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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Erbitux

cetuximab

Procedure No.: EMEA/H/C/000558/II/0047

Note

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

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck KGaA submitted to the European Medicines Agency on 29 July 2011 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.I.3.b	Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	II

Submission of data from the Nordic VII study in order to fulfil an Annex II condition adopted with variation EMEA/H/C/000558/II/0042. Based on all available data from combination studies with oxaliplatin, the MAH proposed to update section 4.1 of the SmPC with extension of the current indication in combination with FOLFOX4 to the combination with continuous infusional 5-fluoruracil/folinic acid plus oxaliplatin.

The Agency considered this variation application to be an extension of indication (variation category C.I.6.a) and finalised the procedure as such.

1.2. Steps taken for the assessment

Submission date:	29 July 2011
Start of procedure:	21 August 2011
Rapporteur's variation assessment report circulated on:	26 September 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 October 2011
MAH's responses submitted to the CHMP on:	26 October 2011
Rapporteur's assessment report on the MAH's responses circulated on:	1 November 2011
CHMP opinion:	17 November 2011

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/345/2010 for the following condition:

- Treatment of adenocarcinoma of the colon and rectum
- Treatment of oropharyngeal, laryngeal or nasal epithelial carcinoma (excluding nasopharyngeal carcinoma or lymphoepithelioma)

on the granting of a class waiver.

2. Scientific discussion

2.1. Introduction

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 or FOLFOX4

– 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) submitted high level results of the Nordic VII study, which was an independent study not sponsored by the MAH, as well as responses to additional questions in order to fulfil the Annex II condition adopted by the CHMP in conclusion to the EMEA/H/C/000558/II/0042 (II/42) variation. With variation II/42, the mCRC indication 'in combination with chemotherapy' had been restricted to the 'combination with irinotecan-based chemotherapy or FOLFOX4' based on all relevant available data at the time and the CHMP proposed to revisit this indication upon availability of the results of the Nordic VII study.

In accordance with the conclusion of the variation II/42, conditions were imposed as set out in the Annex II of the marketing authorisation and which were as follows:

- As data for the Nordic VII study, which also employed a combination of cetuximab with an oxaliplatin/fluoropyrimidine regimen, were not available at the time of the assessment, the Marketing

Authorisation Holder (MAH) committed to submit a new variation application with the intention to include data from the Nordic VII study in section 5.1 of the SmPC.

- In 3 out of 4 studies with oxaliplatin-containing chemotherapy background regimens, no add on activity of cetuximab was seen in KRAS wild type tumours, the only positive study being a randomised phase II trial. The MAH should justify why the add-on option to FOLFOX4 should be retained in the SmPC.

- Taking non-clinical and clinical data from MAH sponsored and investigator initiated studies into account, are there reasons to believe that:

- there might be a negative dynamic interaction between oxaliplatin (FOLFOX4) and cetuximab in case of KRAS mutation positive tumours, something not seen for irinotecan?
- the apparent relationship between percentage of EGFR positive tumour cells and negative outcome in KRAS mutation positive tumours has a biological foundation?

Based on the data collected in fulfilment of these above conditions, the MAH proposed through this variation to extend the mCRC indication in combination with FOLFOX4 to the combination with continuous infusional 5-fluoruracil/folinic acid plus oxaliplatin.

2.2. Non-clinical aspects

Cetuximab/oxaliplatin interaction and mechanism of adverse outcome in patients with mutant KRAS tumours

In response to the questions whether:

- there might be a negative dynamic interaction between oxaliplatin (FOLFOX4) and cetuximab in case of KRAS mutation positive tumours, something not seen for irinotecan

- the apparent relationship between percentage of EGFR positive tumour cells and negative outcome in KRAS mutation positive tumours has a biological foundation

the MAH summarised data from non-clinical *in vitro* and *in vivo* studies (data not shown) discussed below. No experiments have been conducted in fresh tumour samples from patients with CRC with wild type or mutated KRAS.

2.2.1. Discussion

The MAH argued that the majority of nonclinical data rather provide evidence for a positive or neutral interaction of cetuximab and oxaliplatin in *in vitro* and *in vivo* models from CRC and other indications, similarly as it is reported for combination of cetuximab with other chemotherapies such as other platinum derivates or topoisomerase I inhibitors. Two major molecular mechanisms contribute to the positive interaction of cetuximab and oxaliplatin:

1. Inhibition of oxaliplatin-induced activation of EGFR-mediated survival pathways by cetuximab.

2. Inhibition of EGFR-mediated DNA damage repair by cetuximab.

Both mechanisms were demonstrated in nonclinical models and were shown to be associated with the efficacy of the combination of cetuximab and oxaliplatin as well as other chemotherapies.

One in vitro study reported a negative interaction between cetuximab and oxaliplatin. It is difficult to put the data of this study into the overall context since:

1. the antagonistic activity was observed in cell lines in which other nonclinical studies saw a positive combination effect and

2. the antagonistic effect was obtained in KRAS wild-type cells, but not in KRAS mutated cell lines which is in contradiction to the situation observed in the clinical setting.

