (EGFR evaluation available only in three of the abovementioned studies) could be categorised as indicated in Table 2:

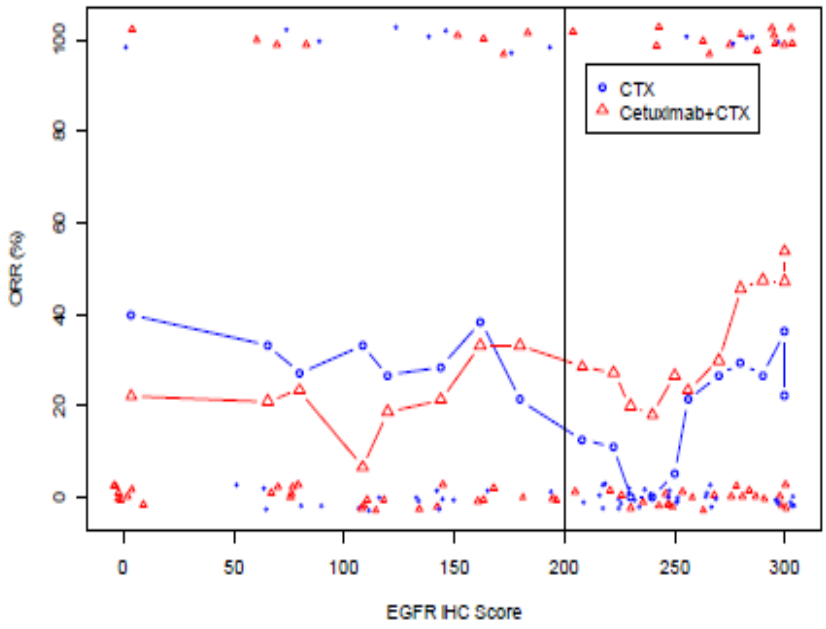
Table 2: Patients with low or high EGFR expression in the randomised controlled studies

Study / population	CTX	Number (%) subjects in population					
		Cetuximab+CTX		CTX		Total	
EMR 62 202-046 (pivotal)	Cisplatin+vinorelbine						
EGFR evaluable		555	(100.0)	566	(100.0)	1121	(100.0)
Low EGFR expression		377	(67.9)	399	(70.5)	776	(69.2)
High EGFR expression		178	(32.1)	167	(29.5)	345	(30.8)
CA225099 (validation)	Carboplatin+taxane						
EGFR evaluable		74	(100.0)	62	(100.0)	136	(100.0)
Low EGFR expression		35	(47.3)	24	(38.7)	59	(43.4)
High EGFR expression		39	(52.7)	38	(61.3)	77	(56.6)
EMR 62 202-011 (supportive)	Cisplatin+vinorelbine						
EGFR evaluable		42	(100.0)	39	(100.0)	81	(100.0)
Low EGFR expression		22	(52.4)	16	(41.0)	38	(46.9)
High EGFR expression		20	(47.6)	23	(59.0)	43	(53.1)

CTX: chemotherapy

A prospectively planned analysis was performed on data from the second phase III study, CA225099, in order to validate EGFR expression with the pre-specified IHC score cut-off of 200 as a predictive biomarker of cetuximab efficacy. The analysis was pre-specified in a statistical analysis plan before the availability of the EGFR IHC score data. Results presented in a similar fashion as for the pivotal EMR 62 202-046 (FLEX) study in Figure 4 above are shown in Figure 5.

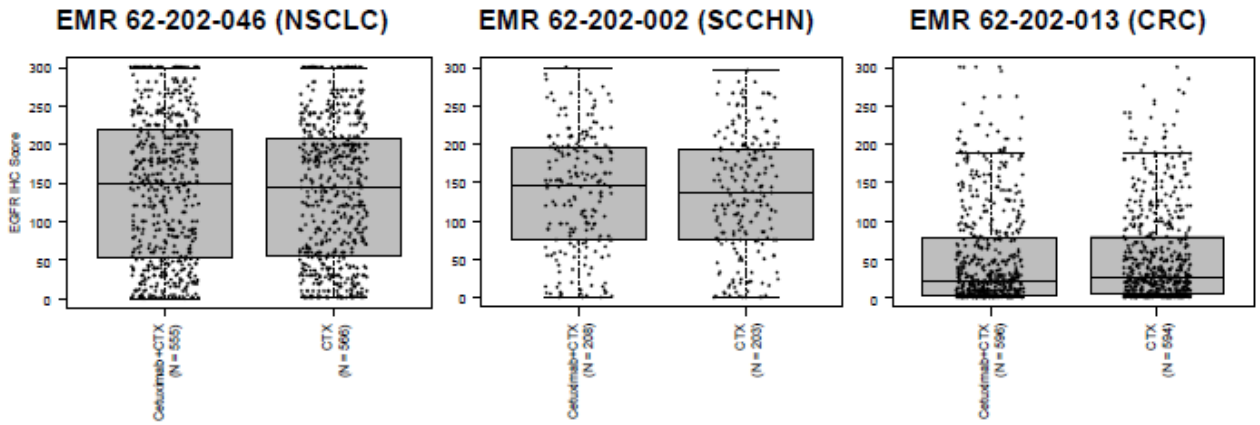
Figure 5: Relationship between EGFR expression (IHC score) and Objective Response Rate (ORR) in study CA225099: EGFR evaluable population= 20% of ITT



No further NSCLC studies were available for this validation exercise, but studies have been undertaken in head and neck cancer (SCCHN) and colorectal cancer (CRC). EGFR IHC scores were available for 411 (93%) of patients in study EMR 62-202-002 (SCCHN) and 99% of patients in EMR 62-202-013 (CRC).

As can be seen Figure 6, there is a major difference between NSCLC and SCCHN (high EGFR expression) and CRC (much lower EGFR expression).

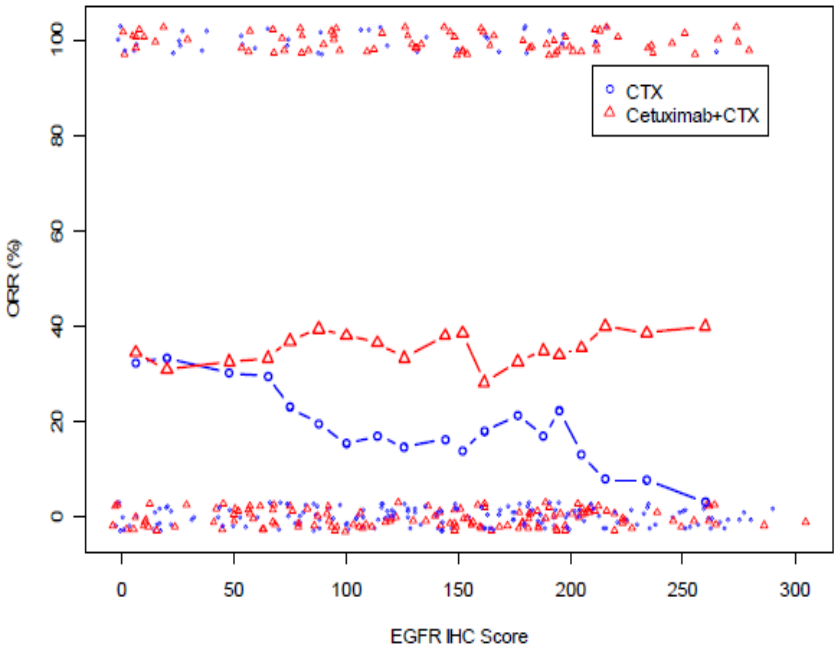
Figure 6: Distribution of EGFR scores by treatment group in the ITT population of NSCLC, SCCHN and CRC studies (one each)



Boxplots with data from individual patients displayed as dots.

The scores were evenly distributed across the range of 0 to 300 in both treatment groups, with a median of 147 for the cetuximab +chemotherapy group and 136 for the chemotherapy group. The results resembled those of study EMR 62 202-046 (NSCLC) with medians of 150 and 144, respectively. An analysis of ORR by EGFR score similar to the one for EMR 62 202-046 is shown in Figure 7 An increase ofcetuximab benefit over the full range of EGFR expression levels is seen, which in contrast tostudy EMR 62 202-046 seems to be largely driven by a decreasing response rate in the CTX arm.

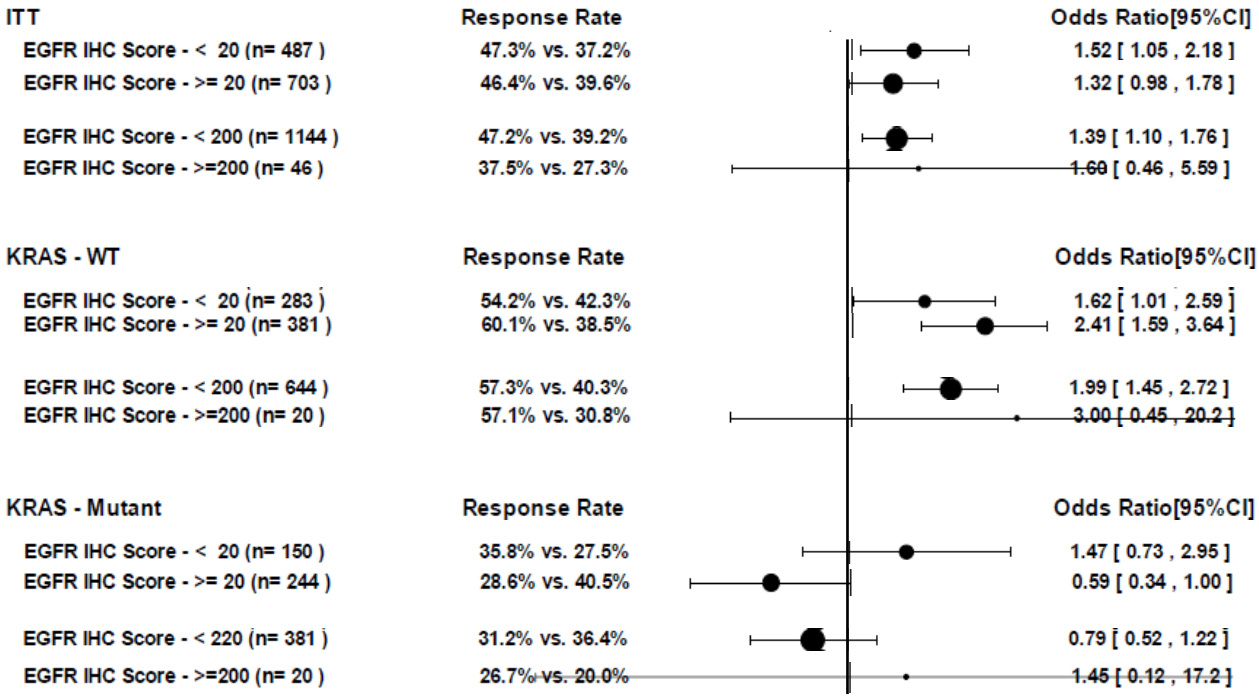
Figure 7: Relationship between EGFR expression (IHC score) and Objective Response Rate (ORR) in study EMR 62 202-002 (SCCHN): ITT population



Evaluable EGFR IHC scores were available for 1190 (99.3%) of the patients in study EMR 62 202-013 (CRC). The score distribution in this study was skewed, resulting in a considerably lower median of 23 for the cetuximab + CTX group and 28 for the CTX group. Within the ITT population of study EMR 62 202-013, similar distributions were seen in patients with KRAS wild type tumors and those with KRAS

mutant tumours (median 24 vs 29). The ORR and odds ratio of ORR at selected EGFR IHC score cut-offs and in both ITT and separately for patients with wild-type of mutant KRAS status in the CRC study EMR 62 202-013 is presented in Figure 8.

Figure 8: ORR and IHC scores in study EMR 62-202-013 (CRC)



Moreover, the MAH was requested to explore the relationship of the EGFR IHC score with a number of other biomarkers within study EMR 62 202-046 (FLEX). These biomarkers included, among others, activating mutations of EGFR, EGFR gene polymorphisms and EGFR gene copy number. EGFR gene copy number as determined by Fluorescence In-Situ Hybridisation (FISH) was weakly correlated with levels of EGFR gene expression, whereas patients with mutated EGFR status showed a higher average EGFR IHC score (data not shown). None of the biomarkers was shown to have a predictive value within either the 'high EGFR' or the 'low EGFR' IHC score subgroups with the exception of the 'mutated EGFR status'. The number of evaluable samples for EGFR kinase domain mutation and the frequency of marker alteration (EGFR mutation) for study EMR 62 202 046 are summarised in Table 3.

Table 3: Evaluable samples and frequency of activating EGFR mutation, EMR 62 202-046

Biomarker	EMR 62 202-046	
	Evaluable subjects N (% of all subjects)	EGFR activating mutations N (% of evaluable subjects)
EGFR kinase domain mutation in ITT (N=1125)	971 (86%)	133 (14%)
EGFR kinase domain mutation in Caucasians (N=946)	820 (87%)	86 (10%)
EGFR kinase domain mutation in Asians (N=121)	106 (88%)	43 (41%)

The relationship between EGFR expression level, EGFR kinase domain mutational status and the efficacy variables OS, PFS, time to treatment failure (TTF) and objective response rate (ORR) in study EMR 62 202 046 are summarised in Table 4.

Table 4: OS, PFS, TTF and ORR by EGFR expression and EGFR activating mutation status, ITT and high/low EGFR expression subsets, EMR 62 202-046

EGFR expression status	EGFR mutational status N	Hazard Ratio (95% CI)			Odds Ratio (95% CI)
		OS	PFS	TTF	ORR
ITT	All subjects	0.87 (0.76,1.00)	0.94 (0.82,1.08)	0.86 (0.76,0.97)	1.39 (1.08,1.78)
ITT	EGFR act. mut. evaluable N = 971	0.95 (0.82,1.09)	0.97 (0.84,1.12)	0.86 (0.75,0.98)	1.42 (1.09,1.87)
ITT	EGFR wt N = 838	0.91 (0.78,1.06)	1.02 (0.87,1.19)	0.90 (0.79,1.04)	1.33 (0.99,1.78)
ITT	EGFR mut N = 133	1.22 (0.79,1.89)	0.70 (0.48,1.04)	0.64 (0.44,0.91)	2.15 (1.07,4.31)
Low, IHC score 0 - <200	All subjects	0.99 (0.84,1.16)	0.98 (0.83,1.15)	0.90 (0.78,1.04)	1.15 (0.85,1.56)
Low, IHC score 0 - <200	EGFR act. evaluable N = 682	1.04 (0.87,1.23)	0.99 (0.83,1.17)	0.89 (0.76,1.04)	1.23 (0.89,1.71)
Low, IHC score 0 - <200	EGFR wt N = 599	0.98 (0.82,1.18)	1.03 (0.86,1.24)	0.92 (0.78,1.09)	1.16 (0.82,1.66)
Low, IHC score 0 - <200	EGFR mut N = 83	1.53 (0.89,2.63)	0.71 (0.43,1.17)	0.64 (0.41,1.02)	1.75 (0.71,4.29)
High, IHC score ≥200	All subjects	0.73 (0.58,0.93)	0.86 (0.68,1.09)	0.78 (0.63,0.97)	2.04 (1.30.3.19)
High, IHC score ≥200	EGFR act. mut. evaluable N = 288	0.78 (0.60.1.01)	0.91 (0.70.1.18)	0.80 (0.63,1.02)	1.88 (1.16,3.05)
High, IHC score ≥200	EGFR wt N = 238	0.76 (0.57,1.00)	0.96 (0.72,1.29)	0.86 (0.66,1.12)	1.73 (1.00.3.00)
High, IHC score ≥200	EGFR mut N = 50	0.86 (0.40.1.84)	0.69 (0.37,1.30)	0.59 (0.33,1.08)	3.27 (1.01,10.6)

2.3.3. Discussion on clinical pharmacology

The apparent absence of importance of activating KRAS mutations for the activity of cetuximab in NSCLC was interpreted previously as indicating that ADCC (rather than EGFR downregulation) might be of importance for the activity of cetuximab in NSCLC. However, durable responses to erlotinib in NSCLC have been reported in patients with activating KRAS mutations. Thus a guarded approach is reasonable. The MAH has repeatedly been encouraged by SAG-oncology and CHMP to try to identify biomarkers predictive of treatment outcome when cetuximab is added to platinum doublets in the treatment of NSCLC.

