EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 2013
EMA/CHMP/701107/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Erbitux

International non-proprietary name: **CETUXIMAB**

Procedure No. EMEA/H/C/000558/II/0062

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

5-FU	5-fluorouracil
AE	adverse event
BSC	best supportive care
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmab	cetuximab
CRC	colorectal cancer
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
FA	folinic acid
FOLFOX	folinic acid, 5-fluorouracil and oxaliplatin
FOLFIRI	folinic acid, 5-fluorouracil and irinotecan
HR	hazard ratio
IRC	Independent Review Committee
IRR	Infusion related reactions
ITT	intent to treat
KRAS	Kirsten rat sarcoma 2 viral oncogene homolog
mCRC	metastatic colorectal cancer
NRAS	neuroblastoma *RAS* viral oncogene homolog
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PFS	progression-free survival
PT	preferred term
qPCR	quantitative polymerase chain reaction
RAS	rat sarcoma proto-oncogene
SAE	serious adverse event
SD	stable disease

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck KGaA submitted to the European Medicines Agency on 22 October 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Erbitux	CETUXIMAB	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Restriction of the indication for the treatment of colorectal cancer to patients with wild-type *RAS* tumours in follow-up to CHMP request

As a consequence, sections 4.1 and 5.1 of the SmPC were proposed to be updated. In addition, relevant safety information on the use of Erbitux in patients with mutant *RAS* tumours was proposed to be updated in accordance in sections 4.2, 4.3 and 4.4 of the SmPC.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Bengt Ljungberg

Submission date:	22 October 2013
Start of procedure:	22 October 2013
Rapporteur's preliminary assessment report circulated on:	1 November 2013
CHMP opinion:	21 November 2013

2. Scientific discussion

2.1. Introduction

Cetuximab is a chimeric monoclonal Immunoglobulin G1 (IgG1) antibody directed against the Epidermal Growth Factor Receptor (EGFR). EGFR signalling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis. Cetuximab binds to the EGFR with an affinity higher than that of endogenous ligands. Cetuximab blocks binding of endogenous EGFR ligands resulting in inhibition of the function of the receptor and induces the internalisation 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 (mCRC):

- 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 (SCCHN):

- 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/m2, and all subsequent weekly doses are 250 mg/m2.

With this variation application, the MAH proposed to further restrict the indication of Erbitux in colorectal cancer to the treatment of patients with *RAS* (i.e. both *KRAS* and *NRAS)* wild-type tumours. This was in follow-up to CHMP request after a similar recent restriction of the Vectibix colorectal cancer indication. Data strictly related to cetuximab in this application come from one study (OPUS) but further relevant data from studies CRYSTAL and FIRE III are expected (see further below).

2.2. Clinical aspects

2.2.1. Introduction

The *RAS* gene family has three broadly expressed members: Kirsten rat sarcoma 2 viral oncogene homolog (*KRAS*), neuroblastoma *RAS* viral oncogene homolog (*NRAS*), and the v-Ha-*RAS* Harvey rat sarcoma viral oncogene (*HRAS*). *RAS* (*KRAS, NRAS, HRAS*) proteins are central nodal points in these signalling pathways regulating the transmission of activation signals from the EGFR to down-stream effectors. The three different isoforms share sequence identity at all regions regulating activation state and effector functions, and high sequence similarity in most of the remaining gene. The region of variability between the isoforms, containing only 23 to 24 amino acids, is involved in membrane binding.

Mutated, activated RAS proteins can bypass inhibition of EGFR by direct activation of the downstream pathways, MAPK and AKT pathways, independent of EGFR. *KRAS* exon 2 mutations at codons 12 and 13 are the most frequently occurring *RAS* mutations in CRC (approximately 40% of subjects) and were demonstrated to be associated with resistance to anti-EGFR therapy in subjects with mCRC. Somatic mutations beyond *KRAS* exon 2, including *KRAS* exon 3 and 4 and *NRAS* exon 2, 3 and 4 mutations, have been documented in CRC and collectively occur in approximately 7% to 22% of wild-type *KRAS* exon 2 CRC cases.

