Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Cetuximab

Proprietary Product Name: Erbitux

Sponsor: Merck Serono Australia Pty Ltd

February 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	5 January 2010
Active ingredient(s):	Cetuximab
Product Name(s):	Erbitux
Sponsor's Name and Address	Merck Serono Australia Pty Limited 3-4, 25 Frenchs Forest Road Frenchs Forest NSW 2086
Dose form(s):	Solution for infusion
Strength(s):	5 mg/mL x 10, 20, 50 and 100 mL
Container(s):	Clear, colourless glass vials with a fluorotec-coated bromobutyl rubber stopper and aluminium/polypropylene seal
Pack size(s):	Single use vial
Approved Therapeutic use:	for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, K-RAS wild-type metastatic colorectal cancer (CRC) · in combination with chemotherapy · as a single agent in patients who have failed or are intolerant to oxaliplatin based therapy and irinotecan-based therapy. Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck · in combination with radiation therapy for locally advanced disease · in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.
Route(s) of administration:	Intravenous
Dosage:	First dose 400 mg/m^2 then 250 mg/m^2 once weekly

Product Background

For many years 5-fluorouracil (5-FU) modulated with folinic acid (FA) has been a common first line treatment for previously untreated metastatic colorectal cancer (CRC) with response rates of 10 to 20%, median progression-free survival (mPFS) times of 3.5 to 5.0 months, and median overall survival (mOS) times of 10 to 14 months reported in randomised studies. Advances in terms of efficacy were achieved with the introduction of the approved and widely accepted triple-drug regimens of 5-FU with FA in combination with either irinotecan or oxaliplatin. These regimens demonstrated significant superiority over 5-FU/FA alone in terms of response rate and median time to progression (mTTP) or mPFS time; however only

the irinotecan-based regimens showed a significantly improved mOS time over 5-FU/FA alone.

The therapeutic value of irinotecan versus oxaliplatin both in combination with an identical intermittent infusional 5-FU/FA regimen has been examined in studies, and in the first line setting, both regimens showed comparable efficacy in terms of response rate and mPFS. Fluoropyrimidine-based therapies with irinotecan (with or without addition of bevacizumab) or with oxaliplatin are currently used for patients with previously untreated metastatic CRC.

Drugs are the main choice for non-resectable metastatic disease, and their use may lead to considerable responses that allow complete resection of residual disease. It has therefore become a primary goal of first line therapy to maximise response rates, thereby improving the chance of potentially curative resection.

For patients with previously treated metastatic CRC, patients who have previously failed on irinotecan-based therapy have two approved treatment options: cetuximab plus irinotecan or oxaliplatin plus intermittent infusional 5-FU/FA. Response rates reported for irinotecan as single agent for treatment after failure of 5-FU-based chemotherapy have been 13 to 17%, a mTTP (or PFS time) of 3.3 to 5.5 months, and mOS times of 7 to 13 months. Poor efficacy results have been reported for both single-agent irinotecan and irinotecan plus intermittent infusional 5-FU/FA.

In clinical studies the combination of cetuximab plus irinotecan has showed improved efficacy over cetuximab alone in patients with metastatic CRC and disease progression, mostly on multiple chemotherapy that included both oxaliplatin- and irinotecan-based regimens. The combination demonstrated statistically significant advantages over single-agent cetuximab in terms of overall response rate (ORR) (23% vs 11%) and mPFS time (4.1 vs 1.5 months), and also induced prolongation of mOS time (8.6 vs 6.9 months). Based on these data cetuximab in combination with irinotecan was approved for treatment of patients who have failed irinotecan-based regimens. The combination of cetuximab and irinotecan is now considered the treatment of choice for patients in the clinical situation stated above and is recommended by European clinical practice guidelines.

Growth factors and their receptors play a significant role in the malignant phenotype of many human cancers. The epidermal growth factor receptor (EGFR) is an established epidermoid proto-oncogene, with a role in pathogenesis of human carcinomas. On tumour cells, EGFR is often overexpressed. Malignancy often correlates with EGFR status. EGFR signalling contributes to tumour progression through promoting growth, tissue invasion and metastasis as well as protection of epidermoid tumours from apoptosis.

Recent research based on retrospective evaluations of tumour samples from heavily pre-treated patients has suggested that the mutation status of the *K-RAS* (Kirsten rat sarcoma 2 viral oncogene homologue) gene might be a predictor for the efficacy of EGFR-targeted monoclonal antibody treatments for metastatic CRC administered both as single agents and as combination therapies. The *K-RAS* protein plays an important role in the EGFR signalling pathway, activating other proteins associated with cell proliferation and survival. Mutations in the *K-RAS* gene can transform it into an oncogene and result in a constitutively activated proliferation/survival pathway.