Basically, it has not been questioned that cetuximab shows activity in patients with NSCLC and it has been made sufficiently likely that cetuximab improves OS, but the magnitude of the treatment effect has been considered too small to outweigh the risk associated with treatment. This forms the basis for these attempts by the MAH to properly define a target population with improved Benefit/Risk balance.

In this submission, the MAH reports the results of retrospective analyses associating EGFR IHC score with treatment outcome. The technique applied, i.e. to grade membrane staining x % positive tumour cells, is one established way to construct an IHC score. While being established, however, this is only one among others. In prior analyses the MAH has, for example, only taken % of EGFR positive tumour

cells into account when the relationship between cetuximab activity and EGFR expression has been explored.

The large pivotal trial EMR 62 202-046, statistically borderline positive for survival benefit, was used to investigate the relationship between EGFR IHC score and ORR.

ORR is considered to be a proper measure of cetuximab activity, but it would have been preferable to use supportive studies for this purpose as all show add-on activity in terms of ORR and to confirm the findings in the pivotal trial.

It is, however, understandable why the MAH selected the approach taken as EGFR IHC score data were available in only 20% of the patients in the other large study CA225099 while the sample size of study EMR 62 202-011, a study with almost complete EGFR IHC data, probably was considered too small (43+43 patients).

As reported above, a positive relationship between EGFR IHC score and ORR was identified in EMR 62 202-046 and rather arbitrarily a score of 200 was used to dichotomise the population.

This cut-off appears (planned prospectively) to identify patients also in study CA225099 with an increased likelihood to achieve ORR benefit if treated with cetuximab. A high IHC score, however, appears to be associated with reduced likelihood for tumour response in patients treated with chemotherapy alone. This was not observed in the pivotal trial. Again, the low percentage of EGFR evaluable samples is a concern. The findings of increased activity of cetuximab in patients with high IHC score could not be confirmed in the small study EMR 62 202-011.

Conceptual support for the importance of EGFR IHC score derive from the study in head and neck cancer, while in colorectal cancer the expression level of EGFR is overall much lower and appears non-informative. The defined IHC score cut-off seems less proper in head and neck cancer; however, differences in the relative contribution of the different mechanisms of cetuximab action and in tumour biology between NSCLC and SCCHN may well explain this difference in the EGFR IHC score cut-off.

E.g. in the SCCHN study (EMR 62 202-002) the association of the benefit from cetuximab treatment with EGFR expression appeared to be influenced by a negative impact of increasing EGFR expression levels on the outcome of patients treated with chemotherapy only (see Figure 7). Thus, a major mechanism of action of cetuximab in this setting seems to be the enhancement of the effect of chemotherapy and the re-sensitization of tumours that became chemotherapy resistant as a consequence of increasing EGFR expression levels. In contrast, the efficacy within the cetuximab treatment arm of the SCCHN study appeared to be rather independent of the EGFR expression levels.

In contrast to SCCHN, in the NSCLC study (EMR 62 202-046), the improved treatment effect (cetuximab + CTX vs. CTX) in patients with high EGFR-expressing tumours (EGFR IHC score ≥200) was also due to an improved outcome within the cetuximab treatment arm (see Figure 4). This points to a strong direct inhibition of EGFR functions that are essential for the tumour cell (survival, proliferation, angiogenesis, metastasis and invasion) as a significant mode of action that contributes to the positive treatment effect of cetuximab in addition to enhancing the effect of chemotherapy. Evidence for this notion comes from the NSCLC explant study in which a benefit from both cetuximab combination therapy and cetuximab monotherapy was strongly associated with an EGFR IHC score ≥200 (see figure 3). The activity of cetuximab monotherapy and its association with EGFR expression levels suggests that a major mode of action of cetuximab in NSCLC is direct inhibition of central EGFR-mediated cellular functions independent of an interaction with chemotherapy.

EGFR mutation status was evaluable in 86.3% (971/1125) of patients in EMR 62 202-046. The percentages of samples with activating EGFR mutations, Asians and Caucasians, are as expected. Due to the small sample of patients with mutation positive tumours, results should be interpreted

cautiously. However, in terms of ORR and PFS/TTF the add-on activity of cetuximab appears higher in case of mutation positive tumours, but this is not born out in terms of survival. Next line treatment with EGFR-TK inhibitors might be of importance here. IHC score seems to be of less importance in case of mutation positive tumours. In patients with wild type tumours and high IHC score, the results with respect to OS and ORR remain essentially unchanged compared with the full population of patients with high IHC score expressing tumours. The absence of a correlation between PFS and OS is if anything reinforced.

Finally, the MAH had planned adequate measures to confirm a consistent high quality application and standardisation of the EGFR IHC scoring in clinical practice.

2.4. Clinical efficacy

Main studies

EMR 62 202-046

Methods

This was an open-label, randomised, multicentre phase III study comparing cisplatin + vinorelbine plus cetuximab vs. cisplatin + vinorelbine as first-line treatment for patients with EGFR-expressing, advanced non-small-cell lung cancer (NSCLC).

The main inclusion criteria were as follows:

- 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.

Enrolled patients were treated in one of the following two ways:

- 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).
- 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 patients who had received cetuximab.

Randomisation (phone) was stratified by ECOG PS of 0–1, versus 2, and disease stage IIIb with pleural effusion versus IV.

The primary endpoint was Overall Survival (OS). Tumour response and progression were assessed at study sites.

Results

There were three amendments to the study protocol, 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 patients for the DSMB). At that point in time 747 patients had signed the second informed consent. Patients who had already started with 30 mg/m² before the amendment remained on 30 mg/m² if the investigator considered that the patient benefited from and tolerated this dose.

Baseline demographic and disease characteristics, exposure to cetuximab and post-study treatment both in the ITT and according to EGFR expression (low, high) are presented in Tables 5-7.

Table 5: Baseline demographic and disease characteristics by EGFR expression

Characteristic	Number (%) of subjects					
	ITT		Low EGFR expression		High EGFR expression	
	Cet + CTX N = 557	CTX N = 568	Cet + CTX N = 377	CTX N = 399	Cet + CTX N = 178	CTX N = 167
Age, years						
Median	59.0	59.5	59.0	59.0	60.0	61.0
Range	18–78	20–83	18–78	20–79	31–78	33–83
Age categories						
< 65 years	385 (69.1)	389 (68.5)	260 (69.0)	279 (69.9)	123 (69.1)	109 (65.3)
≥ 65 years	172 (30.9)	179 (31.5)	117 (31.0)	120 (30.1)	55 (30.9)	58 (34.7)
Gender						
Male	385 (69.1)	405 (71.3)	254 (67.4)	280 (70.2)	129 (72.5)	123 (73.7)
Female	172 (30.9)	163 (28.7)	123 (32.6)	119 (29.8)	49 (27.5)	44 (26.3)
ECOG PS						
0 and 1	465 (83.5)	464 (81.7)	322 (85.4)	333 (83.5)	141 (79.2)	129 (77.2)
2	92 (16.5)	104 (18.3)	55 (14.6)	66 (16.5)	37 (20.8)	38 (22.8)
Ethnic origin[a]						
Caucasian	466 (83.7)	480 (84.5)	321 (85.1)	341 (85.5)	143 (80.3)	139 (83.2)
Asian	62 (11.1)	59 (10.4)	34 (9.0)	38 (9.5)	28 (15.7)	21 (12.6)
Other	29 (5.2)	29 (5.1)	22 (5.8)	20 (5.0)	7 (3.9)	7 (4.2)
Smoker						
Former/current	435 (78.1)	444 (78.2)	291 (77.2)	318 (79.7)	143 (80.3)	125 (74.9)
Never	121 (21.7)	123 (21.7)	85 (22.5)	80 (20.1)	35 (19.7)	42 (25.1)
Stage						
Stage IV	522 (93.7)	535 (94.2)	354 (93.9)	374 (93.7)	166 (93.3)	159 (95.2)
Stage IIIb	35 (6.3)	33 (5.8)	23 (6.1)	25 (6.3)	12 (6.7)	8 (4.8)
Histology						
Adenocarcinoma	255 (45.8)	277 (48.8)	189 (50.1)	205 (51.4)	64 (36.0)	71 (42.5)
Squamous cell	190 (34.1)	187 (32.9)	115 (30.5)	117 (29.3)	75 (42.1)	69 (41.3)
Other	112 (20.1)	104 (18.3)	73 (19.4)	77 (19.3)	39 (21.9)	27 (16.2)

Cet=cetuximab, CTX=chemotherapy

Table 6: Exposure to cetuximab by EGFR expression (EMR 62 202-046)

Characteristic	Safety Population	Low EGFR expression	High EGFR expression
Duration, weeks	N = 548	N = 371	N = 175
Median	17.7	14.4	19.1
Interquartile range	6.0–26.0	5.3–25.3	8.1–28.9
Number of infusions	N = 548	N = 371	N = 175
Median	15.0	12.0	18.0
Range	1–132	1–132	1–119
Cumulative dose, mg/m²	N = 548	N = 371	N = 175
Median	3760.9	3183.1	4444.7
Interquartile range	1534.5–6114.0	1396.0–5931.6	2118.9–6597.1
Relative dose intensity, % subjects [a]	N = 509	N = 342	N = 165
< 60%	2.4	2.3	2.4
60 to < 80%	13.0	14.0	10.9
80 to < 90%	21.6	20.5	23.6
≥ 90%	63.1	63.2	63.0

Table 7: Post-study treatment by EGFR expression (EMR 62 202-046)

	ITT		low EGFR expression		high EGFR expression	
	Cet + CTX N=557	**CTX N=568**	**Cet + CTX N=377**	**CTX N=399**	**Cet + CTX N=178**	**CTX N=167**
Any treatment	299 (53.7%)	344 (60.6%)	201 (53.3%)	246 (61.7%)	96 (53.9%)	95 (56.9%)
CTX	240 (43.1%)	226 (39.8%)	162 (43.0%)	162 (40.6%)	77 (43.3%)	64 (38.3%)
Radiotherapy	117 (21.0%)	131 (23.1%)	77 (20.4%)	101 (26.3%)	39 (21.9%)	31 (18.6%)
Anti-EGFR	**94 (16.9%)**	**153 (26.8%)**	**60 (15.9%)**	**115 (28.8%)**	**34 (19.1%)**	**38 (22.8%)**
Other	38 (6.8%)	41 (7.2%)	22 (5.6%)	31 (7.8%)	15 (8.4%)	11 (6.6%)

The main efficacy results by EGFR expression level are summarised in Table 8.

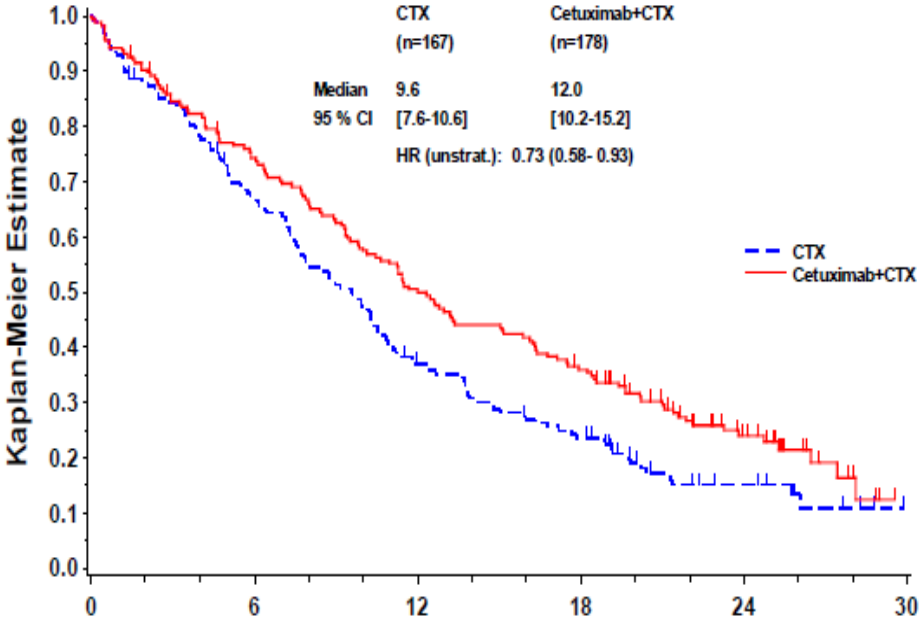
Table 8: Summary of efficacy results by EGFR expression (EMR 62 202-046)

Efficacy endpoint / summary statistic	ITT		Low EGFR expression		High EGFR expression	
	Cet + CTX N = 557	CTX N = 568	Cet + CTX N = 377	CTX N = 399	Cet + CTX N = 178	CTX N = 167
OS time, median (months)	11.3	10.1	9.8	10.3	**12.0**	**9.6**
Hazard ratio [95% CI]	0.871 [0.762, 0.996]		0.99 [0.84, 1.16]		**0.73 [0.58, 0.93]**	
p-value (log-rank test)	0.044		0.879		**0.011**	
p-value (treatment interaction)			**0.044**			
PFS time, median (months)	4.8	4.8	4.6	4.9	**5.0**	**4.6**
Hazard ratio [95% CI]	0.94 [0.82, 1.08]		0.98 [0.83, 1.15]		**0.86 [0.68, 1.09]**	
p-value (log-rank test)	0.387		0.799		**0.216**	
p-value (treatment interaction)			0.536			
TTF, median (months)	4.2	3.7	4.0	3.5	**4.2**	**4.0**
Hazard ratio [95% CI]	0.86 [0.76, 0.97]		0.90 [0.78, 1.04]		**0.78 [0.63, 0.97]**	
p-value (log-rank test)	0.015		0.153		**0.026**	
p-value (treatment interaction)			0.412			
ORR, % subjects	36.4	29.2	32.6	29.6	**44.4**	**28.1**
Hazard ratio [95% CI]	1.39 [1.08, 1.78]		1.15 [0.85, 1.56]		**2.04 [1.30. 3.19]**	
p-value (CMH test)	0.010		0.359		**0.002**	
p-value (treatment interaction)			0.040			

Kaplan-Meier curves and subgroup analyses in terms of the primary endpoint of Overall Survival and by EGFR expression are given in Figures 9-11.