Nevertheless, the study provided a potential mechanistic rationale that might be of relevance to explain the observed antagonistic effect of the combination of cetuximab and oxaliplatin in patients with KRAS mutated tumours: In order to exert its cytotoxic effect, oxaliplatin relied on EGFR-mediated reactive oxygen species (ROS) production via Nox1, a mechanism that was blocked by cetuximab in those cells, so that addition of cetuximab to oxaliplatin produced an antagonistic activity.

The reason for the opposite role of the KRAS mutation status in this study is not known. However, the antagonistic effect occurred in two cell lines (HT-29-D4 and Caco-2) expressing EGFR on the cell surface whereas no combination effect was observed in two cell lines (SW480 and SW620) lacking EGFR expression on the cell surface. This is in line with the clinical data which suggested that the potential antagonistic effect in KRAS mutated tumours is absent or less pronounced in tumours with no or very low EGFR expression.

Cell line data are further complicated by the fact that certain cell lines are sensitive to cetuximab alone. E.g., the mechanistic interaction between cetuximab and oxaliplatin is currently being investigated in the parental CRC cell line SW48 (KRAS wt) and seven isogenic SW48 cell lines harbouring the most commonly occurring KRAS mutations in CRC. The parental, KRAS wt cell line SW48 has low to medium EGFR expression levels, but is very sensitive to EGFR inhibition by cetuximab already in *in vitro* growth assays. Interestingly, introducing KRAS mutations rendered the isogenic cell lines more resistant to cetuximab treatment. The degree of resistance varied among the different isogenic cell lines with KRAS mutations, but they all displayed higher IC50 values and/or less maximal inhibition in the *in vitro* growth assay compared to the parental, KRAS wt cells.

The cell lines showed variable sensitivity to growth inhibition to oxaliplatin, however within the same order of magnitude. No apparent difference was visible between KRAS wt and KRAS mt cells. The addition of cetuximab to oxaliplatin resulted in stronger growth inhibition than oxaliplatin alone for SW48 KRAS wt cells. Similar, but weaker effects were observed for SW48 cells harboring the KRAS mutations with the exception of one cell line, which reacted antagonistically when cetuximab was added to oxaliplatin concentrations particularly at or below the IC50 of oxaliplatin.

In conclusion, the MAH considered that most nonclinical studies point to a rather positive (or at least neutral) interaction of cetuximab and oxaliplatin including mechanistic rationales, similarly as it was described for combinations of cetuximab with other chemotherapies, such as topoisomerase I inhibitors. Until now, only limited nonclinical evidence exists for an antagonistic interaction that appears to occur in the clinical setting under certain circumstances such as mutated KRAS CRC tumours with higher EGFR expression levels. However, first hypotheses have been generated how EGFR signalling might not only protect against the cytotoxic action of chemotherapy, but could also be required for the activity of chemotherapy, thereby providing a mechanistic explanation for a potential negative interaction of cetuximab and oxaliplatin.

So far the nonclinical data do not allow a robust judgement of the influence of the KRAS mutation status and EGFR expression levels on the efficacy of the combination of cetuximab and oxaliplatin. More dedicated studies are needed to identify the main central factors and mechanisms that influence the interaction of the two compounds.

The CHMP considered that robust data on the possible association between EGFR expression level and interaction with oxaliplatin are not available. Further mechanistic studies are underway and might, if explants studies are undertaken, even shed some light on the clinical observation that there seems to

be a negative interaction between oxaliplation containing regimens and cetuximab in KRAS mt CRC. Moreover, it is of obvious interest to investigate the reasons behind the negative effect of cetuximab on the activity of oxaliplatin in the isogeneic SW40 cell line carrying a specific KRAS mutation and to also see results of the above-mentioned cell line experiments (in SW40 cellls with wt KRAS or isogeneic clones carrying KRAS mutations) with irinotecan, too.

In conclusion, in the cell lines tested, KRAS status was non-informative for the interaction between oxaliplatin and cetuximab. The mechanistic background to the observed clinical phenomenon remains unexplained.

2.3. Clinical Efficacy aspects

Nordic VII

The Nordic VII study was an investigator-sponsored trial sponsored by the Nordic Colorectal Cancer Biomodulation Group (NCCBG). The NCCBG owns the data collected in the Nordic VII study and is responsible for statistical analysis, reporting, and publication.

2.3.1. Methods – analysis of data submitted

NORDIC VII was performed in Denmark, Finland, Iceland, Norway, and Sweden from May 2005 until May 2009. Important inclusion criteria were age > 18 and < 75 years, World Health Organization (WHO) performance status 0–2, no prior chemotherapy for advanced/metastatic disease, no previous oxaliplatin, and no current indications for resection with curative intent.