Cetuximab is a chimeric monoclonal antibody that binds specifically and with high affinity to the extracellular domain of human EGFR. Cetuximab antagonises receptor binding of cognate EGFR ligands such as epidermal growth factor (EGF) and transforming growth factor (TGF). Because of the diversity of the EGFR-dependent intracellular signal pathways, the biological effects of the blockade of ligand receptor binding by cetuximab are varied, and

comprise most cellular functions implicated in tumour growth and metastasis such as cell proliferation, cell survival, cell motility, cell invasion, tumour angiogenesis, and deoxyribonucleic acid (DNA) repair. In preclinical *in vitro* and *in vivo* studies, it has been shown that cetuximab inhibits tumour growth and metastasis by interfering with all these processes. EGFR is expressed in many normal epithelial tissues including skin and hair follicles. It is also expressed in many human cancers including squamous cell cancer of the head and neck (SCCHN) and colorectal cancer (CRC). Signal transduction through the EGFR results in activation of wild-type *K-RAS* protein. However, in cells with activating *K-RAS* mutations, the mutant *K-RAS* protein is active independent of EGFR regulation.

Analysis of safety data from the randomised, controlled studies conducted in patients with mCRC showed that the safety profile of cetuximab when given as a single agent or in combination with chemotherapy was consistent with the known safety profile of cetuximab. The majority of the most frequent AEs were typical of the underlying cancer disease and/or study medications. Premedication with an antihistamine and a corticosteroid is required.

The previous CRC indication allowed combination with irinotecan in second line treatment. This is being generalised to combination with chemotherapy and extended to first line. Overall, the use of cetuximab is restricted to *K-RAS* wild-type disease.

Merck Serono Australia Pty Ltd has applied to extend the indications for cetuximab (Erbitux). The new indications are indicated below with *changes to the current indications in italics.*

- Treatment of patients with epidermal growth factor receptor (EGFR)-expressing, *K-RAS wild-type* metastatic colorectal cancer (CRC)
    - *In combination with chemotherapy*
    - As a single agent in patients who have failed *oxaliplatin- and* irinotecan-based therapy and who are intolerant to irinotecan.
- 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*.

Regulatory Status

Erbitux was originally registered by the TGA for second line treatment of mCRC in January 2005 and subsequently for treatment of locally advanced head and neck cancer in combination with radiotherapy in January 2007. In this application the sponsor wishes to extend the indication for both mCRC and head and neck cancer.

A similar application for the new indication in metastatic CRC was approved in the European Union on 22 June 2008. The approved indication in the EU is the same as the proposed indication in the current application. A similar application has also been approved in Argentina, Belarus, Brazil, Chile, Colombia, Croatia, Hong Kong, Iceland, India, Israel, Kazakhstan, Kyrgyzstan, Lebanon, Liechtenstein, Norway, Pakistan, Philippines, Russia, Serbia, South Korea, Thailand and the Ukraine.

A similar application for the new indication in head and neck cancer was approved on 24 November 2008 in the EU. The approved indication in the EU is the same as the proposed indication in the current application. A similar application has also been approved in Argentina, Belarus, Chile, Colombia, Iceland, India, Israel, Kazakhstan, Kyrgyzstan, Liechtenstein, Norway, Russia, Serbia, South Korea, Switzerland and the Ukraine.

The sponsor of this application, Merck Serono, does not hold rights to commercialise Erbitux in the US and Canada. The rights are held by ImClone/Eli Lilly and BMS. Merck Serono is therefore not involved in any applications in the US and Canada, however they did provide a media release statement from ImClone that an application had been lodged in the US on 29 August 2008 to extend the indication for Erbitux to include first line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. No information was provided on the status of the application.

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Cetuximab is a chimeric monoclonal antibody of the immunoglobulin G_1 (IgG_1) subclass, produced in mammalian cell culture by mouse myeloma cells (Sp2/0). It is obtained by attaching the variable regions of the murine monoclonal antibody M225 against epidermal growth factor receptor (EGFR) to constant regions of the human IgG_1. The molecular weight is approximately 152 kDa.

Drug Product

Erbitux 5 mg/mL is a sterile, preservative-free, colourless solution that is intended for intravenous infusion. The pH of the solution is in the range of 5.3 – 5.7 and the osmolality is between 280 and 350 mOsm/kg.

Erbitux 5 mg/mL contains 5 mg cetuximab per millilitre of solution. Erbitux 5mg/mL is available in the following vial sizes: 10 mL, 20 mL, 50 mL or 100 mL of solution. The solution also contains the following inactive ingredients: sodium chloride, glycine, polysorbate 80, citric acid monohydrate, sodium hydroxide and water for injections.