Figure 9: Kaplan-Meier curve of Overall Survival by EGFR expression (EMR 62 202-046)

High EGFR expression



Low EGFR expression

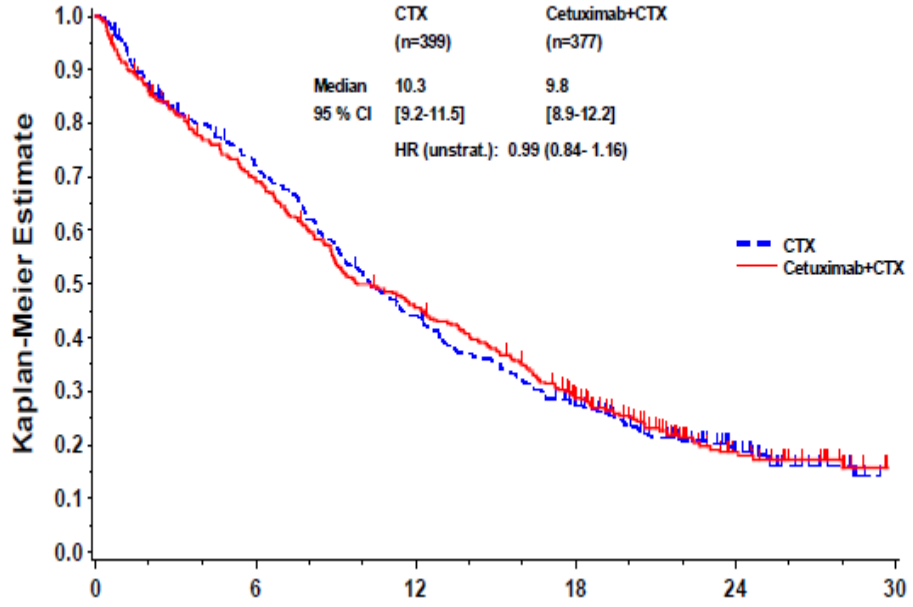
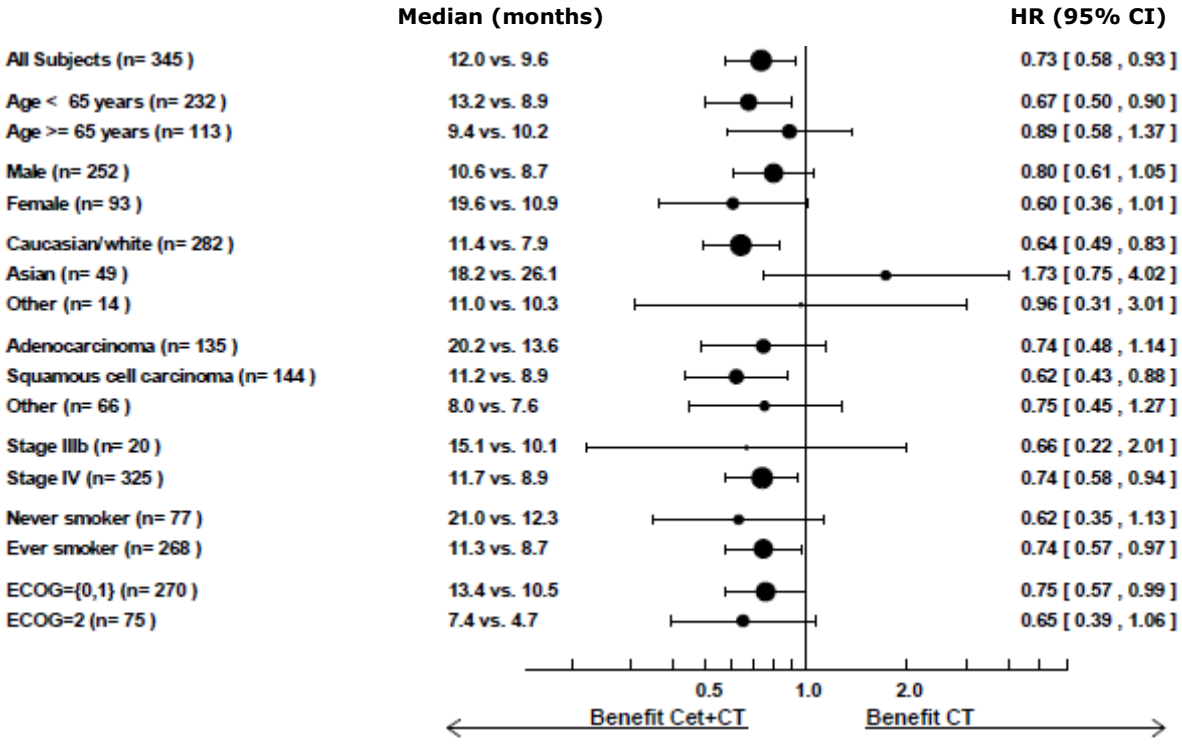


Figure 10: Overall Survival in subgroups by EGFR expression (EMR 62 202-046)

High EGFR expression



Low EGFR expression

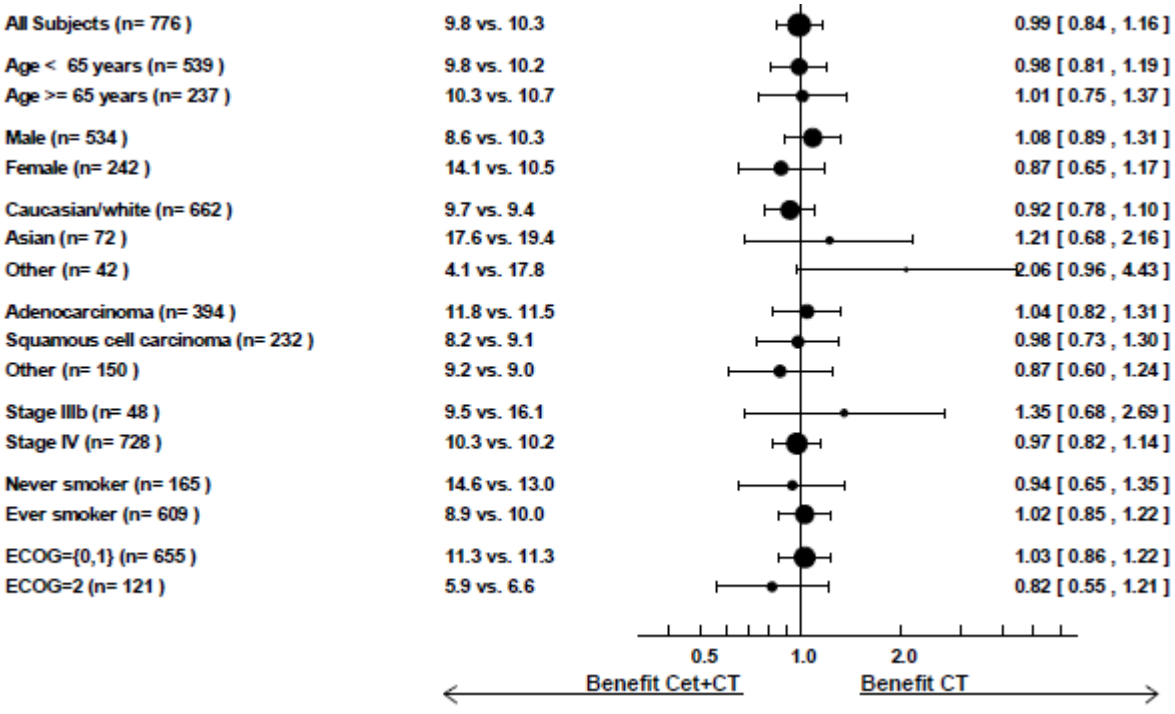
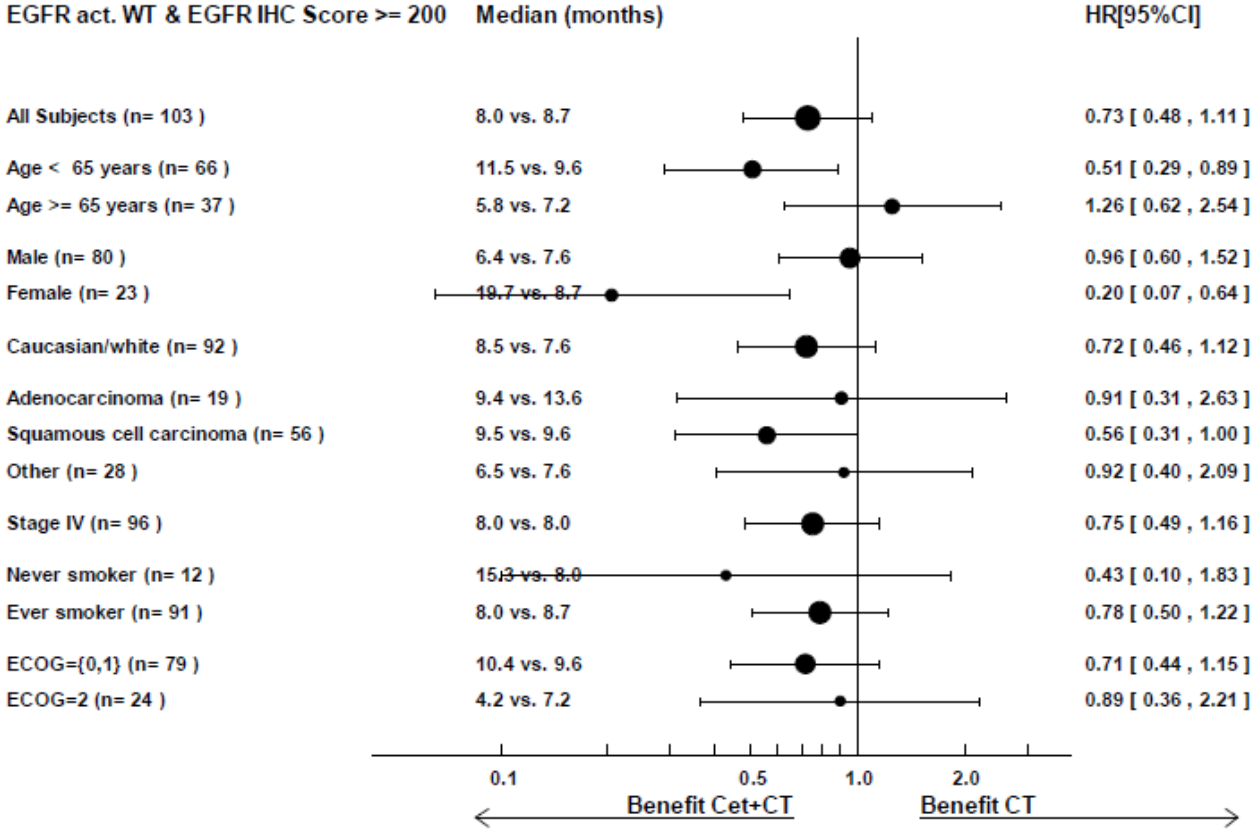


Figure 11: Overall Survival in patients with EGFR wild type Status and high EGFR expression (EMR 62 202-046)



Please note that this figure is based on a smaller number of patients with tumours characterised for EGFR mutation than reported in Table 4.

Ancillary analyses

Differences in stratification factors between IVRS strata and corresponding CRF data were observed for 96 out of 1125 (8.5%) patients of the ITT population; differences on stage were seen for 59 patients, differences on ECOG PS for 38 patients (one patient with both strata different). Differences were observed across 58 out of 155 study sites. There were three centres with 4 differences each; for all other centres, 3 or fewer differences were observed. No pattern across sites was seen. Sensitivity analyses for OS depending on the source of data (IVRS or CRF) are shown in Table 9.

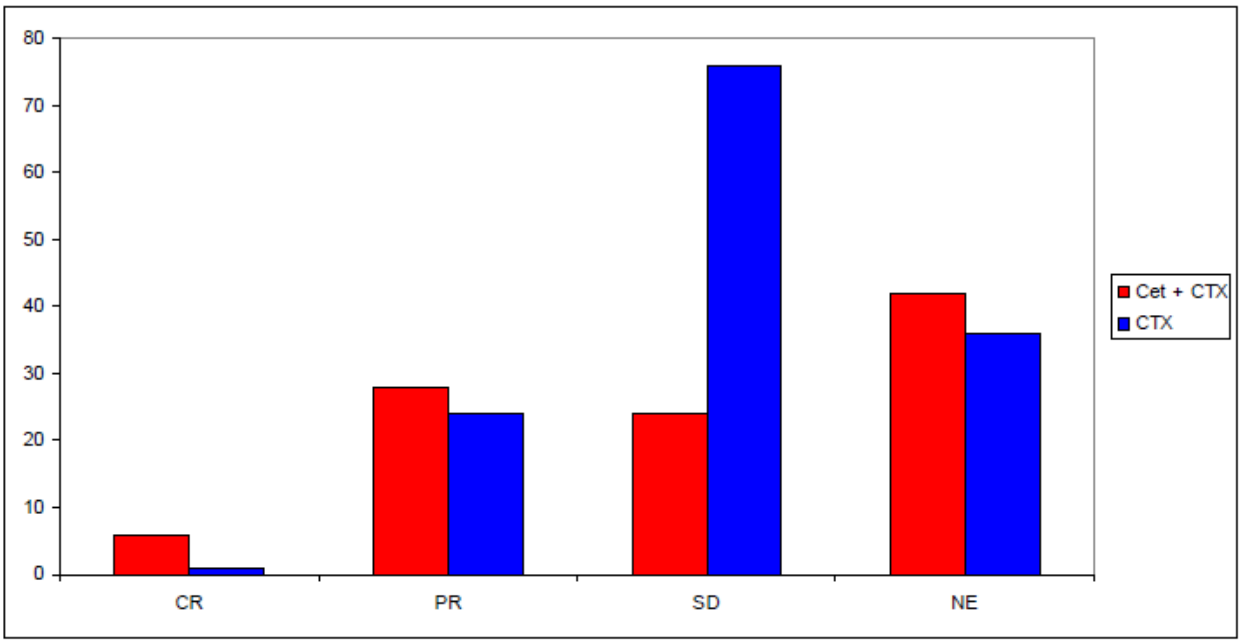
Table 9: Sensitivity analyses for OS (EMR 62 202-046)

Analysis	ITT HR (95% CI) p-value	Low EGFR expression HR (95% CI) p-value	High EGFR expression HR (95% CI) p-value
1. Non-adjusted	0.90 (0.78, 1.02) 0.10	0.99 (0.84, 1.16) 0.88	0.73 (0.58, 0.93) 0.011
2. Stratified (IVRS)	0.87 (0.76, 1.00) 0.044	0.97 (0.82, 1.14) 0.68	0.71 (0.56, 0.91) 0.0065
3. Stratified (CRF)	0.89 (0.78, 1.02) 0.088	0.98 (0.84, 1.15) 0.82	0.73 (0.57, 0.93) 0.011
4. Stratified (IVRS) & adj. for age and gender	0.89 (0.78, 1.02) 0.094	0.99 (0.84, 1.17) 0.93	0.72 (0.57, 0.92) 0.0097
5. Stratified (CRF) & adj. for age and gender	0.91 (0.80, 1.04) 0.18	1.01 (0.86, 1.19) 0.88	0.74 (0.58, 0.94) 0.014

HR: hazard ratio for Cet+CTX versus CTX

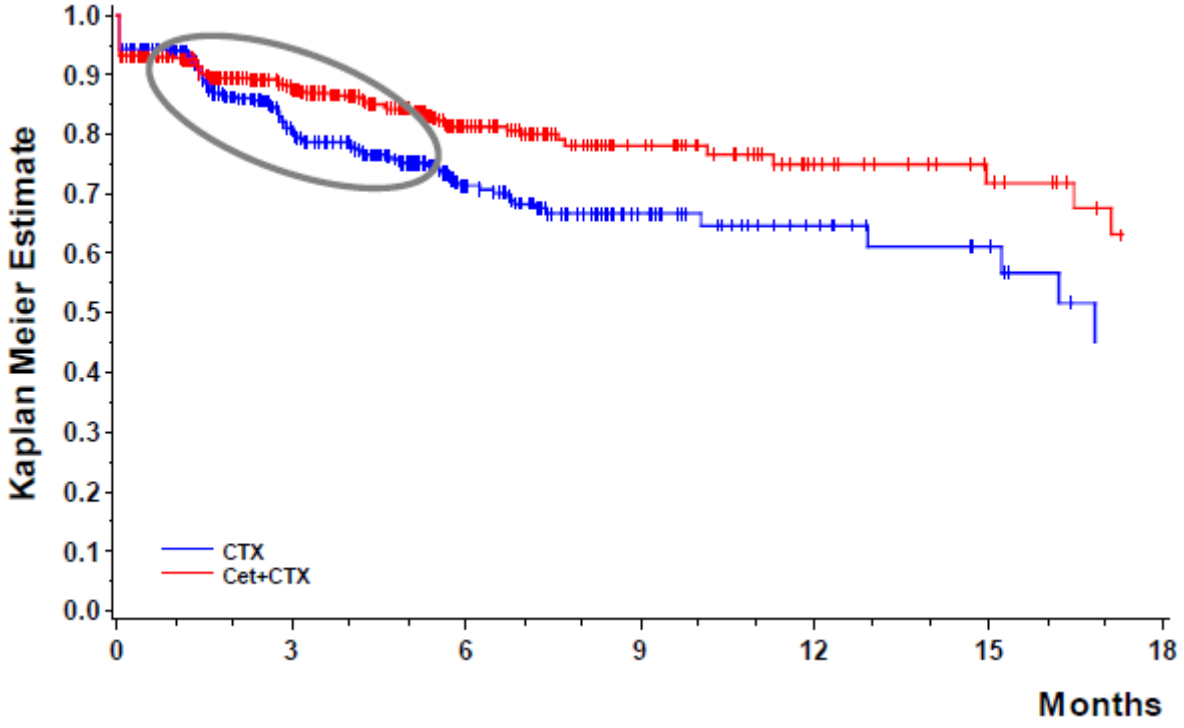
Also of relevance for the discussion, the MAH submitted analyses on both the frequency of and time to censoring for PFS in the pivotal trial (EMR 62 202-046, FLEX) as shown in Figures 12 and 13. As the focus is on time to censoring, Figure 13 is using a reverse Kaplan-Meier approach were progression events are depicted as vertical lines while censoring events lead to a step (drop) in the curve.