In this submission, results of the *RAS* mutational analysis and correlation with efficacy and safety were reported for the phase II OPUS trial, investigating cetuximab plus oxaliplatin, 5-fluorouracil (5-FU), and leucovorin (FOLFOX4) versus FOLFOX4 alone.

GCP

The Clinical trial (OPUS) was performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that the clinical trial (OPUS) conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3. Clinical efficacy aspects

2.3.1. Methods – analysis of data submitted

The BEAMing (Beads, Emulsions, Amplification, and Magnetics) assay was chosen for the detection of *KRAS* and *NRAS* mutations in tumour samples from patients in the OPUS study due to the limited amount of starting material (genomic DNA isolated from one tissue slide). The BEAMing Technology combines polymerase chain reaction (PCR) with flow cytometry to create a mutation detection platform with greater sensitivity and specificity than traditional PCR. The technology allows for detection and quantification of low prevalence mutations and permits detection of mutations in heterogeneous or poor quality samples with rare mutated clones.

The panel of *KRAS* and *NRAS* mutations analysed is presented in the following Table 1.

Table 1: *KRAS* and *NRAS* mutations analysed

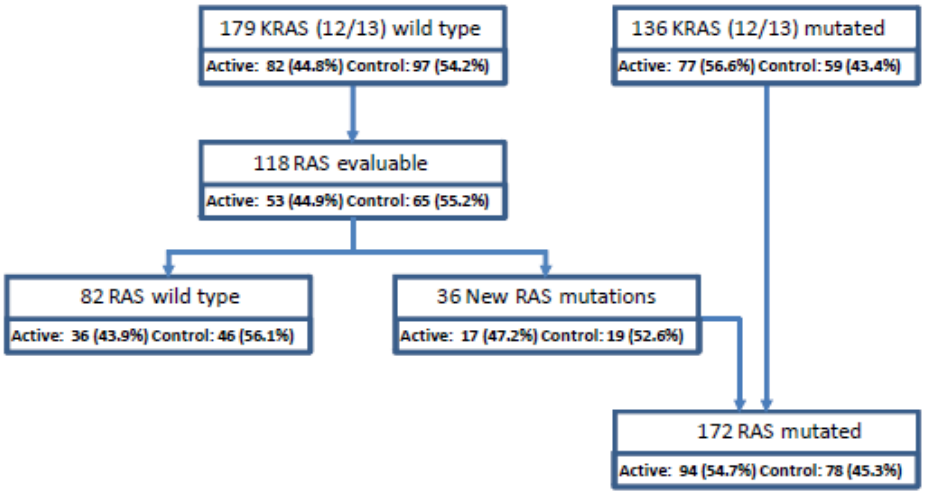
Gene	Exon	Codon	Amino acid change	Gene	Exon	Codon	Amino acid change
KRAS	Exon 2*	12	G12A	*NRAS*	Exon 2	12	G12S
			G12C				G12R
			G12D				G12C
			G12R				G12D
			G12S				G12A
			G12V				G12V
		13	G13D			13	G13R
	Exon 3	59	A59T				G13D
		61	Q61L				G13V
			Q61H		Exon 3	59	A59T
	Exon 4	117	K117N			61	Q61K
		146	A146T				Q61R
			A146V				Q61L
							Q61H
					Exon 4	117	K117N
						146	A146T

* Mutations assessed for stratifying subjects into *KRAS* mutant and *KRAS* wild-type subgroups.
KRAS: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, *NRAS*: neuroblastoma *RAS* viral oncogene homolog.
Mutations at *KRAS* exon 3 and 4 and *NRAS* exon 2, exon 3 and exon 4 in the *KRAS* exon 2 wild-type population define the new *RAS* mutant subgroup. The *Ras* mutant subgroup includes subjects with any mutation in *KRAS* and/or *NRAS* in the locations described above.

2.3.2. Results

Figure 1 summarises the populations used for *KRAS* and *RAS* analysis in the OPUS trial.

Figure 1: Mutational status of the populations



Active: Cetuximab plus FOLFOX4, Compare: FOLFOX4 only. *KRAS*: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, *RAS*: rat sarcoma proto-oncogene.

Note: *Ras* mutant population includes subjects with any *KRAS* exon 2 to 4 and/or *RAS* exon 2 to 4 mutant tumors.