Quality Summary and Conclusions

There is no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Introduction

The current submission includes a pharmacodynamics study, an embryofetal development study in cynomolgus monkeys and 167 literature references in support of an extension of the colorectal cancer (CRC) indication for cetuximab. No nonclinical data were submitted in support of the proposed extension to the head and neck squamous cell carcinoma (SCCHN) indication, although limited data were obtained from the submitted published literature. Only those references considered to be directly relevant to the indication extension or to proposed changes to the Product Information (PI) have been evaluated in this report.

Nonclinical studies submitted in support of proposed Product Information changes were adequate and GLP compliant. Limited efficacy data in support of the extension to indications were provided in submitted published papers. No nonclinical data addressing the safety of the extension to indications was submitted.

Pharmacology

Primary pharmacodynamics

Animals models of cetuximab toxicity

Four studies (studies PAI IM 108, GRA00406, PAI IM 748, DS02124) investigating the immunoreactivity of cetuximab with tissues of laboratory animal origin were conducted in order to determine if a relevant animal species exists for nonclinical safety testing. An *in vitro* study (study DS02124) investigated the binding of cetuximab to oesophageal, skeletal muscular, dermal, testicular, ovarian and placental tissues from mice, rats, rabbits, monkeys and humans (human placental and muscle tissue were used as positive and negative controls, respectively). The number of tissue samples analysed per species was relatively low (n=2); nevertheless the data provide some information for the species specificity of cetuximab cellular binding. Cetuximab did not bind to any of the tissues tested from mice or rats, and binding to tissues from rabbits was very limited (slight staining was observed in oesophageal and skin tissue only). Cetuximab binding was strongest and most similar between monkeys and humans; binding to oesophageal, dermal, testicular, ovarian and placental tissue, but not to skeletal muscle occurred in both species. Weaker (qualitative) staining was reported in the testes of monkeys compared with humans, located in the follicular epithelium and stromal cells, and in stromal cells only in humans. The monkey was therefore considered the most appropriate nonclinical species for a reproductive toxicity study.

Mechanism of action

Two published studies investigated the potential of cetuximab to mediate antibody-dependent cellular cytotoxicity (ADCC) in human oesophageal SCC and non-small cell lung cancer (NSCLC) cell lines *in vitro*. Incubation of cetuximab with either type of cell line resulted in increased ADCC (that is, 65-85% specific lysis in ^{51}Cr-release assays) in the presence of peripheral blood mononuclear cells from healthy donors or SCC or NSCLC patients. The degree of cell lysis was cetuximab concentration-related (in the range 0.05 to 5 µg/mL for SCC cells and $2.5x10^{-6}$ to $2.5x10^{-2}$ µg/mL for NSCLC cells) and dependent on the level of EGFR expressed by cells and the ratio of effector to target tumour cells (greatest lysis of SCC cells occurred with a ratio of 40:1, compared with 20:1 or 10:1). Evidence for cetuximab-mediated ADCC activity was evaluated in a previous report for cetuximab. Cetuximab-mediated ADCC is potentially clinically relevant, given a C_{max} of 158 µg/mL in a clinical trial with cetuximab.

Efficacy in CRC

Four published studies investigated the link between tumour *K-RAS* gene mutation status and response to cetuximab therapy in metastatic CRC. Direct DNA sequencing was conducted on EGFR-expressing CRC tumours from patients who subsequently received cetuximab monotherapy or combination therapy (usually with irinotecan, but occasionally with 5-fluorouracil/folinic acid or oxaliplatin). *K-RAS* gene mutations (exclusively point mutations of codons 12 or 13) were identified in a subset of CRC tumours, all of which were from patients described as non-responders to cetuximab (that is, stable or progressive disease), irrespective of treatment regimen. No *K-RAS* mutations were identified in patients with partial or complete disease regression. Thus, *K-RAS* gene mutation was significantly associated with the absence of response to cetuximab in CRC patients, and may be predictive of resistance to cetuximab.

A published study investigated the effects of combination treatment with oxaliplatin on the *in vivo* growth of four CRC cell lines (HT-29, HCT-8, HCT-116 and SW620). The first three cell lines expressed EGFR protein, whereas SW620 cells did not. Analysis of the basal phosphorylation status of EGFR in these cells *in vitro* showed relatively low phosphorylation in SW620 and HCT-116 cells compared with the other two cell lines. Treatment of athymic mouse xenograft models of all four tumour types with cetuximab alone (1 mg/day intraperitoneally (IP) every 3 days; approximately 33 mg/m^2/day, which is equivalent to 0.08

times the maximum clinical exposure, based on mg/m^2) resulted in a slight delay in tumour growth[1] (by 0.9 to 3.5 days, compared with vehicle-treated mice), whereas combination treatment with oxaliplatin (10 mg/kg intravenously (IV) on Day 1) further delayed tumour growth in HT-29 and HCT-8 tumours (by 5.3 and 11.7 days compared with vehicle-treated mice, respectively). There was no appreciable effect on the rate of growth of the other two tumour types. Thus, combination treatment with oxaliplatin increased the efficacy of cetuximab against some CRC tumour cells *in vivo*, in a manner related to the presence of EGFR expression and/or phosphorylation. No nonclinical data investigating the efficacy of other cetuximab/chemotherapy combinations were submitted.