Figure 12: Frequency of censoring for PFS by type of response, EMR 62 202-046



CR: complete response, PR: partial response, SD: stable disease, NE: not evaluable

Figure 13: Time to censoring for PFS, EMR 62 202-046, ITT population



Analysis performed across trials (pooled analyses and meta-analysis)

The MAH submitted analyses pertaining to all four randomised, controlled NSCLC trials. Key baseline disease characteristics are summarised in Table 10.

Table 10: Baseline disease characteristics in randomised controlled NSCLC 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.

Key efficacy results are summarised in Tables 11-13.

Table 11: Overall Survival time in the randomised controlled NSCLC trials

Study / statistic	ITT		Low EGFR expression		High EGFR expression	
	Cet + CTX	CTX	Cet + CTX	CTX	Cet + CTX	CTX
EMR 62 202-046	N = 557	N = 568	N = 377	N = 399	N = 178	N = 167
Median OS time (months) 95% CI	11.3 [9.4, 12.4]	10.1 [9.1, 10.9]	9.8 [8.9, 12.2]	10.3 [9.2, 11.5]	12.0 [10.2, 15.2]	9.6 [7.6, 10.6]
Hazard ratio[a] 95% CI	0.871 [0.762, 0.996]		0.99 [0.84, 1.16]		0.73 [0.58, 0.93]	
Log-rank p-value	0.044		0.879		0.011	
Treatment interaction p-value			**0.044**			
CA225099	N = 338	N = 338	N = 35	N = 24	N = 39	N = 38
Median OS time (months) 95% CI	9.7 [8.3, 11.5]	8.4 [7.3, 9.9]	8.1 [7.0, 11.2]	12.4 [9.9, 16.9]	9.3 [6.0, 12.4]	7.6 [6.5, 10.2]
Hazard ratio[a] 95% CI	0.89 [0.75, 1.05]		1.63 [0.91, 2.93]		0.76 [0.47, 1.23]	
Log-rank p-value	0.168		0.098		0.263	
Treatment interaction p-value			**0.042**			
EMR 62 202-011	N = 43	N = 43	N = 22	N = 16	N = 20	N = 23
Median OS time (months) 95% CI	8.3 [6.1, 9.9]	7.3 [5.6, 9.5]	8.6 [6.1, 16.4]	8.0 [5.6, 14.3]	7.7 [5.1, 13.6]	8.0 [5.6, 11.2]
Hazard ratio[a] 95% CI	0.71 [0.45, 1.12]		0.79 [0.39, 1.62]		0.71 [0.37, 1.36]	
CA225100	N = 65	N = 66	Not available		Not available	
Median OS time (months) 95% CI	12.0 [8.8, 15.2]	9.3 [7.4, 11.8]				
Hazard ratio[a] 95% CI	0.84 [0.55, 1.27]					

Cet=cetuximab, CI=confidence interval, CTX=chemotherapy
[a]Hazard ratio of cetuximab+CTX over CTX alone

Table 12: Progression-Free Survival time in the randomised controlled NSCLC trials

Study / statistic	ITT		Low EGFR expression		High EGFR expression	
	Cet + CTX	CTX	Cet + CTX	CTX	Cet + CTX	CTX
EMR 62 202-046	N = 557	N = 568	N = 377	N = 399	N = 178	N = 167
Median PFS time (months) 95% CI	4.8 [4.2, 5.3]	4.8 [4.4, 5.4]	4.6 [4.1, 5.3]	4.9 [4.4, 5.4]	5.0 [4.2, 5.5]	4.6 [4.1, 5.5]
Hazard ratio[a] 95% CI	0.94 [0.82, 1.08]		0.98 [0.83, 1.15]		0.86 [0.68, 1.09]	
Log-rank p-value	0.387		0.799		0.216	
Treatment interaction p-value			0.536			
CA225099	N = 338	N = 338	N = 35	N = 24	N = 39	N = 38
Median PFS time (months) 95% CI	4.4 [4.1, 5.1]	4.2 [3.9, 4.6]	4.5 [3.0, 7.3]	6.0 [5.4, 7.1]	4.6 [2.6, 5,9]	4.2 [2.8, 4.5]
Hazard ratio[a] 95% CI	0.90 [0.76, 1.07]		1.04 [0.58, 1.86]		1.01 [0.61, 1.69]	
Log-rank p-value	0.234		0.891		0.956	
Treatment interaction p-value			0.914			
EMR 62 202-011	N = 43	N = 43	N = 22	N = 16	N = 20	N = 23
Median PFS time (months) 95% CI	5.0 [4.5, 5.8]	4.6 [2.5, 6.0]	5.4 [4.5, 6.4]	4.6 [2.9, 8.9]	4.6 [3.0, 7.5]	4.2 [1.8, 5.2]
Hazard ratio[a] 95% CI	0.71 [0.41, 1.21]		0.76 [0.33, 1.77]		0.68 [0.33, 1.40]	
CA225100	N = 65	N = 66	Not available		Not available	
Median PFS time (months) 95% CI	5.1 [4.2, 6.0]	4.2 [3.8, 5.5]				
Hazard ratio[a] 95% CI	0.80 [0.55, 1.16]					

Cet=cetuximab, CI=confidence interval, CTX=chemotherapy

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

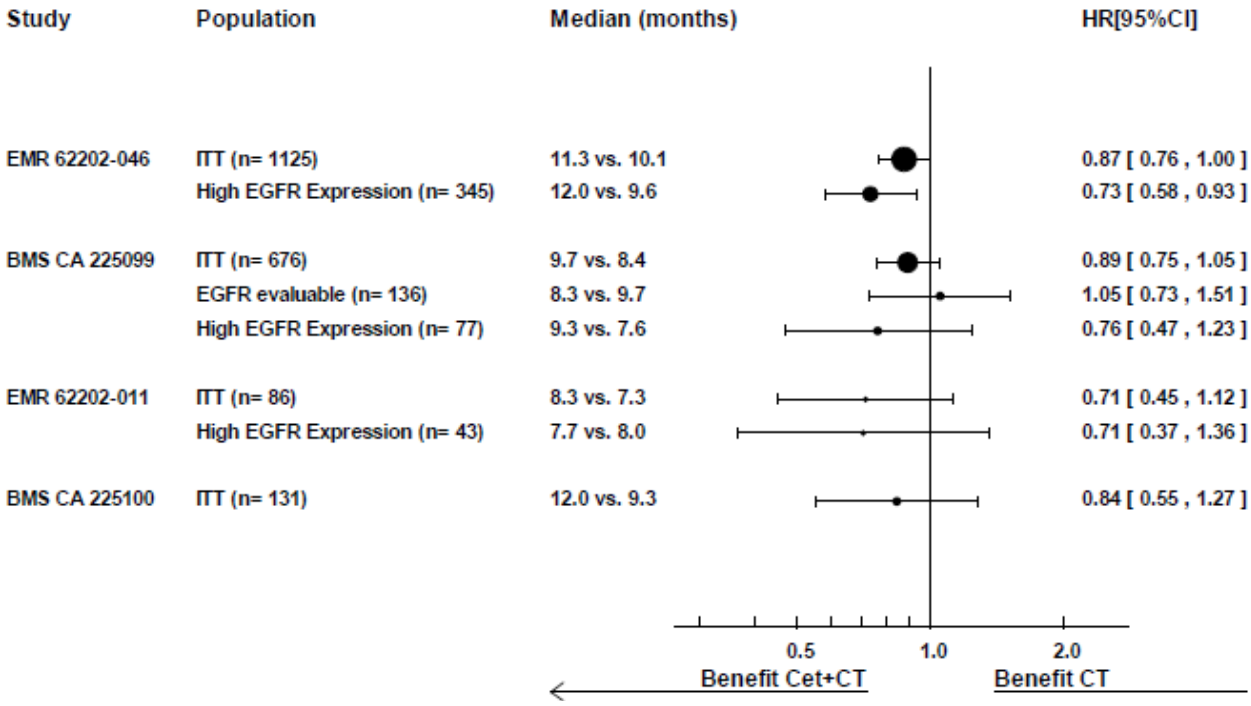
Table 13: Objective Response Rate in the randomised controlled NSCLC trials

Study / statistic	ITT		Low EGFR expression		High EGFR expression	
	Cet + CTX	CTX	Cet + CTX	CTX	Cet + CTX	CTX
EMR 62 202-046	N = 557	N = 568	N = 377	N = 399	N = 178	N = 167
ORR (% subjects) 95% CI	36.4 [32.4, 40.6]	29.2 [25.5, 33.2]	32.6 [27.9, 37.6]	29.6 [25.1, 34.3]	44.4 [37.0, 52.0]	28.1 [21.5, 35.6]
Odds ratio[a] 95% CI	1.39 [1.08, 1.78]		1.15 [0.85, 1.56]		2.04 [1.30, 3.19]	
p-value (CMH test)	0.010		0.359		0.002	
Treatment interaction p-value			0.040			
CA225099	N = 338	N = 338	N = 35	N = 24	N = 39	N = 38
ORR (% subjects) 95% CI	25.7 [21.2, 30.7]	17.2 [13.3, 21.6]	22.9 [10.4, 40.1]	33.3 [15.6, 55.3]	35.9 [21.2, 52.8]	13.2 [4.4, 28.1]
Odds ratio[a] 95% CI	1.68 [1.15, 2.45]		0.59 [0.19, 1.89]		3.70 [1.18, 11.6]	
p-value (CMH test)	0.007		0.378		0.022	
Treatment interaction p-value			0.028			
EMR 62 202-011	N = 43	N = 43	N = 22	N = 16	N = 20	N = 23
ORR (% subjects) 95% CI	34.9 [21.0, 50.9]	27.9 [15.3, 43.7]	36.4 [17.2, 59.3]	25.0 [7.3, 52.4]	30.0 [11.9, 54.3]	30.4 [13.2, 52.9]
Odds ratio[a] 95% CI	1.38 [0.55, 3.46]		1.71 [0.41, 7.14]		0.98 [0.27, 3.61]	
CA225100	N = 65	N = 66	Not available		Not available	
ORR (% subjects) 95% CI	27.7 [17.3, 40.2]	18.2 [9.8, 29.6]				
Odds ratio[a] 95% CI	1.72 [0.75, 3.95]					

Cet=cetuximab, CI=confidence interval, CMH=Cochran-Mantel-Haenszel, CTX=chemotherapy
[a]Odds ratio of cetuximab+CTX over CTX alone

Overall survival time is acknowledged as the clinically most relevant efficacy endpoint for studies in patients with advanced NSCLC. Hazard ratios for OS are shown in Figure 14 for the 4 randomised, controlled studies (wherever possible also for high EGFR expression patients).

Figure 14: Overview of Hazard Ratios for OS in randomised studies



Supportive studies

CA225099

Methods

This was a randomised, open-label, multicenter phase III study of taxane + carboplatin + cetuximab vs. taxane + carboplatin as first-line treatment for patients with advanced metastatic non-small cell lung cancer.

The main inclusion criteria were as follows:

- 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.

Patients were treated in one of the two following ways:

- Cetuximab (initial dose 400 mg/m²; subsequent weekly doses 250 mg/m²)

+ 3-weekly cycles of paclitaxel (225 mg/m² on Day 1) or docetaxel (75 mg/m² on Day 1)

+ carboplatin (dose calculated based on the target area under the curve -AUC 6- for each patient).

- Paclitaxel or docetaxel + carboplatin alone at the same dosages.

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

Patients who met eligibility criteria were randomised (phone) in a 1:1 ratio to either C/T/C or T/C. The investigator specified which taxane the patient would receive, either paclitaxel or docetaxel. Randomisation 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 (Independent Radiology Review Committee) assessments.

Results

There were four protocol amendments. Amendment 3 changed the primary endpoint from response rate to PFS and increased the sample size from 300 to 660.

EGFR expression levels could only be determined in a subset of patients (136/676 (20%)-validation set). Baseline demographic and disease characteristics in the ITT, validation set and by EGFR expression level are given in Table 14.

Table 14: Baseline demographic and disease characteristics by EGFR expression (study CA225099)

Characteristic	Number (%) of subjects							
	ITT		EGFR-evaluable (validation set)		Low EGFR expression		High EGFR expression	
	Cet+CTX N = 338	CTX N = 338	Cet+CTX N = 74	CTX N = 62	Cet+CTX N = 35	CTX N = 24	Cet+CTX N = 39	CTX N = 38
Age, years								
Median	64.0	65.0	63.8	65.5	65.0	65.5	61.0	68.5
Range	37–87	34–85	46–83	34–83	46–83	34–79	47–78	47–83
Age categories								
< 65 years	171 (50.6)	165 (48.8)	42 (56.8)	21 (33.9)	16 (45.7)	11 (45.8)	26 (66.7)	10 (26.3)
≥ 65 years	167 (49.4)	173 (51.2)	32 (43.2)	41 (66.1)	19 (54.3)	13 (54.2)	13 (33.3)	28 (73.7)
Gender								
Male	192 (56.8)	204 (60.4)	41 (55.4)	36 (58.1)	20 (57.1)	16 (66.7)	21 (53.8)	20 (52.6)
Female	146 (43.2)	134 (39.6)	33 (44.6)	26 (41.9)	15 (42.9)	8 (33.3)	18 (46.2)	18 (47.4)
ECOG PS								
0 and 1	331 (97.9)	334 (98.8)	73 (98.6)	61 (98.4)	35 (100.0)	24 (100.0)	38 (97.4)	37 (97.4)
2	4 (1.2)	2 (0.6)	1 (1.4)	1 (1.6)	0 (0.0)	0 (0.0)	1 (2.6)	1 (2.6)
Ethnic origin								
Caucasian	296 (87.6)	300 (88.8)	66 (89.2)	59 (95.2)	33 (94.3)	23 (95.8)	33 (84.6)	36 (94.7)
Asian	6 (1.8)	10 (3.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Other[a]	36 (10.7)	28 (8.3)	8 (10.8)	2 (3.2)	2 (5.7)	1 (4.2)	6 (15.4)	1 (2.6)
Smoker								
Former/current	310 (91.7)	313 (92.6)	70 (94.6)	58 (93.5)	33 (94.3)	22 (91.7)	37 (94.9)	36 (94.7)
Never	28 (8.3)	25 (7.4)	4 (5.4)	4 (6.5)	2 (5.7)	2 (8.3)	2 (5.1)	2 (5.3)
Stage [b]								
Stage IV	314 (92.9)	303 (89.6)	71 (95.9)	55 (88.7)	33 (94.3)	22 (91.7)	38 (97.4)	33 (86.8)
Stage IIIb	24 (7.1)	35 (10.4)	3 (4.1)	7 (11.3)	2 (5.7)	2 (8.3)	1 (2.6)	5 (13.2)
Histology								
Adenocarcinoma	172 (50.9)	182 (53.8)	40 (54.1)	33 (53.2)	19 (54.3)	14 (58.3)	21 (53.8)	19 (50.0)
Squamous cell	67 (19.8)	65 (19.2)	15 (20.3)	16 (25.8)	8 (22.9)	6 (25.0)	7 (17.9)	10 (26.3)
Other	99 (29.3)	91 (26.9)	19 (25.7)	13 (21.0)	8 (22.9)	4 (16.7)	11 (28.2)	9 (23.7)

An overview of key efficacy results by EGFR expression is given in Table 15.