Eligible patients were randomly assigned, independently of KRAS status, in a ratio of 1:1:1 to one of 3 intravenous (IV) treatment regimens, administered in cycles of 2 weeks, with stratification by study centre:

Arm A: (Nordic) FLOX (oxaliplatin 85 mg/m² over 1 h (30 to 90 min), 5-FU 500 mg/m² as a bolus infusion (< 5 min), followed 30 min later by bolus FA 60 mg/m² (< 10 min) on days 1 and 2)

Arm B: Cetuximab plus FLOX (Cetuximab was given as an initial infusion of 400 mg/m² followed by weekly infusions of 250 mg/m²)

Arm C: Cetuximab and intermittent FLOX

The primary endpoint was progression-free survival (PFS) (RECIST) assessed every 8 weeks, calculated from randomisation to first recorded progression or death. Patients who had not progressed or died by a pre-specified cut-off date (approximately 12 months after last enrolled patient) were treated as censored. The main comparison was between arm B and A. As PFS is not considered an appropriate endpoint with regard to the stop and go principle (arm C), comparisons including arm C are primarily of interest for the secondary endpoint overall survival (OS).

2.3.2. Results

In terms of biomarkers of interest, the following numbers were reported at baseline:

- KRAS: evaluable 88% (498/566), wild type 61% (303/498), mutant 39% (195/498)

- KRAS wild type: arm A 63% (97/155), arm B 57% (97/169), arm C 63% (109/174)

- BRAF: Evaluable 81% (457/566), mutant: 12% (55/457)

- BRAF mutant in KRAS wild type: arm A 21%, arm B 22% and arm C 17%.

Efficacy results are reported in the following tables and figure. Results presented in the tables are taken from the draft study report. Figures were copied from the relevant ASCO GI 2011 presentation and results reported in it were based on a slightly smaller number of events.

Table 1: Confirmed ORR by treatment arm; ITT, wtKRAS, mtKRAS populations; Nordic VII

Population	Arm A		Arm B		Arm C		Odds ratio[a]	
	n/N	%	n/N	%	n/N	%	B vs A	C vs A
ITT	74/185	40	94/194	48	84/187	45	1.41	1.22
KRAS wild type	43/97	44	45/97	46	56/109	51	1.09	1.33
KRAS mutant	23/58	40	35/72	49	24/65	37	1.44	1.23

n = number of patients with confirmed partial or complete response, N = number of patients in specified treatment arm and analysis population.

[a] Chi-square test was used for treatment comparisons.

Table 2: PFS and OS by treatment arm; ITT, wtKRAS, mtKRAS populations; Nordic VII

Variable / population	Arm A		Arm B		Arm C	
	N	Median (95% CI)	N	Median (95% CI)	N	Median (95% CI)
PFS time, months						
ITT	185	7.9 (7.3, 8.7)	194	8.3 (7.7, 9.5)	187	7.4 (6.7, 8.1)
KRAS wild type	97	8.7 (7.6, 9.6)	97	7.9 (7.0, 10.2)	109	7.5 (6.6, 9.1)
KRAS mutant	58	7.9 (6.9, 9.0)	72	9.3 (7.7, 11.2)	65	7.3 (6.3, 8.3)
OS time, months						
ITT	185	20.4 (18.0, 24.1)	194	19.7 (17.0, 23.4)	187	20.3 (16.9, 22.9)
KRAS wild type	97	22.0 (18.4, 26.0)	97	20.1 (15.8, 25.4)	109	21.4 (15.1, 25.5)
KRAS mutant	58	20.4 (16.1, 29.0)	72	21.1 (16.8, 25.1)	65	20.5 (17.1, 25.1)

CI = confidence interval, N = number of patients in specified treatment arm and analysis population.

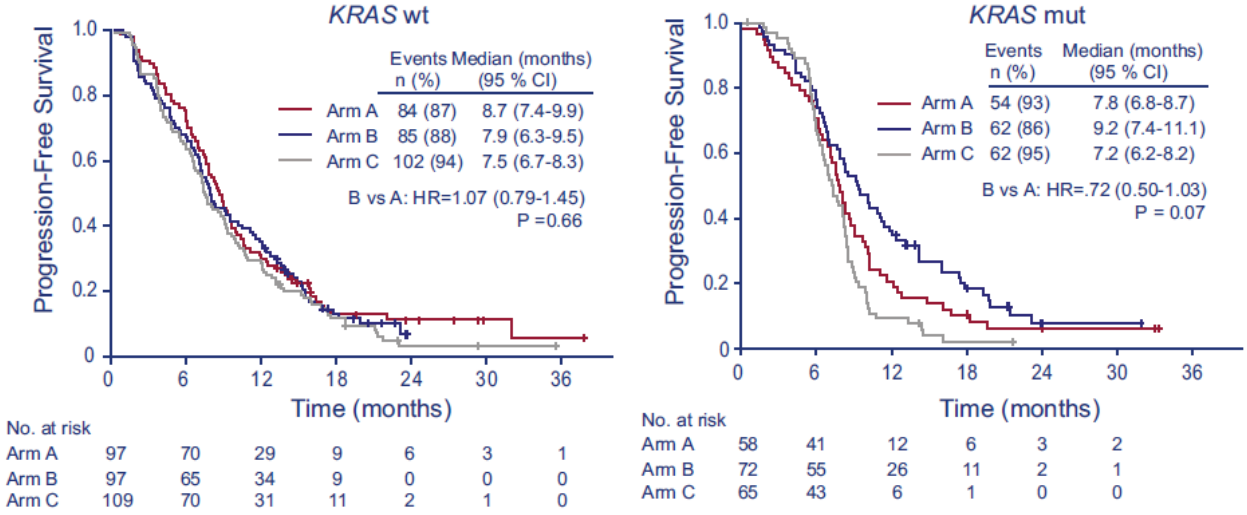
Note: The time period was from date of randomization to 31 October 2008 (PFS) or to 30 April 2009 (OS).