Efficacy in SCC

A published study investigated the effect of cetuximab on the proliferation, cell cycle distribution and induction of apoptosis in combination with platinum-based compounds in oesophageal SCC cells *in vitro*. Combination treatment with cisplatin, carboplatin or oxaliplatin resulted in varying effects on cell proliferation, depending on the sequence of administration. Cetuximab treatment (3 days; 0.01-2.5 µg/mL) followed by incubation with each of the three platinum compounds (24 hours; 0.05-10 µM) demonstrated an antagonistic effect on inhibition of cell proliferation, whereas treatment in the reverse order demonstrated a quantitatively strong synergistic effect. Combination treatment with oxaliplatin (2.5 µg/mL cetuximab, 5 µg/mL oxaliplatin) resulted in a cell cycle arrest in G2/M phase, and increased apoptosis compared with either agent alone and untreated cells. Thus, *in vitro* studies offered some evidence for the improved efficacy of cetuximab in combination with platinum-based chemotherapy agents against an SCC cell line under certain conditions, although additional experiments would have enhanced the robustness of this finding. No corresponding *in vivo* efficacy data were submitted.

Secondary pharmacodynamics

The specificity of cetuximab binding to EGFR has been previously evaluated, however additional supportive data were provided in the current submission. As reported in the previous evaluation, ELISA experiments in an unpublished report showed binding of cetuximab to EGFR (≥ 0.25 ng/mL), but no binding to the other three known HER family members: ErbB2, ErbB3 or ErbB4 (≤ 4 ng/mL). In new data, flow cytometry analysis confirmed these results, with binding of cetuximab approximately 8-fold higher to human HEK293 cells transiently over-expressing EGFR than cells over-expressing ErbB2, ErbB3 or ErbB4. Similarly, immunoprecipitation experiments with the above cells showed specific co-precipitation of cetuximab with EGFR, but not ErbB2, ErbB3 or ErbB4.

Pharmacology: Summary and Conclusions

Cetuximab mediated ADCC in SCC and NSCLC tumour cells, in a manner dependent on cetuximab concentration and EGFR expression levels, at clinically-relevant concentrations. *K-RAS* gene mutation was significantly associated with an absence of clinical response to cetuximab in CRC patients, and may be predictive of resistance to cetuximab. Combination treatment with oxaliplatin increased the efficacy of cetuximab against some CRC tumour cells *in vivo*, in a manner dependent on the presence of EGFR expression and/or phosphorylation. The *in vitro* efficacy of cetuximab against an SCC cell line was improved by combination treatment with platinum derivatives (cisplatin, carboplatin and oxaliplatin), but was dependent on the sequence of treatment.

[1] Measured as time taken to five doublings in tumour volume.

Pharmacokinetics

Relative exposure

Exposure levels of cetuximab in the submitted reproductive toxicity study were compared with exposure data from human CRC patients (n=11) at the proposed clinical dose in a clinical trial with cetuximab monotherapy, and are presented in Table 1 below. The No Adverse Effect Level (NOAEL) for developmental toxicity is highlighted in bold; an NOAEL for maternal toxicity was not established due to toxicity at all administered doses, as discussed under *Reproductive toxicity* below. The recommended dose and schedule of administration of cetuximab is an initial loading dose of 400 mg/m^2, followed one week later by weekly maintenance doses of 250 mg/m^2/day.

Table 1: Exposure comparisons following IV administration in a reproductive toxicity study

Study no.	Species	Treatment regimen	Dose (mg/kg/week)[a]	Sex	AUC_{0-t}[b] (µg.h/mL)	Exposure multiples (AUC)
DN04030	Monkey	Weekly	**12/7.5**, 38/24, 120/75	F	**18100**, 73700, 213000	**1.4**, 5.6, 16
EMR 62 202-028	Human	Weekly	400/250 mg/m^2/week[c]	M/F	13181	NA

[a]The treatment regimen in both species involved an initial loading dose, followed by weekly maintenance doses.
[b]t=120-336 h for monkeys, 168 h for humans
[c]Human data taken from sponsor's Clinical summary. NA = not applicable

Toxicology

Reproductive toxicity

The submitted study comprised an embryofetal development study in monkeys. No fertility or pre-/postnatal development studies were submitted in this application, which was considered acceptable for the indicated population. The studies were GLP compliant and generally adequate; the appropriate species was selected based on known cetuximab binding activity.