Table 15: Key efficacy results by EGFR expression (study CA225099)

Efficacy endpoint / summary statistic	ITT		EGFR validation set		Low EGFR expression		High EGFR expression	
	Cet+CTX N = 338	CTX N = 338	Cet+CTX N = 74	CTX N = 62	Cet+CTX N = 35	CTX N = 24	Cet+CTX N = 39	CTX N = 38
OS, median (months)	9.7	8.4	8.3	9.7	8.1	12.4	9.3	7.6
Hazard ratio, unadjusted [95% CI]	0.89 [0.75, 1.05]		1.05 [0.73, 1.51]		1.63 [0.91, 2.93]		0.76 [0.47, 1.23]	
p-value (log-rank test)	0.168		0.792		0.098		0.263	
p-value (treatment interaction test)					**0.042**			
Hazard ratio, age adjusted [95% CI]					1.73 [0.96, 3.12]		0.77 [0.46, 1.30]	
PFS time, median (months)	4.4	4.2	4.6	5.3	4.5	6.0	4.6	4.2
Hazard ratio, unadjusted [95% CI]	0.90 [0.76, 1.07]		1.04 [0.71, 1.52]		1.04 [0.58, 1.86]		1.01 [0.61, 1.69]	
p-value (log-rank test)	0.234		0.830		0.891		0.956	
p-value (treatment interaction test)					0.914			
Hazard ratio, age adjusted [95% CI]					1.09 [0.61, 1.96]		0.84 [0.47, 1.51]	
TTF, median (months)	2.9	2.7	3.2	2.8	3.4	4.2	2.9	2.3
Hazard ratio, unadjusted [95% CI]	0.77 [0.66, 0.90]		0.81 [0.57, 1.14]		1.11 [0.65, 1.88]		0.58 [0.36, 0.93]	
p-value (log-rank test)	< 0.001		0.217		0.708		0.023	
p-value (treatment interaction test)					0.079			
Hazard ratio, age adjusted [95% CI]					1.07 [0.62, 1.82]		0.59 [0.35, 0.98]	
ORR, % subjects	25.7	17.2	29.7	21.0	22.9	33.3	35.9	13.2
Odds ratio, unadjusted [95% CI]	1.68 [1.15, 2.45]		1.59 [0.72, 3.51]		0.59 [0.19, 1.89]		3.70 [1.18, 11.6]	
p-value (CMH test)	0.007		0.246		0.378		0.022	
p-value (treatment interaction test)					0.028			
Odds ratio, age adjusted [95% CI]					0.59 [0.18, 1.89]		5.69 [1.55, 20.9]	

Cet=cetuximab, CTX=chemotherapy, CMH=Cochran-Mantel-Haenszel

EMR 62 202-011

This was an open-label, randomised 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 patients with advanced EGFR-positive NSCLC.

The main inclusion criteria were as follows:

- 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.

Patients received one of the two folowing treatments:

- Cetuximab (initial dose 400 mg/m²; subsequent weekly doses 250 mg/m²)

3-weekly cycles of cisplatin (80 mg/m² on Day 1) + vinorelbine (25 mg/m² on Days 1 and 8)

- 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 patients who had received cetuximab.

Key efficacy results are summarised in Table 16.

Table 16: Efficacy results in study EMR 62 202-011

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

CA225100

This was a randomised multicentre phase II study of gemcitabine/platinum/cetuximab vs. chemotherapy alone as first-line treatment for patients with advanced/metastatic non-small cell lung cancer. EGFR expression levels were not availbale for this study, but because results were included in the pooled analyses, the study is briefly described here.

The main inclusion citeria were as follows:

- 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 patients received one of the two following treatments:

- 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).

- 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 patients who had received cetuximab.

Key efficacy results are summarised in Table 17.

Table 17: Efficacy results in study CA225100

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

2.4.1. Discussion on clinical efficacy

Based on clinical data in metastatic colorectal cancer (mCRC) and squamous cell carcinoma of the head & neck (SCCHN), a role for EGFR expression as a predictive biomarker for cetuximab efficacy has not been obvious so far. The EGFR is part of a highly complex system that can bind multiple different ligands, while various possibilities exist for homo- and heterodimerization with HER family members, for direct and indirect interactions with other cell surface receptors and for engaging many different cell signalling pathways in different indications. As a consequence, the functional biological role of EGFR is highly context dependent and can vary from indication to indication and biomarkers for anti-EGFR therapies cannot be automatically transferred from one indication to another.

In previous applications in NSCLC (Avastin, Alimta), the biologic agent seemed to work more favourably in patients with non-squamous histology. Treatment effect of Erbitux is enhanced in both major histologic subgroups (adeno- and non adeno-ca) in the high expressing EGFR groups. The slightly higher benefit for squamous cell NSCLC patients already noted in the evaluation of the ITT data in the II/29 application was confirmed upon review of the new analysis (see Figure 10).

By and large the conclusions of the assessment of the previous variation (II/29) still hold true. Analyses and conclusions must largely be founded on the pivotal trial (EMR62202-046), for which EGFR expression was an inclusion criterion and nearly all patients could be classified as high or low expressors. The smaller validation (CA225099) and supportive (EMR62202-011) studies are not convincing: both analyses only concern comparatively small patient groups and the validation study is only a retrospectively analysed subset of patient data which concerns only 20% of the original study population. Some questions arise whether these retrospective subgroups are representative of the overall patient population, since in some instances the control group fares much better or worse for no obvious reason.

Regarding outcome, cetuximab as add-on to chemotherapy in the first-line treatment of advanced NSCLC has convincingly been demonstrated to increase tumour response rates. In the new analysis of the pivotal trial, patients with high EGFR expression have even higher ORRs, the odds ratio is improved and the therapeutic interaction test is significant. The smaller validation (CA225099) and supportive (EMR62202-011) studies give conflicting results for patients with high EGFR expression which may be due to the retrospective analysis of these small patient populations.

Time related endpoints improve in the new differential EGFR analysis and especially data concerning the primary endpoint of Overall Survival in the pivotal study are more pronounced: the treatment effect between cetuximab-treated and control groups becomes larger, the HR leads to a clinically meaningful reduction in the risk of death (HR 0.73 in high EGFR vs 0.87 in the ITT) and the treatment interaction is significant. These observations are somewhat confirmed in the smaller validation set (HR 0.76 in high EGFR vs 0.89 in the ITT) and supportive study (HR unchanged: 0.71), but questions arise as to whether these may be artificial effects due to imbalances in the control arms which lead to unfavourable results in the low EGFR and in the ITT. With the new analysis, it still cannot be excluded that the benefit in OS is induced through second line therapies, especially TK inhibitors, after disease progression or 'treatment failure'.

In terms of additional number of months life gained, the treatment effect is modest, albeit not unimportant, with 12.0 months OS in the high EGFR expressor group and 9.6 mo in the control arm, i.e 2.4 months longer median OS, against which any additional risk (AEs, quality of life ..) must be weighed carefully.

Importantly, there is difference between the OS results obtained if stratified by IVRS (p=0.044) and CRF (p=0.088, see Table 9). This indicates that there is a difference between CRF and IVRS in factors used for stratification (tumour stage and performance status). According to the SAP, IVRS should be used in the primary analysis as this was how patients were actually stratified. The analyses originally undertaken were done in accordance with the SAP and the results were found to be consistent. Moreover, the primary analysis based on stratification according to IVRS was supported by the sensitivity analysis where step wise selection of co-variates was undertaken and with CRF data for stratification factors forced into the model. The reason for using the CRF data for this analysis was that these data were source data verified (SDV) and underwent a cleaning process. As the CRF data for the stratification factors were included in the model, this analysis also accounts for the differences between CRF and IVRS data. The result of this analysis (hazard ratio (HR) = 0.86 (95% CI 0.75, 0.99), p=0.039) are in agreement with those of the primary analysis (HR = 0.87 (95% CI 0.76, 1.00), p=0.044). Therefore, there was no evidence that the treatment effect in the primary analysis was biased. A total of 1051 patients were included in this model.

Finally, an additional exploratory analysis of OS in the ITT population was conducted using a multivariable Cox model that includes the variables with strongest prognostic value only: ECOG performance status, number of organs involved, histology, and smoking status. This resulted in a HR of 0.84 (95% CI 0.73, 0.97) with a p-value of 0.017.

With respect to PFS, neither the ITT-based nor the new EGFR expression-based analysis could demonstrate an improvement. In a pooled PFS analysis in the ITT the results were borderline significant (0.036, please refer to variation II/29). As pointed out before, this lack of significant PFS differences may be related to biased censoring. Figures 12 and 13 suggest that patients in the control arm of the pivotal FLEX trial, particularly patients with stable disease, were switched to subsequent treatment in the absence of radiologically confirmed progression more frequently and more quickly than patients receiving cetuximab, hence they were censored for the PFS analysis. This introduces bias in favour of the control arm which could explain the apparent absence of effect in terms of PFS. To account for this, the MAH submitted a sensitivity time-to-treatment-failure (TTF) analysis based on investigator data which treated switches to subsequent therapy as events rather than censoring for them. Such analysis showed statistically significant effect for TTF in both phase III trials (EMR 62 202-046 and CA 225099) and in both the ITT and the 'high EGFR expression' population (Tables 8, 15). Moreover, further sensitivity analyses (Figure 12) showed that most patients taken off study prior to progression of disease in the control arm had Stable Disease (SD) as best response to first line therapy and that more patients in the control arm were offered second line therapy compared to the

experimental arm. In any case, next-line therapy and/or too brief first-line therapy (currently, 4 cycles are normally followed, not 6) are unlikely to have biased the results in favour of the experimental arm to such an extent that it has caused the reported difference in OS.

The MAH re-analysed the data of EMR 62 202-046 according to EGFR mutation status (86.3% (971/1125) of the ITT population, see Table 4). The percentages of samples with activating EGFR mutations, Asians and Caucasians, were as expected. Due to the small sample of patients with mutation positive tumours, results should be interpreted cautiously. Nevertheless, this analysis showed that in the ITT and in terms of ORR and PFS/TTF, the add-on activity of cetuximab appears higher in case of mutation positive tumours, but this is not born out in terms of survival. Within the 'high EGFR expression' population, the HR for OS is further improved when EGFR is wild-type and, on the contrary, it is worse in case of EGFR (activating) mutations, but data on PFS, TTF and ORR within the different EGFR mutation subgroups were again not consistent with the OS data possibly due to next line treatment with EGFR-TK inhibitors. In any case, the MAH acknowledged that EGFR TKIs are standard 1st line treatment for patients carrying EGFR mutations and reflected the topic of EGFR mutation status appropriately in the product information including by means of a revised indication.

In CA2255099, median OS was longer in the chemotherapy only group in tumours with low EGFR IHC score (12.4 months) in contrast to tumours with high EGFR IHC score (7.6 months, see Tables 11 and 15). This discrepancy was also observed for the ORR analysis (see Tables 13 and 15) and is not in agreement with the data presented in the NSCLC primary explant study (see Figure 3). It was also observed to a much lesser degree for the main study EMR 62 202-046 (see Tables 7, 11 and 13) and may point to the limitations of the retrospective analysis of study CA225099 (e.g. the number of patients in the two arms was 24 and 35) leading to imbalances in treatment arms in the retrospective analysis according to IHC status.

2.5. Clinical safety

The primary evaluation of safety is based on the 4 randomised, controlled studies with a total of 1970 first-line treated NSCLC patients; 979 of the patients received cetuximab in combination with various platinum-based chemotherapies. Safety data were evaluated for the overall safety population (N = 1970) and by EGFR expression level (high EGFR expression N = 463, low EGFR expression N = 859).

Patient exposure

Exposure to cetuximab and chemotherapy in the ITT and by EGFR expression level in the 4 randomised, controlled studies is summarised in Table 18.

In the three trials with EGFR evaluable patients, exposure to chemotherapy in the high EGFR expression subgroup was higher in the cetuximab arm compared to the chemotherapy only control arm. Exposure to chemotherapy was also higher in the high EGFR expression subgroup compared to the low EGFR expression subgroup of the pivotal trial EMR 62 202-046 (FLEX), while an opposite trend was observed in the other phase III trial (CA225099) in which only 20% of patients were evaluable for EGFR expression, though (data not shown).

Table 18: Exposure to cetuximab and chemotherapy in the randomised, controlled studies

Study / population	CTX	Number (%) subjects					
		Cetuximab + CTX		CTX		Total	
EMR 62 202-046	Cisplatin + vinorelbine						
Safety		548		562		1110	
EGFR evaluable [a]		546	(100.0)	560	(100.0)	1106	(100.0)
Low EGFR expression		371	(67.9)	392	(70.0)	763	(69.0)
High EGFR expression		175	(32.1)	168	(30.0)	343	(31.0)
CA225099	Taxane + carboplatin						
Safety		325		320		645	
EGFR evaluable		74	(100.0)	62	(100.0)	136	(100.0)
Low EGFR expression		35	(47.3)	24	(38.7)	59	(43.4)
High EGFR expression		39	(52.7)	38	(61.3)	77	(56.6)
EMR 62 202-011	Cisplatin + vinorelbine						
Safety		42		43		85	
EGFR evaluable		41	(100.0)	39	(100.0)	80	(100.0)
Low EGFR expression		21	(51.2)	16	(41.0)	37	(46.3)
High EGFR expression		20	(48.8)	23	(59.0)	43	(53.7)
CA225100	Gemcitabine + carboplatin						
Safety		64		66		130	
EGFR evaluable		NA		NA		NA	
Total							
Safety		979		991		1970	
EGFR evaluable		661	(100.0)	661	(100.0)	1322	(100.0)
Low EGFR expression		427	(64.6)	432	(65.4)	859	(65.0)
High EGFR expression		234	(35.4)	229	(34.6)	463	(35.0)

Adverse events

In the safety population of study EMR 62 202-046, the most frequent AEs reported for > 25% patients in either treatment arm were neutropenia, nausea, anemia, vomiting, anorexia, constipation, fatigue, and leukopenia. Rash was reported in > 25% patients in the cetuximab + CTX arm. These were also the most frequent AEs in the EGFR expression groups.

The AE profiles in patients with low and high EGFR expression in studies CA225099 and EMR 62 202-011 were generally in accordance with those in the overall safety population of the studies (data not shown).

Severe AEs were more frequent in patients treated with cetuximab add-on (grade 3 or 4 AEs 91.1% vs. 86.3%; Grade 4 AEs 62.4% vs. 52.3%, safety population of study EMR 62 202-046; see Table 19). These AEs include febrile neutropenia, diarrhoea, pneumonia, deep vein thrombosis, pulmonary embolism and sepsis/septic shock among others.

AEs of special interest

Special analyses were performed for the following composite AEs (special AE categories): acne-like rash, infusion-related reactions (IRRs), mucositis, haemorrhages, thromboembolic events, cardiac events and septic events. The analyses presented are based on results from the 4 randomised, controlled studies.