The number and percentage of patients per treatment arm of the OPUS study evaluable for *RAS* analysis and their disposition according to the *RAS* status of their tumours are presented in Table 2.

Table 2: Number of patients with *(K)RAS* wild-Type and *(K)RAS* mutant tumour status

Population	Number of Subjects n (%)		
	Cmab+ FOLFOX4	FOLFOX4	Overall
KRAS Wild-Type	82 (100)	97 (100)	179 (100)
RAS Evaluable	53 (64.6)*	65 (67.0)*	118 (65.9)*
RAS Wild-Type	36 (67.9)#	46 (70.8)#	82 (69.5)#
New *RAS* Mutant	17 (32.1)#	19 (29.2)#	36 (30.5)#
KRAS Mutant	77 (100)	59 (100)	136 (100)
RAS Mutant+	94	78	172

KRAS: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, *RAS*: rat sarcoma proto-oncogene, Cmab: Cetuximab, FOLFOX4: chemotherapy regimen for treatment of colorectal cancer, made up of the folinic acid, 5-fluorouracil and oxaliplatin.

* nominator refers to *KRAS* wild-type population

nominator refers to *RAS* evaluable population

+ RAS mutant population includes patients with any KRAS exon 2 to 4 and/or NRAS exon 2 to 4 mutant tumours and thus also includes the patients originally identified as carriers of KRAS (i.e. exon 2 only) tumours
The new RAS mutant population includes patients with KRAS exon 3 and 4 and NRAS exon 2 to 4 mutant tumours

Baseline demographic and disease characteristics according to *RAS* status are presented in the following Tables 3 and 4.

Table 3: Baseline demographic characteristics by *RAS* status

Parameter	*KRAS* Wild-Type		*KRAS* Mutant		*RAS* Evaluable		New *RAS* Mutant		*RAS* Mutant		*RAS* Wild-Type	
	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4
	N=82	N=97	N=77	N=59	N=53	N=65	N=17	N=19	N=94	N=78	N=36	N=46
Gender												
Male n (%)	42 (51.2)	55 (56.7)	40 (51.9)	31 (52.5)	28 (52.8)	36 (55.4)	9 (52.9)	9 (47.4)	49 (52.1)	40 (51.3)	19 (52.8)	27 (58.7)
Female n (%)	40 (48.8)	42 (43.3)	37 (48.1)	28 (47.5)	25 (47.2)	29 (44.6)	8 (47.1)	10 (52.6)	45 (47.9)	38 (48.7)	17 (47.2)	19 (41.3)
Age (years)												
Median	62.0	59.0	60.0	61.0	62.0	60.0	63.0	64.0	61.5	62.0	60.5	59.0
Range	24-75	36-82	34-82	30-76	24-75	36-79	24-74	46-75	24-82	30-76	24-75	36-79
<65 years n (%)	46 (56.1)	63 (64.9)	45 (58.4)	38 (64.4)	31 (58.5)	44 (67.7)	10 (58.8)	12 (63.2)	55 (58.5)	50 (64.1)	21 (58.3)	32 (69.6)
≥65 years n (%)	36 (43.9)	34 (35.1)	32 (41.6)	21 (35.6)	22 (41.5)	21 (32.3)	7 (41.2)	7 (36.8)	39 (41.5)	28 (35.9)	15 (41.7)	14 (30.4)
Ethnic Origin n (%)												
Caucasian	82 (100)	96 (99.0)	77 (100)	59 (100)	53 (100)	65 (100)	17 (100)	19 (100)	94 (100)	78 (100)	36 (100)	46 (100)
Other	0	1 (1.0)	0	0	0	0	0	0	0	0	0	0
Eastern Cooperative Oncology Group Performance Status n (%)												
0	32 (39.0)	38 (39.2)	29 (37.7)	32 (54.2)	22 (41.5)	27 (41.5)	5 (29.4)	12 (63.2)	34 (36.2)	44 (56.4)	17 (47.2)	15 (32.6)
1	44 (53.7)	49 (50.5)	42 (54.5)	21 (35.6)	28 (52.8)	34 (52.3)	10 (58.8)	7 (36.8)	52 (55.3)	28 (35.9)	18 (50.0)	27 (58.7)
2	6 (7.3)	10 (10.3)	6 (7.8)	6 (10.2)	3 (5.7)	4 (6.2)	2 (11.8)	0	8 (8.5)	6 (7.7)	1 (2.8)	4 (8.7)

KRAS: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, *RAS*: rat sarcoma proto-oncogene, Cmab: Cetuximab, FOLFOX4: chemotherapy regimen for treatment of colorectal cancer, made up of the folinic acid, 5-fluorouracil oxaliplatin.