Administration of cetuximab (12/7.5, 38/24, 120/75 mg/kg/week IV) during organogenesis (between GD20-GD48; a high initial IV loading dose was followed by four reduced weekly maintenance doses) was associated with increased embryofetal loss/death at doses ≥ 38/24 mg/kg/week (exposures ≥ 6 times greater than clinical exposure; exposure at the NOAEL was 1.4 times greater than the maximum AUC-based clinical exposure). Although the incidence was not greatly increased compared with the control group (27-31% vs. 18%), it was considered to be treatment-related, based on similar findings for other drugs. This was hypothesised to be related to the known high density of EGFR in placenta, the high, specific binding of cetuximab in monkey placental epithelium and the roles of EGFR in embryofetal development and intrauterine growth.

No teratogenic effects were observed. All fetuses examined appeared normal at gross external, visceral and skeletal examination. Evaluation of selected fetal organ weights revealed no abnormalities. Mean fetal weights at GD100 were slightly (but not significantly) increased in treated monkeys due to slightly increased weights of individual fetuses in each treatment group triggering some other minor changes of mean group values for fetal findings, including slightly increased mean group values for fetal dimensions including increased mean overall fetal size, reduced mean fetal relative adrenal and heart weight, increased mean placental weight and increased mean amniotic fluid volume. These findings were not considered to be treatment related, as they (i) represented only slight, non-significant differences to control groups, due to individual fetuses in each treatment group (ii) did neither

occur in a dose-dependent manner nor were not consistent with the pharmacology of cetuximab and (iii) were not associated with other fetal abnormalities.

Maternal clinical signs (skin irritation/rash and scales, swollen or abnormal eyes and nasal discharge for example) were consistent with a possible allergic response, and were similar to those seen in previous studies with cetuximab in monkeys. No NOAEL for maternal toxicity was established, based on clinical signs, reduced body weight gain or weight loss and reduced food consumption at all doses.

Cetuximab was detected in amniotic fluid, using validated methods, from 20-67% of pregnant monkeys at all doses administered, although average concentrations (up to 13 µg/mL) were generally two orders of magnitude smaller than maternal plasma C_{max} values. There was no dose-response relationship. Similarly, cetuximab was detected at low levels (22 µg/mL and 24 µg/mL) in umbilical cord serum from one low-dose, and one high-dose fetus (the only two fetuses analysed), indicative of placental transfer of cetuximab.

Immunogenicity

Serum obtained from pregnant monkeys in the embryofetal development study was analysed for anti-cetuximab antibodies. As expected, monkeys with detectable antibodies were identified in all treatment groups, with a dose-related incidence (ranging from 27% to 40%). These antibodies were shown to be cetuximab-specific. Highest levels were usually reported on GD100 (the highest reported concentration was 304 ng/mL), and two treated females had detectable antibodies prior to cetuximab treatment. Also in one control group female specific anti-cetuximab antibodies were measured, which was considered to be a false positive result.

Toxicology Summary and Conclusions

An embryofetal development study in monkeys identified an increased incidence of embryofetal loss/death at doses associated with maternal toxicity (≥ 6 times greater than clinical exposure; exposure at the developmental NOAEL was approximately similar to the expected clinical exposure). Cetuximab was not teratogenic in monkeys. Cetuximab was antigenic in monkeys; the development of specific anti-cetuximab antibodies in monkeys was cetuximab dose-related (27-40% of treated monkeys).

Nonclinical Summary and Conclusions

No nonclinical safety data in support of the proposed extension to indications was submitted. Thus, the safety assessment of the new indications will rely on clinical data. The submitted published literature provided *in vitro* evidence in support of the efficacy of cetuximab for (i) the restriction of the CRC indication to patients with *K-RAS* wild type tumours, (ii) extension of the CRC indication to include combination therapy with chemotherapy (i.e. oxaliplatin) and (iii) extension of the CRC indication to include combination therapy with platinum-based chemotherapy for head and neck SCC.

Cetuximab was not teratogenic in monkeys. Cetuximab doses≥ 6 times greater than clinical exposure were associated with increased embryofetal toxicity in monkeys (maternotoxic doses); exposure at the developmental NOAEL was approximately similar to the expected clinical exposure. Cetuximab was antigenic in monkeys, as evidenced by the development of cetuximab dose-related, specific anti-cetuximab antibodies.

There are no nonclinical objections to the extension of indications for cetuximab, provided that the safety of the new indications is supported by clinical data.