Table 3: Statistical comparisons of PFS and OS between treatment arms; ITT, wtKRAS, mtKRAS populations; Nordic VII

Variable / population	A (ref) versus B		A (ref) versus C		B (ref) versus C	
	Hazard ratio	p-value (log rank)	Hazard ratio	p-value (log rank)	Hazard ratio	p-value (log rank)
PFS time, months						
ITT	0.89	0.31	1.24	0.11	1.39	0.006
KRAS wild type	1.06	0.67	1.21	0.20	1.14	0.39
KRAS mutant	0.73	0.08	1.48	0.09	2.1	0.0002
OS time, months						
ITT	1.06	0.65	1.08	0.78	1.02	0.87
KRAS wild type	1.20	0.47	1.12	0.64	1.14	0.78
KRAS mutant	0.99	0.89	1.11	0.86	1.13	0.95

Note: Hazard ratios were estimated using the Cox proportional hazards model.

Figure 1: Kaplan-Meier curves of PFS in wtKRAS and mtKRAS populations, Nordic VII



In terms of exposure and in the ITT population, the dose intensities and number of cycles for 5-FU and oxaliplatin were similar in arms A and B. However, relative dose intensities compared to the expected intensity without dose adjustments were not reported.

2.3.3. Discussion

The description of the results for the Nordic VII study was based on the study protocol, a draft study report prepared by an involved contract research organization and records from a poster published at the ASCO GI 2011 conference.

With regard to study treatments, 5-FU was administered in Nordic VII as a bolus infusion (FLOX regimen) while the FOLFOX regimens utilise continuous infusion. The Nordic FLOX regimen is used almost exclusively within the Nordic area.

On the biomarker data, mutated BRAF appears to be a prognostic factor of poor outcome in CRC; whether it is also predictive of poor cetuximab activity is disputed.

With regard to ORR data (Table 1), the MAH stated that 95% CI and p-values were not available. The seemingly higher ORR in arm B than in arm A in the mutant KRAS groups prompted the assessor to calculate the 95% CI for the difference between arms A and B: this was (-8%, +26%), B performing 'better' than A. Even though the difference is not statistically significant, note that the ORRs in the wild type KRAS groups are rather similar in arms A and B. Thus the results must be regarded as unexpected in that they are showing a tendency for benefit from cetuximab in the mutant KRAS group and no difference in the wild type KRAS group.

In terms of PFS (Tables 2 and 3, Figure 1), the comparison of primary interest is between arms A and B. In KRAS wild type, results are similar, while in the KRAS mutant groups, arm B tends to be better than A (HR 0.7, p=0.07), again clearly unexpected.

OS results (Tables 2 and 3) indicate similarity.

Overall, available results were considered by the MAH as incomplete as, among other information, the following were missing: results for the KRAS-evaluable and non-evaluable populations, relative dose densities, safety analyses by KRAS status, and second-line treatment. Based on this, reported results were considered to be preliminary. Therefore, a meaningful and complete assessment of the outcome of the Nordic VII study is not yet possible.

The CHMP considered that NORDIC VII is the only study where cetuximab as add-on to chemotherapy in CRC appears to be associated with add-on activity in patients with KRAS mutant disease, albeit statistically formally not significant (p=0.07 for PFS). Actually, as add-on to FOLFOX a negative interaction between FOLFOX and cetuximab has been seen in this population (in contrast to irinotecan based regimens). No mechanistic explanation has been identified as discussed previously. In contrast, no discernable add-on activity is seen in the target population, i.e. patients with wild type KRAS tumours.

Absence of add-on activity in the target population could be related to the background chemotherapy regimen, i.e. 5-FU as bolus instead of infusional as in FOLFOX, but why that should be the case is not obvious. Alternative explanations include differences in study populations, less rigorous assessment of events of progression, censoring rules etc., i.e. factors reducing 'assay sensitivity' (as in the COIN study). However, the dose intensity of the FLOX regimen seems similar in arms A and B.