Table 19: Frequencies of selected special AE categories and AEs (Safety Population)

AE category or preferred term / grade	Number (%) subjects							
	EMR 62 202-046		CA225099		EMR 62 202-011		CA225100	
	Cet + CTX N = 548	CTX N = 562	Cet + CTX N = 325	CTX N = 320	Cet + CTX N = 42	CTX N = 43	Cet + CTX N = 64	CTX N = 66
AE any grade	545 (99.5)	549 (97.7)	324 (99.7)	319 (99.7)	41 (97.6)	42 (97.7)	64 (100.0)	65 (98.5)
AE grade 3 or 4	499 (91.1)	485 (86.3)	257 (79.1)	196 (61.3)	33 (78.6)	34 (79.1)	48 (75.0)	35 (53.0)
AE grade 4	342 (62.4)	294 (52.3)	93 (28.6)	70 (21.9)	16 (38.1)	20 (46.5)	25 (39.1)	19 (28.8)
Acne-like rash								
AE any grade	382 (69.7)	42 (7.5)	255 (78.5)	71 (22.2)	33 (78.6)	2 (4.7)	50 (78.1)	15 (22.7)
AE grade 3 or 4	57 (10.4)	1 (0.2)	35 (10.8)	0 (–)	3 (7.1)	0 (–)	9 (14.1)	0 (–)
IRRs								
AE any grade	53 (9.7)	17 (3.0)	52 (16.0)	24 (7.5)	3 (7.1)	1 (2.3)	17 (26.6)	4 (6.1)
AE grade 3 or 4	19 (3.5)	7 (1.2)	20 (6.2)	5 (1.6)	1 (2.4)	1 (2.3)	4 (6.3)	0 (–)
Mucositis								
AE any grade	148 (27.0)	56 (10.0)	112 (34.5)	60 (18.8)	7 (16.7)	0 (–)	15 (23.4)	11 (16.7)
AE grade 3 or 4	10 (1.8)	2 (0.4)	9 (2.8)	3 (0.9)	0 (–)	0 (–)	1 (1.6)	1 (1.5)
Hypomagnesemia								
AE any grade	54 (9.9)	27 (4.8)	31 (9.5)	3 (0.9)	1 (2.4)	0 (–)	3 (4.7)	2 (3.0)
AE grade 3 or 4	16 (2.9)	5 (0.9)	2 (0.6)	1 (0.3)	1 (2.4)	0 (–)	0 (–)	0 (–)
Lab any grade[a]	55 (50.9)	16 (28.1)	166 (56.1)	77 (27.7)	Not available		37 (61.7)	19 (31.7)
Lab grade 3 or 4[a]	12 (11.1)	3 (5.3)	26 (8.8)	2 (0.7)	Not available		2 (3.3)	1 (1.7)
Thromboembolic events								
AE grade 3 or 4	40 (7.3)	29 (5.2)	25 (7.7)	12 (3.8)	2 (4.8)	2 (4.7)	0 (–)	5 (7.6)
DVT	12 (2.2)	5 (0.9)	9 (2.8)	5 (1.6)	1 (2.4)	1 (2.3)	0 (–)	4 (6.1)
PE	23 (4.2)	16 (2.8)	9 (2.8)	5 (1.6)	1 (2.4)	0 (–)	0 (–)	2 (3.0)
AE grade 4	23 (4.2)	12 (2.1)	9 (2.8)	3 (0.9)	1 (2.4)	1 (2.3)	0 (–)	1 (1.5)
DVT	0 (–)	0 (–)	0 (–)	1 (0.3)	1 (2.4)	1 (2.3)	0 (–)	0 (–)
PE	23 (4.2)	11 (2.0)	8 (2.5)	1 (0.3)	1 (2.4)	0 (–)	0 (–)	1 (1.5)
Cardiac events								
AE grade 3 or 4	31 (5.7)	28 (5.0)	22 (6.8)	10 (3.1)	1 (2.4)	1 (2.3)	4 (6.3)	4 (6.1)
AE grade 4	22 (4.0)	13 (2.3)	13 (4.0)	6 (1.9)	0 (–)	0 (–)	4 (6.3)	4 (6.1)
Febrile neutropenia								
AE grade 3 or 4	119 (21.7)	87 (15.5)	15 (4.6)	11 (3.4)	Not applicable[b]		3 (4.7)	1 (1.5)
AE grade 4	34 (6.2)	25 (4.4)	2 (0.6)	2 (0.6)	Not applicable[b]		1 (1.6)	0 (–)
Neutropenia								
AE grade 3 or 4	289 (52.7)	289 (51.4)	28 (8.6)	19 (5.9)	Not applicable[b]		5 (7.8)	7 (10.6)
AE grade 4	210 (38.3)	212 (37.7)	19 (5.8)	12 (3.8)	Not applicable[b]		3 (4.7)	3 (4.5)
Lab grade 3 or 4[a]	420 (79.1)	380 (69.7)	198 (62.7)	176 (55.9)	35 (83.3)	23 (53.5)	31 (48.4)	32 (49.2)
Lab grade 4[a]	320 (60.3)	281 (51.6)	135 (42.7)	102 (32.4)	21 (50.0)	16 (37.2)	15 (23.4)	8 (12.3)
Leukopenia								
AE grade 3 or 4	139 (25.4)	109 (19.4)	1 (0.3)	1 (0.3)	21 (50.0)	22 (51.2)	2 (3.1)	2 (3.0)
Lab grade 3 or 4[a]	350 (65.4)	294 (53.7)	139 (44.0)	97 (30.7)	21 (50.0)	16 (37.2)	21 (32.8)	28 (43.1)
Septic events								
AE grade 3 or 4	25 (4.6)	9 (1.6)	9 (2.8)	3 (0.9)	2 (4.8)	0 (–)	4 (6.3)	0 (–)
AE grade 4	21 (3.8)	2 (0.4)	1 (0.3)	1 (0.3)	0 (–)	0 (–)	1 (1.6)	0 (–)

Table 20: Frequencies of selected special AE categories and AEs in the phase III studies (low and high EGFR expression groups)

AE category or preferred term / grade	Number (%) subjects							
	EMR 62 202-046				CA225099			
	Low EGFR		High EGFR		Low EGFR		High EGFR	
	Cet + CTX N = 371	CTX N = 392	Cet + CTX N = 175	CTX N = 168	Cet + CTX N = 35	CTX N = 24	Cet + CTX N = 39	CTX N = 38
AE any grade	368 (99.2)	382 (97.4)	175 (100.0)	165 (98.2)	35 (100.0)	24 (100.0)	39 (100.0)	38 (100.0)
AE grade 3 or 4	345 (93.0)	333 (84.9)	153 (87.4)	151 (89.9)	26 (74.3)	10 (41.7)	31 (79.5)	20 (52.6)
AE grade 4	237 (63.9)	198 (50.5)	104 (59.4)	96 (57.1)	9 (25.7)	4 (16.7)	9 (23.1)	5 (13.2)
Acne-like rash								
AE any grade	257 (69.3)	31 (7.9)	123 (70.3)	11 (6.5)	28 (80.0)	7 (29.2)	29 (74.4)	5 (13.2)
AE grade 3 or 4	39 (10.5)	1 (0.3)	18 (10.3)	0 (–)	3 (8.6)	0 (–)	4 (10.3)	0 (–)
IRRs								
AE any grade	40 (10.8)	12 (3.1)	13 (7.4)	5 (3.0)	5 (14.3)	3 (12.5)	8 (20.5)	2 (5.3)
AE grade 3 or 4	15 (4.0)	4 (1.0)	4 (2.3)	3 (1.8)	1 (2.9)	1 (4.2)	1 (2.6)	0 (–)
Mucositis								
AE any grade	109 (29.4)	43 (11.0)	39 (22.3)	13 (7.7)	11 (31.4)	4 (16.7)	17 (43.6)	7 (18.4)
AE grade 3 or 4	9 (2.4)	2 (0.5)	1 (0.6)	0 (–)	0 (–)	0 (–)	1 (2.6)	0 (–)
Hypomagnesemia								
AE any grade	44 (11.9)	17 (4.3)	10 (5.7)	10 (6.0)	3 (8.6)	0 (–)	5 (12.8)	0 (–)
AE grade 3 or 4	13 (3.5)	4 (1.0)	3 (1.7)	1 (0.6)	0 (–)	0 (–)	0 (–)	0 (–)
Lab any grade[a]	41 (59.4)	11 (27.5)	14 (36.8)	5 (29.4)	13 (40.6)	6 (26.1)	19 (51.4)	9 (26.5)
Lab grade 3 or 4[a]	8 (11.6)	2 (5.0)	4 (10.5)	1 (5.9)	2 (6.3)	1 (4.3)	3 (8.1)	1 (2.9)
Thromboembolic events								
AE grade 3 or 4	30 (8.1)	21 (5.4)	10 (5.7)	8 (4.8)	2 (5.7)	0 (–)	5 (12.8)	1 (2.6)
DVT	9 (2.4)	4 (1.0)	3 (1.7)	1 (0.6)	1 (2.9)	0 (–)	2 (5.1)	0 (–)
PE	18 (4.9)	10 (2.6)	5 (2.9)	6 (3.6)	1 (2.9)	0 (–)	3 (7.7)	0 (–)
AE grade 4	18 (4.9)	8 (2.0)	5 (2.9)	4 (2.4)	1 (2.9)	0 (–)	3 (7.7)	1 (2.6)
DVT	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
PE	18 (4.9)	7 (1.8)	5 (2.9)	4 (2.4)	1 (2.9)	0 (–)	3 (7.7)	0 (–)
Cardiac events								
AE grade 3 or 4	24 (6.5)	17 (4.3)	7 (4.0)	11 (6.5)	3 (8.6)	0 (–)	1 (2.6)	2 (5.3)
AE grade 4	18 (4.9)	8 (2.0)	4 (2.3)	5 (3.0)	2 (5.7)	0 (–)	0 (–)	1 (2.6)
Febrile neutropenia								
AE grade 3 or 4	80 (21.6)	60 (15.3)	39 (22.3)	27 (16.1)	0 (–)	0 (–)	3 (7.7)	2 (5.3)
AE grade 4	23 (6.2)	14 (3.6)	11 (6.3)	11 (6.5)	0 (–)	0 (–)	0 (–)	0 (–)
Neutropenia								
AE grade 3 or 4	199 (53.6)	202 (51.5)	89 (50.9)	87 (51.8)	3 (8.6)	1 (4.2)	5 (12.8)	0 (–)
AE grade 4	143 (38.5)	148 (37.8)	66 (37.7)	64 (38.1)	1 (2.9)	1 (4.2)	3 (7.7)	0 (–)
Lab grade 3 or 4[a]	282 (78.6)	265 (69.7)	137 (80.6)	114 (69.9)	23 (65.7)	12 (50.0)	26 (66.7)	19 (50.0)
Lab grade 4[a]	215 (59.9)	194 (51.1)	104 (61.2)	87 (53.4)	16 (45.7)	9 (37.5)	15 (38.5)	11 (28.9)
Leukopenia								
AE grade 3 or 4[a]	90 (24.3)	76 (19.4)	49 (28.0)	33 (19.6)	1 (2.9)	0 (–)	0 (–)	0 (–)
Lab grade 3 or 4[a]	233 (64.5)	206 (53.9)	116 (67.4)	88 (54.0)	19 (54.3)	5 (20.8)	14 (35.9)	14 (36.8)
Septic events								
AE grade 3 or 4	19 (5.1)	8 (2.0)	6 (3.4)	1 (0.6)	1 (2.9)	0 (–)	1 (2.6)	0 (–)
AE grade 4	15 (4.0)	2 (0.5)	6 (3.4)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)

Due to their importance, details of cardiac events observed in the two phase III trials are presented in Table 21.

Table 21: Number (%) of patients with 'cardiac events' in the phase III randomised controlled trials

Study	Safety population				Low EGFR expression				High EGFR expression			
AE grade	Cet+CTX		CTX		Cet+CTX		CTX		Cet+CTX		CTX	
Medical concept	n	%	n	%	n	%	n	%	n	%	n	%
EMR 62 202-046												
Total subjects	548	100.0	562	100.0	371	100.0	392	100.0	175	100.0	168	100.0
Any grade	76	13.9	68	12.1	51	13.7	48	12.2	25	14.3	20	11.9
Infarction/ischaemia	13	2.4	10	1.8	8	2.2	6	1.5	5	2.9	4	2.4
Grade 3 or 4	31	5.7	28	5.0	24	6.5	17	4.3	7	4.0	11	6.5
Infarction/ischaemia	8	1.5	4	0.7	6	1.6	1	0.3	2	1.1	3	1.8
Grade 4	22	4.0	13	2.3	18	4.9	8	2.0	4	2.3	5	3.0
Infarction/ischaemia	7	1.3	3	0.5	6	1.6	1	0.3	1	0.6	2	1.2
Sudden death	4	0.7	0	–	2	0.5	0	–	2	1.1	0	–
CA225099												
Total subjects	325	100.0	320	100.0	35	100.0	24	100.0	39	100.0	38	100.0
Any grade	58	17.8	26	8.1	5	14.3	0	–	5	12.8	3	7.9
Arrhythmia	45	13.8	19	5.9	4	11.4	0	–	3	7.7	2	5.3
Grade 3 or 4	22	6.8	10	3.1	3	8.6	0	–	1	2.6	2	5.3
Arrest	6	1.8	3	0.9	1	2.9	0	–	0	–	0	–
Arrhythmia	12	3.7	4	1.3	2	5.7	0	–	1	2.6	1	2.6
Grade 4	13	4.0	6	1.9	2	5.7	0	–	0	–	1	2.6

Serious adverse event/deaths/other significant events

Overall frequencies of SAEs in the four randomised, controlled studies are summarised in Table 22.

Table 22: Overall frequencies of SAEs in randomised controlled studies

Study	Safety population				Low EGFR expression				High EGFR expression			
Type of SAE	Cet+CTX		CTX		Cet+CTX		CTX		Cet+CTX		CTX	
	n	%	n	%	n	%	n	%	n	%	n	%
EMR 62 202-046												
Total subjects	548	100.0	562	100.0	371	100.0	392	100.0	175	100.0	168	100.0
Any SAE	325	59.3	244	43.4	227	61.2	168	42.9	97	55.4	76	45.2
Treatment-related SAE	239	43.6	170	30.2	166	44.7	115	29.3	73	41.7	55	32.7
CA225099												
Total subjects	325	100.0	320	100.0	35	100.0	24	100.0	39	100.0	38	100.0
Any SAE	180	55.4	121	37.8	17	48.6	5	20.8	25	64.1	12	31.6
Treatment-related SAE	87	26.8	39	12.2	6	17.1	2	8.3	12	30.8	4	10.5
EMR 62 202-011												
Total subjects	42	100.0	43	100.0	21	100.0	16	100.0	20	100.0	23	100.0
Any SAE	20	47.6	18	41.9	8	38.1	7	43.8	12	60.0	9	39.1
Treatment-related SAE	15	35.7	13	30.2	5	23.8	6	37.5	10	50.0	5	21.7
CA225100												
Total subjects	64	100.0	66	100.0	Not applicable				Not applicable			
Any SAE	31	48.4	26	39.4								
Treatment-related SAE	17	26.6	7	10.6								

The overall frequency of SAEs across the 4 randomized, controlled studies was approximately 15% higher in the combined cetuximab + chemotherapy group than in the chemotherapy group: 56.8% (556/979) vs 41.3% (409/991) patients.

The most frequent SAEs in the combined cetuximab + chemotherapy arms and the combined chemotherapy arms of the large randomised, controlled studies EMR 62 202-046 and CA225099 included neutropenia in 6.4% (56/873) vs 4.2% (37/882) patients, febrile neutropenia in 12.6% (110/873) vs 8.5% (75/882) patients, and pneumonia in 4.2% (37/873) vs 2.7% (24/882) patients. All of these events were more common in the cetuximab + chemotherapy group than the chemotherapy group but consistent with the known safety profile of cetuximab.