IV. Clinical Findings

Introduction

Clinical development programme in metastatic colorectal cancer

Cetuximab as single agent

The 9 new studies (3 randomised, controlled, phase III studies highlighted in boldface; 6 uncontrolled phase I or II studies) that are included in the current submission to support the extension of the metastatic CRC indication are listed in Table 2. Cetuximab as a single agent (target dose) was investigated in 2 studies on previously treated subjects. The randomised, controlled ***study CA225025*** was performed on subjects who had failed all currently available standard chemotherapy treatments. It was conducted in collaboration with the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the Australasian Gastro-Intestinal Trials Group (AGITG). It was nominated as the pivotal study supporting the extension of indication for use of cetuximab as a single agent.

The supportive uncontrolled ***study IMCL CP02-0144*** investigated subjects who had failed both irinotecan and oxaliplatin. ***Study EMR 62 202-028*** was a dose escalation study using cetuximab as a single agent in patients with mCRC.

Cetuximab in combination with Irinotecan-based regimens

Two studies were conducted with the target dose of cetuximab in combination with standard irinotecan regimens in previously treated subjects. ***Study CA225006*** was a randomised, controlled study that investigated subjects who had failed oxaliplatin/fluoropyrimidine-based therapy for metastatic disease. The uncontrolled ***study EMR 62 202-501*** was performed to confirm the efficacy and safety of cetuximab in combination with standard irinotecan regimens.

In the original application for registration, cetuximab was shown to be safe and efficacious in combination with irinotecan. The first phase I/II studies in subjects with previously untreated metastatic CRC investigated combinations of the standard weekly cetuximab regimen with irinotecan plus 5-FU/FA given weekly (***study EMR 62 202-009***) or every 2 weeks (***EMR 62 202-010***). Both combination regimens were found to have acceptable safety profiles and showed promising therapeutic efficacy. The biweekly regimen is more widely used than the regimen used in study EMR 62 202-009, and was thus chosen for the randomised, controlled phase III study (***EMR 62 202-013***) that investigated cetuximab in combination with infusional 5-FU/FA (FOLFIRI) versus FOLFIRI in subjects with metastatic CRC previously untreated for metastatic disease.

Cetuximab in combination with Oxaliplatin-based regimens

Other studies have been performed to investigate the efficacy and safety of cetuximab in combination with oxaliplatin and 5-FU/FA in subjects with previously untreated metastatic CRC (exploratory controlled ***studies CA225014, EMR 62 202-047***; uncontrolled studies ***EMR 62 202-018, EMR 62 202-021***). Data from these studies were also provided in the submission.

Research has indicated that the wild type status of the *K-RAS* gene might be a positive predictor for the efficacy of EGFR-targeted monoclonal antibody treatments such as cetuximab. The proposed indication is for treatment of patients with “epidermal growth factor receptor (EGFR)-expressing, *K-RAS* wild-type metastatic colorectal cancer”. In support of this indication the applicant submitted additional analyses of the controlled studies (CA225025, CA225006, EMR 62 202-013, and EMR 62 202-047). These analyses were

based on efficacy and safety analyses of subjects with wild-type *K-RAS* genes in their tumours.

All studies were conducted according to Good Clinical Practice (GCP) guidelines.

Table 2: Clinical studies on cetuximab as single agent or in combination with chemotherapy-based regimens included in the submission

Study	Design / subject population (mCRC) (bold = pivotal)	Phase	Study treatments *	ITT N
CETUXIMAB AS SINGLE AGENT				
CA225025	**Randomized, controlled / subjects failing irinotecan and oxaliplatin**	**III**	**Cetuximab+BSC vs BSC**	**287 285**
IMCL CP02-0144	Uncontrolled / subjects failing chemotherapy regimens including irinotecan, oxaliplatin, and a fluoropyrimidine	II	Cetuximab	346
EMR 62 202-028	Uncontrolled / subjects failing standard therapy regimen	I	Cetuximab (dose escalation)	49
CA225045	Uncontrolled / subjects failing at least 1 prior chemotherapeutic regimen or refusing prior treatment	II	Cetuximab (dose escalation)	110
CETUXIMAB + IRINOTECAN-BASED REGIMENS				
CA225006	**Randomized, controlled / irinotecan-naive subjects who failed chemotherapy containing fluoropyrimidine and oxaliplatin**	**III**	**Cetuximab+irinotecan vs irinotecan**	**648 650**
EMR 62 202-501	Uncontrolled / subjects with documented PD on irinotecan-based therapy as most recent treatment	II	Cetuximab+irinotecan	1147
EMR 62 202-013	**Randomized, controlled / previously untreated subjects with nonresectable mCRC**	**III**	**Cetuximab+FOLFIRI vs FOLFIRI**	**599 599**
EMR 62 202-009	Uncontrolled / previously untreated subjects	I/II	Cetuximab+5-FU/FA+ irinotecan (AlO regimen)	61
EMR 62 202-010	Uncontrolled / previously untreated subjects (pilot study for EMR 62 202-013)	IIa	Cetuximab+FOLFIRI	52
CETUXIMAB + OXALIPLATIN-BASED REGIMENS				
EMR 62 202-047	**Randomized, controlled / nonresectable CRC**	**II**	**Cetuximab+FOLFOX vs FOLFOX**	**169 168**
EMR 62 202-018	Uncontrolled / nonresectable CRC (pilot study for EMR 62 202-047)	II	Cetuximab+FOLFOX	43
EMR 62 202-021	Uncontrolled	I/II	Cetuximab+FUFOX	49