Apparent add-on activity in mutant KRAS tumours could be a spurious finding related to imbalances in hidden and important prognostic factors (but not predictive of cetuximab activity) as all available clinical data indicate that cetuximab (and panitumumab) are devoid of activity in this population. As the study was not stratified by KRAS status for obvious reasons, such imbalances could affect results in both wild type and mutant KRAS subgroups and could produce the reported results seemingly contradicting all available prior data independently of and without any consequence for the predictive value of KRAS mutation status.

The results, as reported by the MAH, were reviewed in detail and no convincing explanation to the rather surprising results of an apparent add-on benefit of cetuximab in patients with mutant KRAS tumours has been identified. Whether the full study report, e.g. with respect to dose intensity, discontinuations, distribution of PFS events, sensitivity analyses, etc. will provide further clarity is considered rather unlikely. However, the MAH should still provide the final clinical study report of Nordic VII, when available although provision of this report is no longer considered key to the benefit-risk balance of cetuximab in combination with oxaliplatin-based chemotherapy used in the treatment of metastatic colorectal cancer. This is because the report is unlikely to pinpoint the reason(s) for the unexpected results, while the study also used an oxaliplatin-based regimen with bolus 5-FU administration, which is outside the final indication in combination with FOLFOX in which a continuous 5-FU infusion is being employed.

Cetuximab add-on activity to oxaliplatin-containing chemotherapy

As mentioned earlier, in three out of four studies with oxaliplatin-containing chemotherapy background regimens, no add on activity of cetuximab is seen in KRAS wild type tumours, the only positive study being a randomised phase II trial (OPUS). The MAH was asked to justify why the add-on option to FOLFOX4 should be retained in the SmPC.

2.3.4. Methods – analysis of data submitted

The MAH provided a tabulated overview of studies employing cetuximab in combination with oxaliplatin-containing regimens. This included the four studies mentioned before (OPUS, CAIRO2, COIN, Nordic VII).

Table 4: Overview of studies employing cetuximab and oxaliplatin-containing chemotherapy

Study	Indication	Study design	Regimen	Patients* ITT/KRAS wt
Trials comparing cetuximab plus oxaliplatin and infusional 5-FU/FA with oxaliplatin and infusional 5 FU/FA alone				
EMR 62 202-047 (OPUS)	1st line mCRC	Phase II 2-arm, controlled	cetuximab + FOLFOX4 vs FOLFOX4	169/82
COIN (IST) OxMdG subgroup	1st line mCRC	Phase III 3-arm, controlled	cetuximab + OxMdG vs OxMdG	281/117
Trials comparing cetuximab plus oxaliplatin and infusional 5-FU/FA with cetuximab plus FOLFIRI				
CECOG CORE 1.2.001 (IST)	1st line mCRC	Phase II 2-arm, controlled	cetuximab + FOLFIRI vs cetuximab + FOLFOX6	77/34
CELIM (IST)	neoadjuvant, unresectable liver metastases	Phase II 2-arm, controlled	cetuximab + FOLFIRI vs cetuximab + FOLFOX6	53/NA
Further trials investigating cetuximab plus oxaliplatin and infusional 5-FU/FA				
CECOG CORE 1.2.002 (IST)	1st line mCRC	Phase II 2-arm, controlled	cetuximab q1w + FOLFOX4 vs cetuximab q2w + FOLFOX4	152/152
EMR 200025-001 (FUTURE) FOLFOX4 arm	1st line mCRC	Phase II 2-arm, controlled	cetuximab + FOLFOX4	150/56
Uncontrolled trials investigating cetuximab plus oxaliplatin and infusional 5-FU/FA				
EMR 62 202-018 (ACROBAT)	1st line mCRC	Phase II uncontrolled	cetuximab + FOLFOX4	43/NA
EMR 62 202-021	1st line mCRC	Phase I/II uncontrolled	cetuximab + FUFOX	49/NA
Boccia et al., 2010	1st line mCRC	Phase II uncontrolled	cetuximab + FOLFOX6	67/NA
Colucci et al., 2010	1st line mCRC	Phase II uncontrolled	cetuximab + FOLFOX4	67/22
Ongoing studies				
EMR 62 202-057 (TAILOR)	1st line mCRC Chinese popn	Phase III 2-arm, controlled	cetuximab + FOLFOX4 vs FOLFOX4	Ongoing
EMR 62 202-505 (APEC)	1st line mCRC	Phase II uncontrolled	cetuximab q2w + FOLFIRI or FOLFOX6	Ongoing
CALGB 80405 (IST)	1st line mCRC	Phase III 3-arm, controlled	cetuximab + FOLFIRI or FOLFOX vs beva + FOLFIRI or FOLFOX**	Ongoing
Studies using other oxaliplatin-based regimens				
SAKK (IST)	1st line mCRC	Phase II 2-arm, controlled	cetuximab + XELOX vs XELOX	37/NA
COIN (IST) XELOX subgroup	1st line mCRC	Phase III 3-arm, controlled	cetuximab + XELOX vs XELOX	543/245
EXPERT-C (IST)	neoadjuvant CT then CRT high-risk rectal cancer	Phase II 2-arm, controlled	cetuximab + CAPOX vs CAPOX	83/46
CAIRO2 (IST)	1st line mCRC	Phase III 2-arm, controlled	cetuximab + beva+ XELOX vs beva+ XELOX	368/158
EMR 200025-001 (FUTURE), UFOX arm	1st line mCRC	Phase II 2-arm, controlled	cetuximab + UFOX	152/40
Nordic VII (IST)	1st line mCRC	Phase III 3-arm, controlled	cetuximab + FLOX vs cetuximab + intermittent FLOX vs FLOX	194/97