Table 4: Baseline disease characteristics by *RAS* status

	KRAS Wild-Type		*KRAS* Mutant		*RAS* Evaluable		New *RAS* Mutant		*RAS* Mutant		*RAS* Wild-Type	
	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4
Parameter	N=82	N=97	N=77	N=59	N=53	N=65	N=17	N=19	N=94	N=78	N=36	N=46
Duration of Colorectal Cancer (months)												
Median	2.1	2.6	2.3	2.1	2.0	2.0	1.8	1.9	2.1	2.0	2.2	2.9
Range	0-126	1-89	0-76	1-58	0-126	1-60	1-49	1-31	0-76	1-58	0-126	1-60
Duration of Metastatic Colorectal Cancer (months)												
Median	1.3	1.6	1.6	1.4	1.4	1.7	1.6	1.7	1.6	1.5	1.4	1.7
Range	0-32	0-20	0-18	0-21	0-32	0-20	1-10	0-20	0-18	0-21	0-32	0-19
Prior Adjuvant Therapy n (%)												
No	68 (82.9)	71 (73.2)	65 (84.4)	48 (81.4)	45 (84.9)	48 (73.8)	15 (88.2)	16 (84.2)	80 (85.1)	64 (82.1)	30 (83.3)	32 (69.6)
Yes	14 (17.1)	26 (26.8)	12 (15.6)	11 (18.6)	8 (15.1)	17 (26.2)	2 (11.8)	3 (15.8)	14 (14.9)	14 (17.9)	6 (16.7)	14 (30.4)
Tumor Localization												
Colon n (%)	42 (51.2)	53 (54.6)	46 (59.7)	31 (52.5)	27 (50.9)	36 (55.4)	10 (58.8)	12 (63.2)	56 (59.6)	43 (55.1)	17 (42.2)	24 (52.2)
Rectum n (%)	40 (48.8)	44 (45.4)	30 (39.0)	28 (47.5)	26 (49.1)	29 (44.6)	7 (41.2)	7 (36.8)	37 (39.4)	35 (44.9)	19 (52.8)	22 (47.8)
Colon and Rectum n (%)	0	0	1 (1.3)	0	0	0	0	0	1 (1.1)	0	0	0
Tumor Staging n(%)												
I	2 (2.4)	1 (1.0)	2 (2.6)	1 (1.7)	2 (3.8)	0	1 (5.9)	0	3 (3.2)	1 (1.3	1 (2.8)	0
II	9 (11.0)	6 (6.2)	4 (5.2)	1 (1.7)	4 (7.5)	3 (4.6)	2 (11.8)	0	6 (6.4)	1 (1.3)	2 (5.6)	3 (6.5)
III	7 (8.5)	19 (19.6)	9 (11.7)	6 (10.2)	5 (9.4)	12 (18.5)	2 (11.8)	2 (10.5)	11 (11.7)	8 (10.3)	3 (8.3%)	10 (21.7)
IV	58 (70.7)	62 (63.9)	56 (72.7)	46 (78.0)	37 (69.8)	44 (67.7)	12 (70.6)	16 (84.2)	68 (72.3)	62 (79.5)	25 (69.4)	28 (60.9)
Unknown	5 (6.1)	8 (8.2)	6 (7.8)	5 (8.5)	4 (7.5)	5 (7.7)	0	1 (5.3)	6 (6.4)	6 (7.7)	4 (11.1)	4 (8.7)
Missing	1 (1.2)	1 (1.0)	0	0	1 (1.9)	1 (1.5)	0	0	0	0	1 (2.8)	1 (2.2)

Tumour response, progression-free survival (PFS) and overall survival (OS) by *RAS* status are presented in the following Tables 5-7.