CRC=colorectal cancer, ITT=intention to treat

BSC=best supportive care, FA=folinic acid, FOLFIRI= infusional 5-FU/FA with irinotecan, 5-FU=5-fluorouracil, PD=progressive disease

* Unless otherwise specified cetuximab was administered at the target dose: initial dose 400 mg/m² followed by weekly doses of 250 mg/m²

NOTE: Not all studies are discussed. All studies except for EMR 62 202-013 were completed as of 31 July 2007. Study EMR 62 202-013 was completed for the primary efficacy analysis. Studies EMR 62 202-018 and 021 were completed as of 31 July 2007. Study EMR 62 202-047 was completed for the primary efficacy analysis on this date. In the updated report submitted with this addendum the study was completed for all efficacy endpoints except survival.

Clinical development programme in head and neck cancer

The standard chemotherapeutic treatments for recurrent and/or metastatic (R/M) squamous cell cancer of the head and neck (SCCHN) include methotrexate, bleomycin, 5-fluorouracil (5-FU), and platinum compounds. Cisplatin is the most widely used drug in the treatment of R/M SCCHN and is considered as partner in the most active combination chemotherapies.

The combination of cisplatin and infusional 5-FU showed superior response rates in comparison to the single agents.

The original SCCHN application was based on efficacy data from one phase III study in locally advanced disease (EMR 62 202-006) and three phase II studies in R/M SCCHN after failure of platinum-based therapy (EMR 62 202-016, EMR 62 202-001, IMCL CP02- 9816).

The sponsor stated that the present application is based on efficacy data from three studies in the first line treatment of R/M SCCHN; a pivotal ***study EMR 62 202-002*** and two supportive studies ***EMR 62 202-008 and ECOG E539***. A tabular summary of these studies is provided in Table 3. Study EMR 62 202-002 was a multinational, open-label, phase III, randomised, parallel-group study comparing overall survival (OS) time, progression-free survival (PFS) time, best overall response and disease control, duration of response, time to treatment failure, safety, and quality of life (QoL) under treatment with cetuximab + cisplatin or carboplatin + 5-FU versus cisplatin or carboplatin + 5-FU.

Table 3: Clinical studies supporting the efficacy of cetuximab in the first line treatment of R/M SCCHN

Study	Phase	Study treatments	No. subjects treated	Submission	
				Current	Previous
EMR 62 202-002 (pivotal)	III	5-FU+cisplatin or carboplatin vs Cetuximab+5-FU+cisplatin or carboplatin	215 219	X	
EMR 62 202-008 (supportive, pilot for EMR 62 202-002)	I/II	Cetuximab+5-FU+cisplatin vs Cetuximab+5-FU+carboplatin	27 25		X *
ECOG E5397 (supportive)	III	Placebo + cisplatin vs Cetuximab+cisplatin	60 57		X **

ECOG=Eastern Cooperative Oncology Group, 5-FU=5-fluorouracil

* Report included in initial SCCHN dossier for evaluation of pharmacokinetics and safety but not for evaluation of efficacy.
** Report included in initial SCCHN dossier for evaluation of safety but not for evaluation of efficacy.

In relation to the head and neck cancer indication a final clinical study report for the pivotal study EMR 62 202-002 was provided but the final clinical study reports were not provided for studies EMR 62 202-008 and ECOG E5397. The only data presented from these studies were brief paragraphs in the sponsor's Summaries of Clinical Efficacy and Safety.

Pharmacokinetics

The present submission contained new pharmacokinetic (PK) information from 375 subjects with metastatic CRC who were treated with multiple doses of cetuximab in 7 studies; EMR 62 202-009, 010, 018, 021, 028, 047 and IMCL CP02-0144 (Table 4). Cetuximab was administered at the standard target dose (initial/weekly dose of 400/250 mg/m^2) in all 7 studies. In study EMR 62 202-028, initial/weekly cetuximab doses of 250/250 and 350/350 mg/m^2 were also used.

In 5 of the studies (EMR 62 202-009, 010, 018, 021, 047) cetuximab was administered in combination with chemotherapy to subjects who had not received previous chemotherapy. In the 2 remaining studies, cetuximab was administered as monotherapy to previously treated subjects: after failure of standard chemotherapy in study EMR 62 202-028 and after failure of chemotherapy that had to include irinotecan, oxaliplatin, and a fluoropyrimidine in study IMCL CP02-0144.