beva= bevacizumab, CRT= chemoradiotherapy, CT= chemotherapy, IST= investigator sponsored trial, mCRC= metastatic colorectal cancer, NA= not available, q1w= weekly, q2w= every 2 weeks, wt= wild type
*arm with cetuximab plus continuous CT only in case of controlled studies **third arm using cetuximab+bevacizumab+FOLFIRI or FOLFOX stopped prematurely. All studies were open-label, multicentre; in controlled studies with more than 1 arm randomisation was with equal allocation

2.3.5. Results

Results from the tabulated studies were reported by the MAH. The most pertinent results for the discussion are presented below.

The first line studies 'OPUS' and 'COIN' have been discussed in detail before. For COIN, the MAH has focused on the modified De Gramont regimen (OxMdG), i.e. the arm with infusional 5-FU and presents pooled results of OPUS and COIN and then compares the results with "CRYSTAL" i.e. the first-line FOLFIRI +/- cetuximab study.

Table 5: Comparison of pooled efficacy results in OPUS and COIN (OxMdG) vs CRYSTAL

Efficacy endpoint / parameter	Pooled analysis* EMR 62 202-047 (OPUS) and COIN OxMdG subgroup KRAS wild-type population		EMR 62 202-013 (CRYSTAL) KRAS wild-type population	
	Cetuximab + FOLFOX	FOLFOX	Cetuximab + FOLFIRI	FOLFIRI
ORR, OR [95% CI]	1.87 [1.07, 3.28]		2.069 [1.515, 2.826]	
PFS, HR [95% CI]	0.69 [0.52, 0.92]		0.696 [0.558, 0.867]	
OS, HR [95% CI]	0.90 [0.73, 1.11]		0.796 [0.670, 0.946]	

CI = confidence interval, HR = hazard ratio, OR = odds ratio, ORR = overall response rate, OS = overall survival, PFS = progression-free survival

* random effect model

In the CECOG CORE study, the FOLFIRI or FOLFOX6 regimens were compared, each with cetuximab as add-on.

Table 6: Efficacy of cetuximab+infusional 5-FU/FA+oxaliplatin vs cetuximab+FOLFIRI, study CECOG CORE 1.2.001

Study / endpoint	ITT population (independent of KRAS status)		KRAS wild-type population	
CECOG CORE 1.2.001	Cetuximab+ FOLFIRI	Cetuximab + FOLFOX6	Cetuximab+ FOLFIRI	Cetuximab + FOLFOX6
Number of patients	74	77	28	34
ORR, % patients [95% CI]	45 [33, 57]	43 [32, 55]	50 [31, 69]	56 [38, 73]
Odds ratio [95% CI]	0.93 [0.49, 1.77]		NA	
p-value (CMH test)	NA		NA	
Median PFS, months [95% CI]	8.3 [7.4, 8.7]	8.6 [6.3, 9.7]	8.4 [3.2, 11.3]	9.1 [8.3, 11.1]
Hazard ratio [95% CI]	1.06 [0.74, 1.52]		NA	
p-value (log rank test)	0.7375		NA	
Median OS, months [95% CI]	18.9 [14.7, 23.9]	17.4 [14.9, 22.6]	19.9 [11.9, NA]	22.5 [17.1, 28.9]
Hazard ratio [95% CI]	0.98 (0.67, 1.44)		NA	
p-value (log rank test)	0.9230		NA	

Moreover, the MAH has tabulated the results of single arm studies where cetuximab was used as add-on to infusional 5-FU and oxaliplatin. The table also contains the controlled CECOG CORE 1.2.002 study which did not employ any treatment arm without cetuximab, as well as the controlled FUTURE study, in which the control (no-cetuximab) arm received an non-infusional fluoropyrimidine regimen; hence,

these two studies were considered as single-arm for the purposes of this table. As reference, EMR 62 202-047 (OPUS) was also included in the table.