In the case of other common SAEs, frequencies were either comparable between treatment groups or higher in the cetuximab + chemotherapy group but consistent with the known safety profile of cetuximab. The SAE general physical health deterioration was more common in the cetuximab + chemotherapy group of only 1 study: 22 (4.0%) vs 4 (0.7%) in study EMR 62 202-046. The imbalance in this SAE may be due to the longer observation period resulting in a higher rate of tumor progressions in the cetuximab + chemotherapy arm during the treatment phase.

With regard to EGFR expression subgroups, across the 3 studies evaluated for EGFR expression, combined frequencies of SAEs were as follows for the cetuximab + chemotherapy vs chemotherapy treatment arms: high EGFR expression group 57.3% (134/234) vs 42.4% (97/229); low EGFR expression group 59.0% (252/427) vs 41.7% (180/432). In the pivotal study EMR 62 202-046, the overall frequencies of SAEs in the high EGFR expression group were similar to those in the safety population: high EGFR expression group 55.4% vs 45.2%, safety population 59.3% vs 43.4%. The most frequently reported SAEs were (febrile) neutropenia; frequencies of this SAE in the high EGFR expression group were comparable with those in the overall safety population. Overall, the SAE profile in the targeted patient population (i.e. patients with high EGFR expression) in study EMR 62 202-046 is in line with the product information. Treatment-related SAEs (relationship to cetuximab or chemotherapy as assessed by the investigator) were reported more frequently in the cetuximab + chemotherapy vs chemotherapy arm of the safety population (43.6% vs 30.2%), the low EGFR expression group (44.7% vs 29.3%) and the high EGFR expression group (41.7% vs 32.7%).

The SAE profiles in the smaller EGFR expression groups of studies CA225099 and EMR 62 202-011 were difficult to interpret due to the low numbers of patients. However, there were no unexpected findings.

Frequencies and primary reasons for deaths occurring on study treatment or up to 30 days after the last dose of study medication are summarised for the safety populations and the EGFR expression groups of the 4 randomised, controlled studies in Table 23.

Table 23: Deaths during study treatment and up to 30 days after last dose of study treatment in randomised controlled studies

Study Primary reason for death	Safety population				Low EGFR expression				High EGFR expression			
	Cet+CTX		CTX		Cet+CTX		CTX		Cet+CTX		CTX	
	n	%	n	%	n	%	n	%	n	%	n	%
EMR 62 202-046												
Total subjects	548	100.0	562	100.0	371	100.0	392	100.0	175	100.0	168	100.0
Total subjects who died	103	18.8	76	13.5	72	19.4	48	12.2	30	17.1	26	15.5
Disease progression	33	6.0	30	5.3	24	6.5	21	5.4	8	4.6	8	4.8
Reasons other than PD	60	10.9	36	6.4	42	11.3	19	4.8	18	10.3	17	10.1
Unknown	10	1.8	10	1.8	6	1.6	8	2.0	4	2.3	1	0.6
CA225099												
Total subjects	325	100.0	320	100.0	35	100.0	24	100.0	39	100.0	38	100.0
Total subjects who died	37	11.4	27	8.4	6	17.1	1	4.2	1	2.6	3	7.9
Tumor related disease	31	9.5	19	5.9	6	17.1	1	4.2	1	2.6	1	2.6
Reasons other than PD	6	1.8	8	2.5	0	–	0	–	0	–	2	5.3
EMR 62 202-011												
Total subjects	42	100.0	43	100.0	21	100.0	16	100.0	20	100.0	23	100.0
Total subjects who died	6	14.3	4	9.3	1	4.8	1	6.3	5	25.0	3	13.0
Disease progression	2	4.8	1	2.3	0	–	0	–	2	10.0	1	4.3
Reasons other than PD	3	7.1	2	4.7	0	–	0	–	3	15.0	2	8.7
Unknown	1	2.4	1	2.3	1	4.8	1	6.3	0	–	0	–
CA225100												
Total subjects	64	100.0	66	100.0	Not applicable				Not applicable			
Total subjects who died	8	12.5	8	12.1								
Tumor related disease	7	10.9	7	10.6								
Reasons other than PD	1	1.6	1	1.5								
TOTAL (ALL STUDIES)												
Total subjects	979	100.0	991	100.0	427	100.0	432	100.0	234	100.0	229	100.0
Total subjects who died	154	15.7	115	11.6	79	18.5	50	11.6	36	15.4	32	14.0

In study EMR 62 202-046, of the 96 patients (60 treated with cetuximab + chemotherapy vs 36 treated with chemotherapy alone) who died on treatment or up to 30 days after the last dose of study treatment due to reasons other than PD, AEs with fatal outcome were reported for 92 patients (59 vs 33) and affected mainly the SOCs blood and lymphatic system disorders (9 vs 5 patients; mainly [febrile] neutropenia), cardiac disorders (12 vs 6 patients), infections and infestations (14 vs 5 patients; mainly pneumonia and sepsis), and respiratory, thoracic and mediastinal disorders (20 vs 15 patients; mainly pulmonary embolism and respiratory failure. Respiratory failure occurred in 6 vs 1 patients and was a consequence of other causes: cetuximab + chemotherapy arm infections in 3 patients, pulmonary embolism, PD, and surgical complication in 1 patient each; chemotherapy arm infection in 1 patient.

One of the 979 patients (0.1%) treated with cetuximab died due to a cetuximab-related event (anaphylactic shock in study EMR 62 202-046).

Across the 3 studies evaluated for EGFR expression, combined frequencies of patients who died on treatment or up to 30 days after the last dose of study medication were more balanced between treatments in the high EGFR expression group (cetuximab + chemotherapy, 15.4% vs chemotherapy, 14.0% than in the low EGFR expression group, 18.5% vs 11.6%). In both EGFR expression groups, the patterns of AEs with reported outcome death were consistent with the safety population.

Laboratory findings

In all of the 4 randomised controlled studies, neutrophil and/or leukocyte counts in the cetuximab + chemotherapy treatment arms were lower than in the chemotherapy control groups. A higher frequency of grade 3 and 4 low platelets in the cetuximab + chemotherapy group compared to the chemotherapy group was observed only in study CA225100; there were no differences between the treatment groups in the 3 other randomised, controlled studies.

In the 2 larger phase III studies (EMR 62 202-046 and CA225099), the addition of cetuximab led to a higher frequency of increases in liver enzymes and bilirubin, but the majority of abnormal findings were grade 1 or 2. The addition of cetuximab also consistently enhanced the depletion of magnesium, calcium, and potassium in all 4 studies in the cetuximab + chemotherapy arms compared to the chemotherapy arms. Grade 3 hyponatremia was reported more frequently as an AE in the cetuximab + chemotherapy vs chemotherapy arms of the safety population of study EMR 62 202-046 in 2.4% (13/548) vs 0.7% (4/562) patients and in study CA225099 in 1.5% (5/325) vs 0 patients. However, in these studies there were no differences between the treatment arms in grade 3 or 4 hyponatremia.

Safety in special populations

No formal studies in special patient populations were submitted. AE frequencies were analysed for subgroups based on age, gender, race, and ECOG PS. In addition, specific analyses of 'cardiac events' (special AE category) by age were submitted.

With regard to age, almost one third of the patients in the safety population in the pivotal study EMR 62 202-046 were ≥ 65 years: 30.7% (168/548) in the cetuximab + chemotheapy arm and 31.3% (176/562) in the chemotherapy arm.

In the safety population, severe AEs that were more common with the addition of cetuximab in elderly patients but not in younger patientsincluded fatigue, hypokalaemia, and leukopenia.

In the high EGFR expression group, AEs of any grade reported more often with the addition of cetuximab to chemotherapy in elderly patients but not in younger patients included: fatigue, neutropenia, anorexia, constipation, diarrhoea, hypokaelemia, peripheral sensory neuropathy, and vomiting.

In the same group, several severe AEs were more common with the addition of cetuximab in elderly patients but not in younger patients, such as AEs related to decreased WBCs (leukopenia, neutropenia, febrile neutropenia), fatigue and anorexia.

In the safety population of study EMR 62 202-046, an increase of severe (grade 3 or 4) cardiac events was observed in patients ≥ 65 years of age treated with cetuximab + chemotherapy compared to chemotherapy alone: 12.5% (21) vs 5.1% (9) patients, including events with fatal outcome in 13 vs 2 patients. The higher frequencies of cardiac events were due to the medical terms 'CHF' and 'infarction/ischaemia'. Corresponding frequencies of severe cardiac events in younger patients were 2.6% (10) vs 4.9% (19) patients. A similar difference in severe cardiac events was seen in the low EGFR expression group but not in the high EGFR expression group.

Table 24: Cardiac events in patients ≥ 65 years in study EMR 62 202-046

Cardiac events	Safety population Cet+CTX vs. CTX	Low EGFR expression Cet+CTX vs. CTX	High EGFR expression Cet+CTX vs. CTX
Grade 3 or 4	12.5 vs. 5.1%	14.8 vs. 2.6%	7.5 vs. 10.2%
Grade 4	10.1 vs. 2.3%	13 vs. 0%	3.8 vs. 6.8%

Cet=cetuximab, CTX=chemotherapy

In the safety population of study CA225099, the difference in frequency of severe (grade 3 or 4) cardiac events between the treatment arms was more pronounced in patients ≥ 65 years of age treated with cetuximab + chemotherapy vs chemotherapy: 8.9% vs 3.6% patients. This was attributable to the medical terms 'arrhythmia' and 'arrest', and it was also reflected in the frequency of grade 4 cardiac events. The outcome of 'cardiac events' was reported as fatal in the cetuximab + chemotherapy vs chemotherapy arm for: 4 vs 2 patient aged < 65 years and for 6 vs 3 patients aged ≥ 65 years.

Some differences in the safety profile were noted between genders and racial groups. Finally, there was no obvious difference in the toxicity of cetuximab in relation to performance status (data not shown).

Discontinuation due to adverse events

Overall, AEs most frequently leading to discontinuation of chemotherapy were (febrile) neutropenia in study EMR 62 202-046, dehydration in study CA225099, asthenia and leukopenia in study EMR 62 202-011, and infections in study CA225100. The most frequently reported AEs leading to discontinuation of cetuximab included asthenia, dehydration, fatigue, hypersensitivity, nausea, and rash.

Post marketing experience

The present submission considers post-marketing experience from 9 consecutive periodic safety update reports (PSURs) that cover the period from 1 December 2003 until the overall safety cut-off for this submission (30 September 2010). It is estimated that up to 30 September 2010 a total of about 318,000 patients had been treated with cetuximab world-wide: about 309,000 with the commercially available drug and about 9,000 in clinical studies.

2.5.1. Discussion on clinical safety

In the pivotal study EMR 62 202-046, exposure to cetuximab was higher for the high EGFR expression group compared to the low EGFR expression group, but there was no such difference in study CA225099. There was also a higher exposure to chemotherapy in the cetuximab +chemotherapy arm of the high EGFR expression group compared to the respective arm of the low EGFR expression group in the pivotal study, while the contrary was noted in study CA225099. This pattern corresponds to the pattern of ORR differences between high and low EGFR expression groups in the two studies. In the high EGFR expression group there was a higher exposure to chemotherapy in the cetuximab +chemotherapy arm compared to chemotherapy alone which was reproduced in studies CA225099 and EMR 62 202-011. The fact that in all three studies for the high EGFR expression group a higher exposure to chemotherapy was notable with the add-on of cetuximab might be a hint for a better efficacy of the cetuximab treatment arm, which led to a longer chemotherapy treatment before progression. The same could be true for the longer cetuximab exposure for the high EGFR expression group compared to the low EGFR expression group.

The considerably higher rates of AEs of any grade for the cetuximab add-on are consistent with the product information. The AEs that occurred more often (≥ 5%) with the cetuximab add-on included skin-related reactions, asthenia (fatigue), anorexia including weight decrease, diarrhoea with or without hypokalaemia, epistaxis, headache, hypomagnesaemia, mucositis, leukopenia and neutropenia. Concerning the AEs of any grade there were no relevant differences between the safety population and the different EGFR expression groups.

There was also a higher rate of severe AEs in subjects treated with cetuximab add-on (grade 3 or 4 AEs 91.1% vs. 86.3%; Grade 4 AEs 62.4% vs. 52.3%, safety population of study EMR 62 202-046). These AEs include febrile neutropenia, diarrhoea, pneumonia, deep vein thrombosis, pulmonary embolism and sepsis/septic shock among others. Apart from grade 3 or 4 'general physical health deterioration' the AE profile is consistent with the SmPC. But the higher rate of severe AEs is considered clinically relevant and surely affects patients' quality of life.

The overall frequency of SAEs across the 4 randomised, controlled studies was approximately 15% higher (56.8% vs. 41.3%) in the combined cetuximab +chemotherapy group than in the chemotherapy only group. This difference was caused by the known toxicity of cetuximab like febrile neutropenia, pulmonary embolism, pneumonia, dehydration, hypersensitivity etc. Moreover 'general physical health deterioration' was observed in 4 vs. 0.7% in study EMR 62 202-046.

Concerning the EGFR expression groups it was noticeable that the rate of SAE was higher in the low EGFR expression group than in the high EGFR expression group with the cetuximab add-on in study EMR 62202-046 (61 vs. 55%), but this difference was lower for the treatment related SAEs and for the combined frequencies of SAEs across all 3 studies evaluated for EGFR expression. On the other hand, study CA225099 showed a higher rate of any SAEs and treatment related SAEs for the cetuximab add-on arm in the high EGFR expression group (64% vs. 49% in the low EGFR expression group).

In the controlled studies overall, there was a higher rate of 'patients who died' in the combined treatment arm (15.7% vs. 11.6% with chemotherapy alone). In study EMR 62 202-046, this difference was lower in the period up to 30 days after the last dose of chemotherapy (15.5 vs. 13.5%) compared to the period up to 30 days after the last dose of study treatment (18.8 vs. 13.5%, data not shown). At the end of the study treatment phase, the difference in death rates between the treatment arms in the safety population was mainly due to the higher number of deaths due to reasons other than disease progression in the cetuximab +chemotherapy arm. This was most likely influenced by the added toxicity of cetuximab (data not shown). Among the 96 patients (60 treated with cetuximab +chemotherapy vs. 36 treated with chemotherapy alone) who died on treatment or up to 30 days after the last dose of study treatment due to reasons other than PD, AEs with fatal outcome were reported for 92 subjects (59 vs. 33 patients).

Severe AEs, SAEs and AEs leading to death in study EMR 62-202-046 were more frequent with cetuximab add-on in the low EGFR expression group than in the high EGFR expression group (grade 3 or 4 AEs 93 vs. 87%, grade 4 AEs 64 vs. 60%, SAEs 61 vs. 55%, AE leading to death 15 vs. 13%). On the other hand, it is striking that there were fewer AEs for chemotherapy alone in the low EGFR expression group compared to the high EGFR expression group (grade 3 or 4 AEs 85 vs. 90%, grade 4 AEs 51 vs. 57%, SAEs 43 vs. 45%, AE leading to death 8 vs. 12.5%). This apparently more pronounced 'cetuximab toxicity' in the low EGFR expression group compared to the apparently more balanced in terms of toxicity high EGFR expression group could not be explained conclusively. Overall, the safety profiles in groups of patients with low or high EGFR expression in study EMR 62-202-046 were similar and consistent with the overall safety population in the 4 randomised controlled NSCLC studies. However, it could not be ruled out ultimately that the imbalances in the safety profile might have been caused by an imbalance in the patient populations. Moreover, there is a concern that the higher difference in the rate of 'AE leading to death' in the treatment arms of the low EGFR expression group may have contributed to the worse OS outcome in contrast to the better OS of the high EGFR expression group.