Table 5: Tumour response by *RAS* status

	KRAS Wild-Type		*KRAS* Mutant		*RAS* Evaluable		New *RAS* Mutant		*RAS* Mutant		*RAS* Wild-Type	
	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4
Parameter	N=82	N=97	N=77	N=59	N=53	N=65	N=17	N=19	N=94	N=78	N=36	N=46
Complete Response n (%)	3 (3.7)	1 (1.0)	0	2 (3.4)	3 (5.7)	1 (1.5)	1 (5.9)	1 (5.3)	1 (1.1)	3 (3.8)	2 (5.6)	0
Partial Response n (%)	44 (53.7)	32 (33.0)	26 (33.8)	29 (49.2)	27 (50.9)	20 (30.8)	7 (41.2)	6 (31.6)	33 (35.1)	35 (44.9)	20 (55.6)	14 (30.4)
Stable Disease n (%)	24 (29.3)	42 (43.3)	36 (46.8)	21 (35.6)	14 (26.4)	28 (43.1)	4 (23.5)	9 (47.4)	40 (42.6)	30 (38.5)	10 (27.8)	19 (41.3)
Progressive Disease n (%)	5 (6.1)	15 (15.5)	13 (16.9)	5 (8.5)	4 (7.5)	10 (15.4)	2 (11.8)	2 (10.5)	15 (16.0)	7 (9.0)	2 (5.6)	8 (17.4)
Not Evaluable n (%)	6 (7.3)	7 (7.2)	2 (2.6)	2 (3.4)	5 (9.4)	6 (9.2)	3 (17.6)	1 (5.3)	5 (5.3)	3 (3.8)	2 (5.6)	5 (10.9)
Overall Response Rate (%)	57.3	34.0	33.8	52.5	56.6	32.3	47.1	36.8	36.2	48.7	61.1	30.4
95% CI	45.9, 68.2	24.7, 44.3	23.4, 45.5	39.1, 65.7	42.3, 70.2	21.2, 45.1	23.0, 72.2	16.3, 61.6	26.5, 46.7	37.2, 60.3	43.5, 76.9	17.7, 45.8
Odds Ratio	2.5512		0.4591		2.7375		1.500		0.6059		3.4599	
95% CI	1.3799, 4.7169		0.2280, 0.9244		1.2883, 5.8168		0.3783; 5.9482		0.3281, 1.1188		1.3749, 8.7067	
p value[1]	0.0027		0.0290		0.0086		0.5691		0.1099		0.0081	
Disease Control Rate (%)	86.6	77.3	80.5	88.1	78.7	87.2	70.6	84.2	78.7	87.2	88.9	71.7
95% CI	77.3, 93.1	67.7, 85.2	69.9, 88.7	77.1, 95.1	69.1, 86.5	77.7, 93.7	44.0; 89.7	60.4; 96.6	69.1, 86.5	77.7, 93.7	73.9, 96.9	56.5, 84.0
p value[2]	0.1251		0.2516		0.3694		0.4338		0.1626		0.0978	

KRAS: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, *RAS*: rat sarcoma proto-oncogene, p-value for difference between treatment groups determined by CMH test. CI=confidence interval, Cmab: cetuximab; FOLFOX4: chemotherapy regimen for treatment of colorectal cancer, made up of the folinic acid, 5-fluorouracil and oxaliplatin.
[1]) Cochran Mantel Haenzel test, [2]) Fischer test

Table 6: Progression-free survival (PFS) by *RAS* status

	KRAS Wild-Type		*KRAS* Mutant		*RAS* Evaluable		New *RAS* Mutant		*RAS* Mutant		*RAS* Wild-Type	
	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4
Parameter	N=82	N=97	N=77	N=59	N=53	N=65	N=17	N=19	N=94	N=78	N=36	N=46
No of Events n (%)	38 (46.3)	62 (63.9)	56 (72.7)	34 (57.6)	23 (43.4)	38 (58.5)	12 (70.6)	10 (52.6)	68 (72.3)	44 (56.4)	11 (30.6)	28 (60.9)
Hazard Ratio	0.567		1.720		0.645		1.023		1.594		0.433	
95% CI	0.375, 0.856		1.104, 2.679		0.380, 1.092		0.411, 2.548		1.079, 2.355		0.212, 0.884	
Log-Rank p Value	0.0064		0.0153		0.1003		0.9608		0.0183		0.0180	
Median PFS (months)	8.3	7.2	5.5	8.6	8.3	6.9	7.3	7.4	5.6	7.8	12.0	5.8
95% CI	7.2, 12.0	5.6, 7.4	4.0, 7.3	6.5, 9.4	7.3, 12.7	5.5, 7.5	3.4, 8.3	6.2, 10.3	4.4, 7.4	6.7, 9.3	7.7, NE	4.5, 7.5