Table 7: Efficacy of cetuximab+infusional 5-FU/FA+oxaliplatin in studies without a control group and comparison with results from OPUS

	ITT population (independent of KRAS status)		KRAS wild-type population	
	Cetuximab + FOLFOX		Cetuximab + FOLFOX	
CECOG CORE 1.2.002 (cetuximab weekly + FOLFOX4)				
Number of patients	Not applicable		75	
ORR, % patients [95%CI]			51	[39, 62]
Median PFS, months [95% CI]			9.5	[7.6, 11.2]
CECOG CORE 1.2.002 (cetuximab every 2 weeks + FOLFOX4)				
Number of patients	Not applicable		77	
ORR, % patients [95%CI]			62	[51, 73]
Median PFS, months [95% CI]			9.2	[7.8, 10.0]
FUTURE (cetuximab weekly + FOLFOX4)				
Number of patients	150		56	
ORR, % patients [95%CI]	51.3	[43.0, 59.6]	62.5	[48.5, 75.1]
Median PFS, months [95% CI]	8.2	[7.5, 9.2]	9.2	[7.4, 9.5]
Median OS, months [95% CI]	Results not mature at time of analysis			
EMR 62 202.018 (ACROBAT, cetuximab weekly + FOLFOX4)				
Number of patients	43		Not available	
ORR, % patients [95%CI]	72	[56, 85]		
Median PFS, months [95% CI]	12.3	[7.7, 15.8]		
Median OS, months [95% CI]	30.0	[17.8, 33.8]		
EMR 62202-021 (cetuximab weekly + FUFOX)				
Number of patients	49		Not available	
ORR, % patients [95%CI]	57	[42, 71]		
Median PFS, months [95% CI]	8.1	[6.0, 9.7]		
Median OS, months [95% CI]	28.2	[14.7, NE]		
Boccia (cetuximab weekly + FOLFOX6)				
Number of patients	67		Not available	
ORR, % patients [95%CI]	44.8	[33.5, 56.7]		
Median PFS, months [95% CI]	9.3	[7.0, 11.3]		
Median OS, months [95% CI]	21.7	[17.5, 27.8]		
Colucci (cetuximab weekly + FOLFOX4)				
Number of patients	67		22	
ORR, % patients [95%CI]	64.2	[52.5, 75.5]	74.7	NA
Median TTP, months [95% CI]	10	NA	12	[9.0, 17.7]
Median OS, months [95% CI]	22	NA	27.3	[19.7, 36.8]
EMR 62 202-047 (cetuximab weekly+ FOLFOX4)				
Number of patients	169		82	
ORR, % patients [95%CI]	45.6	[37.9, 53.4]	57.3	[45.9, 68.2]
Median PFS, months [95% CI]	7.2	[5.6, 7.7]	8.3	[7.2, 12.0]
Median OS, months [95% CI]	18.3	[14.8, 20.4]	22.8	[19.3, 25.9]

CI = confidence interval, CT = chemotherapy, CMH test = Cochran-Mantel Haenszel test, NA = not available, NE = not evaluable, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, TTP = time to progression

Finally, EXPERT-C was a small, complex, randomised study where neoadjuvant capacitabine + oxaliplatin (CAPOX) **+/-** cetuximab (followed by chemoradiotherapy (CRT), surgery and adjuvant CAPOX) were compared.

Table 8: Efficacy results, study EXPERT-C

	ITT		KRAS wild type	
EXPERT-C	Cetuximab+ CAPOX + CRT	CAPOX + CRT	Cetuximab+ CAPOX + CRT	CAPOX + CRT
Number of patients	83	81	46	44
ORR (CT), % patients [95%CI]	59 NA	50 NA	70 NA	50 NA
p-value	0.195		0.028	
ORR (CRT), % patients [95%CI]	78 NA	71 NA	89 NA	72 NA
p-value	0.195		0.028	
PFS rate at 3 years, % patients	71 NA	69 NA	80 NA	77 NA
Hazard ratio [95% CI]	NA		0.62 [0.24, 1.57]	
p-value (log rank test)	0.463		0.308	
OS rate at 3 years, % patients	86 NA	78 NA	96 NA	81 NA
Hazard ratio [95% CI]	NA		0.27 [0.07, 0.99]	
p-value (log rank test)	0.077		0.035	

2.3.6. Discussion

The MAH claimed that studies investigating cetuximab in combination with continuous infusional 5-FU/FA plus oxaliplatin show that this is an effective therapy with consistent results across studies and efficacy endpoints. The results overall compare well with those obtained in the pivotal EMR 62 202-013 (CRYSTAL) study investigating cetuximab in combination with FOLFIRI.

Overall the combinations of cetuximab with continuous infusional 5-FU/FA and oxaliplatin or irinotecan show acceptable and manageable toxicity in the treatment of first-line metastatic CRC. The corresponding safety profile is adequately reflected in the current product information for cetuximab.

The CHMP commented that there are numerous ways to administer 5-FU, folinic acid and oxaliplatin; infusional 5-FU such as in FOLFOX4, FOLFOX6 and OxMdG, but also as bolus 5-FU as in the Nordic FLOX regimen. While these regimens may show differences in terms of benefit/risk, there are no good reasons to assume that the add-on activity of cetuximab should differ if the chemotherapy regimens and the combinations with cetuximab are reasonably well tolerated.