The changes in laboratory parameters (all grades) observed in all 4 randomised controlled studies were consistent with the underlying disease and the administration of cetuximab and the platinum-based chemotherapies. Comparable results were obtained in the safety populations and the low and high EGFR expression groups. The findings for cetuximab are already addressed in the SmPC (lower

neutrophil and/or leukocyte counts, increase in liver enzymes and bilirubin, low magnesium and calcium).

With regard to age, in study EMR 62 202-046 several severe AEs were more common with cetuximab +chemotherapy vs. chemotherapy in elderly subjects but not in younger subjects, such as leukopenia,, fatigue and hypokalaemia. In the same study, there is a notable increase in the fatal 'cardiac events' and severe (CHF and infarction/ischaemia) 'cardiac events' with the add-on of cetuximab for patients aged ≥ 65 years. With the add-on of cetuximab, cardiac event rates were higher in the low EGFR expression group than in the high EGFR one, but the opposite was observed with chemotherapy alone. Moreover it is somehow surprising that in the overall safety population and with chemotherapy alone there was no difference in the cardiac event rate between the patients < and ≥ 65 years as would have been normally expected.

With regard to race, the analysis implies that in the Asian population some cetuximab toxicities might be pronounced. In light of the large difference in size between the Caucasian/White populations (84%) and Asian population (about 10%) in this study, differences in AE frequencies should be interpreted with caution.

The overall frequencies of AEs leading to discontinuation of CTX across the safety populations of the 4 randomised, controlled studies appeared relatively similar across the safety population and the low and high EGFR expression groups. However for the AEs leading to discontinuation of cetuximab there was again an imbalance between the low and high EGFR expression groups with a higher rate in the low EGFR expression group (24.1 vs. 16.7%).

Finally, no meaningful conclusion could be drawn about potential differences of AEs overall, severe AEs and SAEs according to EGFR mutation status (data not shown).

2.6. Benefit-Risk Balance

Benefits

- Beneficial effects

In the largest trial (EMR 62 202-46, "FLEX") designed to demonstrate a survival benefit of cetuximab add-on, a small and borderline significant (HR 0.87, p=0.044) survival effect was shown. New analyses based on EGFR expression showed a improved benefit (compared to ITT) for cetuximab for efficacy variables (OS, TTF, ORR) in terms of hazard/odds ratio analysis in subjects with high tumor EGFR expression compared to subjects with low tumor EGFR expression and the ITT population. For the population bearing tumours with high EGFR expression, the HR was 0.73 (95%CI 0.58, 0.93) and the median survival was 12.0 vs 9.6 months.

Study CA225099 was designed to show a 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 terms of PFS. In a pooled analysis the results were borderline significant (0.036). Censoring pattern and alternative analyses indicate that overall this estimate is conservative, but results mainly based on investigator's interpretation in open label studies are open to criticism.

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

- Uncertainty in the knowledge about the beneficial effects

The MAH proposed to restrict the target population to patients with EGFR IHC high score tumours. This was by necessity based on retrospective analyses. While attempts have been made to properly validate the predictive value of EGFR IHC score and the proposed cut-off, missing EGFR IHC data in the second large NSCLC study and some inconsistencies in the findings make conclusion uncertain.

In patients with tumours with high EGFR expression levels, the estimated survival benefit is about HR 0.75. With regard to EGFR mutations and due to the small sample of patients with mutation positive tumours, results should be interpreted cautiously. These were discussed earlier and no safe conclusions can be made. In any case, the MAH proposed to restrict the indication to patients without activating EGFR mutation, for which a similar OS HR was observed in case of high EGFR expression

EGFR IHC score as a reliable predictive factor and the cut-off leading to this estimate are in need of further validation. This probably cannot be accomplished without a prospective trial to be fully trustworthy. Thus there are uncertainties around these efficacy estimates and frequently retrospective subgroup analyses (also well justified) of a pivotal trial, albeit partly validated in other studies, lead to overestimates of the treatment effect.

Risks

- Unfavourable effects

The tolerability and toxicity profiles of cetuximab as add-on to chemotherapy are relatively well characterised. As a summary measure, the discontinuation rates due to adverse events may be used. This is in the pivotal trial about thirty percent, equally attributed to cetuximab or chemotherapy or both. Apart from well characterised adverse reactions such as rash, mucositis, neutropenia and neutropenic fever, in elderly patients there is also a risk for treatment related cardiovascular deaths.

- Uncertainty in the knowledge about the unfavourable effects

The uncertainties mainly relate to the magnitude of the risk for treatment related deaths, especially in the elderly. In the re-examination procedure for variation II/29, analyses presented by the MAH were compatible with a doubling of the risk for death associated with AEs in patients > 65 years of age (20 vs. 10%). This is most likely an overestimation and should not be read as deaths caused by therapy. Nevertheless, caution is clearly warranted in the treatment of elderly patients. The current SmPC captures this.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

In the treatment of patients with NSCLC, tumour response and a delay in tumour progression is associated with a reduction in tumour related symptoms. Improved survival, if not associated with 'unacceptably negative effects on quality of life', is also conventionally considered beneficial.

However, QoL is by necessity related to individual preferences, it is hard to estimate properly (not least due to informative censoring and high attrition rates frequently seen) and, in the case of cetuximab, it would be assessed in open label studies by necessity. Therefore adverse reactions and discontinuation rates should instead be used as estimates of negative effects on quality of life. The positive impact on tumour related symptoms is considered sufficiently well established.

Clearly a high frequency of cetuximab-related increases in diarrhoea, mucositis, rash and weight loss indicates an unfavourable tolerability profile even though an increase in grade 3/4 events is seen 'only' in about 1 in 20 treated patients.

Obviously, treatment discontinuation rates capture a mixture of adverse events and reactions, apparent non-benefit of therapy, the treating physician's attitude, 'hope', social circumstances, etc. However, 1 in 10 patients more (30% vs. 20%) discontinued therapy for these reasons in the cetuximab arm compared with the control arm.

- Benefit-risk balance

In the context of treatment of patients with NSCLC, the treatment effect in patients bearing tumours with high EGFR expression (OS HR 0.73) would undoubtedly be viewed as clinically highly relevant. However, as discussed above, there are uncertainties due to the fact that the EGFR scoring system and the selected cut-off have not been confirmed in a prospective clinical trial.

2.6.1. Discussion on the benefit-risk balance

On 5 October 2011, a SAG-Oncology was convened by the CHMP to address the issues outlined below together with the SAG responses.

1. Are the results from the retrospectively conducted biomarker analyses in the cetuximab NSCLC studies, which identified 'high EGFR expression' as a biomarker for patient selection and established a specific EGFR expression threshold, considered plausible from a tumour biology perspective?

The biomarker (high EGFR expression) results are considered plausible from a tumour biology perspective.

However, there are a number of possible caveats when exploring subgroups retrospectively. For example, there was an apparent lack of effect in older patients (>65 years), and an apparent inconsistency of results between genders. However, due to the exploratory nature of such analyses the significance of such findings is difficult to assess. In addition, the choice of the proposed EGFR expression cut-off has not been rigorously validated. Lastly, confirmation from other biomarkers and techniques other than IHC is lacking and it is not possible to assess false positive and false negative results of this technique. Although a strong correlation between FISH and IHC for HER2 is established in breast cancer, the corresponding correlation in the case of EGFR (HER1) and NSCLC has not been demonstrated and this needs to be further investigated.

2. Please comment on the results based on EGFR expression data as presented by the MAH

    a. PFS data as reported are not in line with what would be expected given the claimed survival benefit. Is this apparent lack of consistency per se sufficiently strong to refuse the request for a new indication?

The apparent lack of consistency between PFS and OS (the latter being the most robust endpoint) is difficult to explain and a cause of concern, although it is acknowledged that the surrogacy of PFS for OS is not established in this disease setting. A possible explanation for the discordance of the PFS data is related to informative censoring of patients in the chemotherapy arm. However, there is a concern that early cessation of treatment in the control arm may have led to under-treatment of patients in this arm. This aspect should be further investigated.

For the response to the explicit question, the SAG was split (see below).

    b. If not, do you consider that the overall results are convincing enough to establishing the positive benefit-risk of cetuximab in first line treatment of advanced or metastatic NSCLC with high EGFR expression?

The SAG had a split opinion. Some members considered that the overall results were convincing enough to establish a positive benefit-risk balance. Other members considered that a positive benefit-risk could not be established based on the available data due to the uncertainties described in response to questions 1-2.

3. Is there a need for a confirmatory study to establish the acceptability of EGFR expression levels and the specific proposed threshold for patient selection in the first line treatment of NSCLC with cetuximab?

The SAG agreed that a confirmatory trial is needed in order to address the uncertainties described in response to questions 1-2, confirm the OS benefit and validate externally EGFR expression level as predictive biomarker for patient selection. However, some SAG members questioned the necessity of a confirmatory trial before approval (see below).

4. If the answer to question 3 is yes;

    a. Is the design for the confirmatory study as proposed by the MAH (patients with high EGFR expression, RR as primary endpoint, single arm or controlled (2:1 random) trial) considered acceptable?

    b. Should this study be conducted prior to approval?

The SAG did not agree with the full details of the proposed study. In particular, RR was not considered adequate as the sole primary endpoint. Additionally, such study would not allow the validation of the proposed threshold.

Members for whom the positive benefit-risk balance was not established considered that OS should be the primary endpoint for such confirmatory trial and that the trial should be conducted prior to approval of this indication. Other members considered that a trial with OS as the primary endpoint would take too long to complete and that RR may be an acceptable compromise while awaiting mature OS data, and considered that the study should be conducted after approval.

The CHMP considered that over-expression of a growth/survival factor receptor likely makes cells more sensitive to the blocking effect of an antibody and EGFR signaling may make cells more resistant to noxious insults, such as chemotherapy. This has been demonstrated in cell lines. More importantly, in tumour explants from patients with NSCLC a relationship between EGFR expression levels and activity of cetuximab was shown. It is also reminded that cetuximab was shown to reverse resistance to irinotecan in the study leading to the first approval of Erbitux. This would support the hypothesis that EGFR signaling is a reversible resistance mechanism behind resistance to chemotherapy. Altogether biological plausibility has been demonstrated.

On the other hand, there is a strong tumour biology rationale to view NSCLC tumours with mutated EGFR TK status as a biologically defined tumour subgroup with altered prognosis and response to chemotherapy as well as EGFR TK inhibitors. This was not known when the studies were planned, but has been acknowledged since about 2004. More specifically, further retrospective biomarker analyses of mutational status show that patients carrying tumours with high expression of wt EGFR benefit from cetuximab therapy, whereas those whose tumours carry activating EGFR mutations do not. However, determination of wt vs mutated EGFR status may not be warranted for squamous cell tumours, in which the prevalence of EGFR mutations is very low. Cetuximab may provide a meaningful OS advantage in patients with adenocarcinoma lacking EGFR activating mutations and in all patients with squamous cell carcinoma histology.

More generally, the importance of baseline tumour biopsies in clinical studies accommodating for the conduct of scientifically driven 'retrospective' analyses is clearly demonstrated by the studies

submitted. Studies conducted by the MAH have almost complete IHC score data and to a variable extent tumour material for further biomarker analyses. This was not the case for BMS studies making a proper assessment of biomarker expression and clinical outcome hard or impossible in these studies. As for all subgroup analyses, there is an uncertainty as regards the magnitude of the indicated effect of, in this case, excluding patients with certain characteristics. But the approach is considered scientifically valid, whether conducted in retrospect or not.

The magnitude of the treatment effect in terms of OS and in patients with high expression levels of EGFR and without activating EGFR-TK mutations is estimated to be 0.76. If 'true', this would constitute a major improvement in the treatment of NSCLC. This estimate, however, is likely to constitute an overestimate of the treatment effect, the extent of which is unknown, bottom line being the statistically borderline significant effect in the FLEX study and in the full population, i.e. OS HR 0.87.

The secondary endpoint of the pivotal FLEX trial PFS was not met in the ITT population and remained insignificant in the high EGFR enriched population. The primary endpoint of study CA 225099 was PFS and was assessed by a blinded IRRC according to a pre-specified charter. This endpoint was met neither in the ITT nor in the enriched population. The Applicant states that patients with a rather poor prognosis were taken out of study in the CTX arm to receive other therapy. This indicates an operational bias that might invalidate the PFS results in both studies. Due to this bias it may no longer be true that the underlying censoring at random assumption of the PFS analysis holds in study EMR622002-046 and study CA225099 respectively, i.e. that both open label studies are not suitable for a robust assessment of the effect of cetuximab on PFS. In study CA 225099, independent review was undertaken and the results were found to be "negative". A TTF analysis was undertaken and led to a major shift from PFS HR 0.8 to TTF 0.6. The latter is likely to overestimate the treatment effect, but is on the other hand more in line with the expected PFS results given the treatment effect in terms of OS, both in the full treatment group and in the high IHC score group. To what extent independent review indicated biased reporting also of events of progression and therefore likely resulted in additional biased censoring is not clear. In the pivotal trial, OS was the primary endpoint and independent review was not undertaken. Here the difference between TTF and PFS is clearly smaller and the TTF HR is larger than expected when put in relation to the HR for OS.

Of note, putative imbalances at baseline contributing to the OS benefit would similarly affect PFS and although patients in the control group with stable disease on first line therapy received second line therapy more frequently than patients in the active treatment arm, it is unlikely that next line therapy could have biased the results in favour of the experimental arm to such an extent that it has caused the reported difference in OS. Likewise, short first-line treatment is also unlikely to have biased the OS results, as currently 4 cycles of chemotherapy (not 6) seem to be the rule in first line treatment of NSCLC.

The data reported above for obvious reasons constitute one of many reasonable analyses conducted retrospectively aiming at identifying the proper patient group for treatment with cetuximab and the way data were analysed, IHC score represents one possible way to investigate the importance of EGFR expression. Selection based on EGFR expression improves the benefit of therapy, but the magnitude of this improvement and the proper cut-off for high EGFR expression are uncertain and would need to be corroborated in a confirmatory clinical trial. The MAH's US partner has finalised a randomised, second-line study NSCLC with cetuximab as add-on to docetaxel or pemetrexed. The overall results were negative with respect to the primary endpoint, PFS. The MAH is now in the process of analysing the outcome in relation to IHC score. There is in addition a single arm NSCLC study undertaken, also to be analysed with outcome in relation to IHC score. These two studies may provide the necessary confirmatory data.

The MAH was asked to justify why the indication should be as wide as to include combination with all platinum-containing chemotherapy. The MAH argued that different types of platinum-based chemotherapy had been tested in the four clinical trials supporting this application and results in OS were similar. The CHMP considered that, as long as data for the different platinum combinations are included in section 5.1 of the SmPC, a wording in combination with platinum-based chemotherapy doublets could be appropriate for the indication.

Finally, it is normally considered a sine qua non that a study should be 'statistically significant', conventionally defined, to allow for subgroup analyses aimed at forming the basis for regulatory decisions. If there are errors in the data used as input for the stratified analysis, the errors are more likely to be there in IVRS than in CRF as those latter data should have been source verified. However, as described earlier (see discussion on clinical efficacy)and although the MAH may be criticised for not informing CHMP when discrepancies between IVRS and CRF data were noticed, this is not considered critical as the MAH's response overall addressed concerns adequately.

In conclusion, it is not self evident how best to handle the risk of delaying the use of cetuximab in NSCLC if the treatment effect is about survival HR 0.75, versus the risk related to approval if the add-on benefit is smaller than indicated by the subgroup analyses, taking the tolerability and toxicity profiles of cetuximab into account.

Due to uncertainties related to the magnitude of the treatment benefit in the retrospectively identified target population, the benefit – risk balance is considered negative.

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