KRAS: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, *RAS*: rat sarcoma proto-oncogene, CI: confidence interval, FOLFOX4: chemotherapy regimen for treatment of colorectal cancer, made up of the folinic acid, 5-fluorouracil and oxaliplatin, NE: not estimable, No: Number, PFS: Progression free survival.

Table 7: Overall survival (OS) by *RAS* status

	KRAS Wild-Type		*KRAS* Mutant		*RAS* Evaluable		New *RAS* Mutant		*RAS* Mutant		*RAS* Wild-Type	
	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4
Parameter	N=82	N=97	N=77	N=59	N=53	N=65	N=17	N=19	N=94	N=78	N=36	N=46
No of Events n (%)	55 (67.1)	71 (73.2)	61 (79.2)	45 (76.3)	38 (71.7)	46 (70.8)	13 (76.5)	12 (63.2)	74 (78.7)	57 (73.1)	25 (69.4)	34 (73.9)
Hazard Ratio	0.855		1.290		1.014		1.411		1.353		0.833	
95% CI	0.599, 1.219		0.873, 1.906		0.656, 1.568		0.621, 3.208		0.954, 1.918		0.492, 1.412	
Log-Rank p Value	0.3854		0.2004		0.9499		0.4086		0.0890		0.4974	
Median Survival Time (months)	22.8	18.5	13.4	17.5	19.5	17.8	14.8	17.8	13.4	17.8	20.7	17.8
95% CI	19.3, 25.9	16.4, 22.6	10.5, 17.7	14.7, 24.8	15.7, 24.8	15.0, 23.9	8.5, 26.3	15.3, NE	11.1; 17.7	15.9, 24.8	18.3, 26.8	12.4, 23.9

2.3.3. Discussion

With regard to the numbers of tumour samples available for *RAS* analysis and the baseline demographic and disease characteristics of patients in the different subgroups (by *RAS* status), some of the subgroups were small, e.g. the interesting new *RAS* mutant; nevertheless, there were no major imbalances in prognostic factors.

For tumour responses and except for the small group 'new *RAS* mutant', results were directionally as expected and the odds ratio seemed more favourable in the *RAS* wild type compared with *KRAS* wild type. In principle the same patterns were seen also for PFS, but PFS seemed neutral in the 'new *RAS* mutant' subgroup. Finally, OS results were compatible with PFS results taking into account the small sample sizes and diluting effects of post-progression survival.

Of note, all comparisons were made without protection by stratification/randomisation, i.e. baseline imbalances within subgroups were to be expected, although no major imbalances of this type were observed.

Currently available data on cetuximab formally only refer to the randomised phase II study OPUS, but the rationale based on tumour biology is strong and the conclusions are supported by data related to panitumumab.

More data by *RAS* status specifically related to cetuximab are expected from the CRYSTAL and FIRE III studies, but the totality of data provides the evidence needed to restrict the indication as proposed by the MAH.

The CHMP considers the following measures necessary to address issues related to efficacy:

- To submit the results of the CRYSTAL and FIRE III studies by *RAS* status

2.4. Clinical safety aspects

A summary of adverse events in subgroups defined by *RAS* tumour status is presented in the following Table 8.