The current indication for cetuximab is restricted to add-on to FOLFOX4. Submitted data supporting an extension of the indication to 'continuous infusional 5-FU' regimens are weak; only add-on to OxMdG (similar to FOLFOX regimens) provides some insight as regards benefit/risk. Add-on efficacy of cetuximab with all FOLFOX regimens is nevertheless highly likely.

Finally, the MAH was invited to provide data on a possible relationship between rash development in the course of cetuximab treatment and cetuximab efficacy and to comment whether treatment continuation should be re-assessed in the absence of rash development within the first 4-8 weeks of treatment. The MAH provided data from two clinical studies (CRYSTAL and EVEREST, data not shown) which were inconclusive, so that at this stage it is agreed that it cannot be concluded that absence of early rash in patients with CRC warrants reconsideration of cetuximab therapy. A follow-on study to EVEREST (EVEREST-II) is currently ongoing. This study is conducted first-line and as cetuximab add-on to FOLFIRI with dose escalation vs. standard dose in patients with vs. without rash at week 3, respectively.

2.4. Clinical Safety aspects

Nordic VII

2.4.1. Results

With respect to safety, grade 3/4 febrile neutropenia was common in both arms A and B (9.4 vs. 12.9%), grade 3 fatigue was higher in arm B compared to arm A (16 vs. 10%) and so was grade 3 diarrhoea (17 vs. 10%).

2.4.2. Discussion

With regard to skin reactions, the MAH was asked to consider whether other measures should be recommended in addition to interruption of cetuximab treatment, such as use of mild steroids, sun screen, antibiotics etc, and whether such measures could also be of potential benefit used pre-emptively.

The MAH summarised published trial data on the use of antibiotics (data not shown) which, with the exception of one standard tetracycline trial, all indicated that the skin-related Quality of Life was better in those patients receiving antibiotics regardless of the assessment tool used.

One study is ongoing to evaluate in a randomised double-blinded trial setting the use of Vitamin K versus placebo in the prophylactic treatment of skin rash induced by cetuximab. The MAH argued that data from the ongoing trials should be awaited to decide on the value of topical Vitamin K for the treatment of skin rash.

With regard to sunscreen, the MAH submitted a published study (data not shown) which failed to show any benefit from pre-emptive or symptomatic treatment of EGFR inhibitor-induced rash.

Based on randomised data, the recommended preventive therapy for the development of rash would be the topical application of 1% hydrocortisone cream with moisturizer and sunscreen twice daily and systemic monocycline or doxycycline. Reactive use of medium to high-potency topical steroids is also recommended based on pathophysiological considerations, while tetracyclines are a therapeutic option in the treatment of patients who already experienced skin rash, as well.

2.5. Changes to the Product Information

> Based on all data from the combination of cetuximab with oxaliplatin-based chemotherapy, the MAH proposed that cetuximab should be indicated for metastatic CRC in combination with continuous infusional 5-FU/FA plus oxaliplatin.

During the procedure, the CHMP considered that a final amendment of the mCRC indication in combination with oxaliplatin chemotherapy appears warranted as discussed in detail above. More specifically, the indication should be extended from FOLFOX4 to all FOLFOX regimens but restricted to the first line therapy in agreement with clinical trials conducted. Moreover, the requirement for demonstration of wild type KRAS tumour status before starting cetuximab treatment should be strengthened and a contraindication against use of cetuximab with oxaliplatin-containing chemotherapy for patients with mutant *KRAS* mCRC or for whom *KRAS* mCRC status is unknown should be added. Finally, information regarding prevention and treatment of skin rash should be provided.

3. Overall conclusion and impact on the benefit/risk balance

Benefit – risk remains favourable for the use of cetuximab in accordance with the approved and now modified indication.

4. Recommendations

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

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

Modification of the metastatic colorectal cancer indication in combination with FOLFOX4 to an extended combination with FOLFOX but restricted to first line treatment only based on data from the Nordic VII study and additional data on the potential negative dynamic interaction between oxaliplatin (FOLFOX4) and cetuximab in case of KRAS mutation positive tumours and on the potential biological foundation of the apparent relationship between percentage of EGFR positive tumour cells and negative outcome in patients with KRAS mutation positive tumours. Both sets of data are fulfilling an Annex II condition.
As a consequence, sections 4.1, 4.2, 4.3, 4.4 and 5.1 of the SmPC are amended with the modified mCRC indication, strengthening of the wording on the requirement for KRAS testing prior to treatment initiation, adoption of a new contraindication against use of cetuximab in combination with oxaliplatin-containing chemotherapy in patients with mutant *KRAS* metastatic colorectal cancer (mCRC) or for whom *KRAS* mCRC status is unknown, introduction of prophylaxis treatment recommendations for skin reactions and inclusion of statements regarding paediatric use.

The Package Leaflet (PL) is updated accordingly. In addition minor editorial amendments are included in the SmPC and PL. Moreover, the condition imposed on the marketing authorisation is considered fulfilled. Therefore, the obligation to conduct post-authorisation measures is deleted from the Annex II.