Table 8: Summary of adverse events during the treatment phase by *RAS* status

	***RAS* Wild-Type**		***KRAS*-Wild Type**		***RAS* Mutant**		***KRAS* Mutant**	
	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4	Cmab+ FOLFOX4	FOLFOX4
	N=36	N=46	N=82	N=97	N=94	N=78	N=77	N=59
Number of Subjects With	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	36 (100)	46 (100)	82 (100)	95 (97.9)	94 (100)	77 (98.7)	77 (100)	58 (98.3)
Any AE Grade 3 +4	28 (77.8)	29 (63.0)	67 (81.7)	62 (63.9)	65 (69.1)	59 (75.6)	52 (67.5)	45 (76.3)
Any SAE	15 (41.7)	7 (15.2)	29 (35.4)	19 (19.6)	32 (34.0)	22 (28.2)	27 (35.1)	17 (28.8)
Any Fatal AE	1 (2.8)	1 (2.2)	3 (3.7)	3 (3.1)	6 (6.4)	0	4 (5.2)	0
Any AE causing discontin-uation of study treatment	17 (47.2)	14 (30.4)	35 (42.7)	27 (27.8)	36 (38.3)	20 (25.6)	30 (39.0)	14 (23.7)

As *RAS* mutation status refers to the tumour only, there were no good reasons to postulate differences in safety profiles related to *RAS* status other than from the perspective that patients with *RAS* wild type tumours would be treated for longer periods of time. Taking small sample sizes into account, the assumption that safety is independent of tumour *RAS* status was considered to be in-line with reported data.

2.4.1. PSUR cycle

The PSUR cycle remains unchanged.

The latest data lock point was 30 September 2013 (the PSUR being expected by 9 December 2013).

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.5. Risk management plan

No revised RMP was submitted in this variation. An updated RMP will be submitted when data from the CRYSTAL and FIRE III studies are submitted (see discussion on clinical efficacy).

2.6. Update of the Product information

As a consequence of this restricted indication, sections 4.1 and 5.1 of the SmPC have been updated.

Additionally, the pre-existing posology recommendation, contraindication and warning in case of *KRAS* mutations have been amended in accordance in sections 4.2, 4.3 and 4.4 of the SmPC.

The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template (version 9.0), which were reviewed and accepted by the CHMP.

2.7. Direct Healthcare Professional Communication

The CHMP considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the restriction of the colorectal cancer indication to patients with wild-type *RAS* tumour status, as inferior OS has been shown in patients with *RAS* mutations beyond *KRAS* exon 2 who received Erbitux in combination with FOLFOX chemotherapy versus FOLFOX alone.

The final version of this DHPC agreed by the CHMP is provided in Attachment 3 together with the communication plan.

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent upon receipt of the Commission Decision with the revised SmPC with the changes highlighted to oncologists who are expected to prescribe Erbitux, chief pharmacists, and pathologists responsible for testing tumour samples from metastatic colorectal cancer patients for *RAS* status.

3. Benefit-Risk Balance

Restricting the use of cetuximab to patients with metastatic colorectal cancer carrying *RAS* wild type tumours improves the benefit without negatively affecting the risk.

Although cetuximab data by *RAS* status are only derived from the randomised phase II study OPUS, the biological rationale supporting the efficacy in patients with *RAS* wild type tumours only is strong and the conclusions are supported by data related to panitumumab. More data by *RAS* status specifically related to cetuximab are expected from the CRYSTAL and FIRE III studies, but the totality of current data already provides the evidence needed to restrict the Erbitux colorectal cancer indication to the treatment of patients with *RAS* (i.e. *KRAS* and *NRAS*) wild type tumours.

The CHMP considers the following measures necessary to address issues related to efficacy:

- To submit the results of the CRYSTAL and FIRE III studies by *RAS* status

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) accepted		**Type**
C.1.6 a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Restriction of the indication for the treatment of colorectal cancer to patients with wild-type *RAS* tumours in follow-up to CHMP request

As a consequence, sections 4.1 and 5.1 of the SmPC are updated. In addition, relevant safety information on the use of Erbitux in patients with mutant *RAS* tumours is updated in accordance in sections 4.2, 4.3 and 4.4 of the SmPC. Conditions are added in Annex II for submission of results of the CRYSTAL and FIRE III studies by *RAS* status and of an RMP update in consequence to the amended indication. The Package Leaflet is updated in accordance.

Furthermore, the PI is being brought in line with the latest QRD template version 9.0.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

This CHMP recommendation is subject to the following new conditions:

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

When the dates for submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

An updated RMP shall be submitted by 31 March 2014.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
To submit the results of the CRYSTAL and FIRE III studies by *RAS* status	31/03/2014

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.