Study EMR 62 202-009 was a multicentre, open-label, phase I/II study in 61 previously untreated subjects with metastatic, EGFR-expressing CRC. All subjects were treated with a combination of cetuximab plus irinotecan (80 mg/m^2), 5-FU and FA (500 mg/m^2)

administered weekly. Part I of the study was designed with a dose-escalation phase to determine the recommended dose of 5-FU (either 1500 or 2000 mg/m², infused over 24 hours). Based on the results of part I, a 5-FU dose of 1500 mg/m² was further investigated in part II of the study in combination with cetuximab, irinotecan and FA. Cetuximab concentration data were available from a total of 31 subjects for week 1 and 28 subjects for week 4.

Study EMR 62 202-010 was a multicentre, open-label, phase IIa study in 52 previously untreated subjects with metastatic, EGFR-expressing CRC. All subjects were treated with a combination of weekly cetuximab plus irinotecan (180 mg/m² infusion), 5-FU and FA (400 mg/m² infusion) given every 2 weeks. Part I of the study was designed with a dose-escalation phase to determine the recommended dose of 5-FU (300 mg bolus then 2000 mg/m² as 46-hour infusion or 400 mg bolus and then 2400 mg/m² as 46-hour infusion). Based on the results of part I, the higher 5-FU dose was further investigated in part II of the study in combination with cetuximab, irinotecan, and FA. Cetuximab concentration data were available from a total of 37 subjects (23 subjects in part I and

Table 4: Overview of CRC studies providing new PK data

Study / Indication	Study treatment (all intravenous)	Sampling schedule
EMR 62 202-009 Previously untreated CRC	Cetuximab (initial/weekly dose): 400/250 mg/m² Irinotecan: 80 mg/m²; FA: 500 mg/m²; 5-FU: 1500 or 2000 mg/m² 7-week cycle for irinotecan + 5-FU/FA (administration weekly in weeks 1-6 followed by 1 week rest) Subjects in part I received 1500 or 2000 mg/m² 5-FU. Based on rate of DLTs, 1500 mg/m² was selected for part II.	Visits 1 and 4 of cycle 1: just before infusion of cetuximab and 1, 2, 5, 24, 48, 96 (day 5, optional), and 168 h (day 8) after start of infusion. In part II of study these samples were only to be taken at center 004 for approximately 10 additional patients.
EMR 62 202-010 Previously untreated CRC	Cetuximab (initial/weekly dose): 400/250 mg/m² Irinotecan: 180 mg/m² on day 1 of 2-week cycle FA: 400 mg/m² (racemic) or 200 mg/m² (L-form) on day 1 of 2-week cycle 5-FU (low/high dose): 300/400 mg/m² bolus on day 1 of 2-week cycle, followed by 46-h continuous infusion of 2000/2400 mg/m² Subjects in part I received low or high dose 5-FU. Based on rate of DLTs, high dose 5-FU was selected for part II.	Week 1: before (baseline) and 2 h after start of cetuximab infusion Weeks 2 and 3: just before infusion (trough) Weeks 4 and 5 (full profiles): before and 1, 2, 5, 24, 48, 96 and 168 h after start of infusion.
EMR 62 202-018 Previously untreated CRC	Cetuximab (initial/weekly dose): 400/250 mg/m² Oxaliplatin: 85 mg/m² on day 1 of 2-week cycle FA: 200 mg/m² on days 1+2 of 2-week cycle 5-FU: 400 mg/m² bolus, followed by 22-h continuous infusion of 600 mg/m² on days 1+2 of 2-week cycle	19 subjects at selected centers Week 1, just before and at end of cetuximab infusion Weeks 2, 3 and 4, just before cetuximab infusion Week 5, full profile in 19 subjects: just before, at end of, and 1, 2, 5, 24, 48, 96 and 168 h after the start of cetuximab infusion (a 72-h blood sample could be drawn instead of the 96-h sample at the discretion of the investigator). Further visits, just before infusion. All other subjects: week 1 just before and at end of infusion, week 8 just before infusion, and week 13 at any time within 48 h of the end of infusion (trough concentrations available in some subjects up to week 40)
EMR 62 202-021 Previously treated CRC	Cetuximab (initial/weekly dose): 400/250 mg/m² Oxaliplatin: 50 mg/m²; FA: 500 mg/m²; 5-FU: 1500 or 2000 mg/m² 5-week cycle for oxaliplatin + 5-FU/FA (administration on day 1 of weeks 1-4 followed by 1 week rest) Subjects in part I received 1500 or 2000 mg/m² 5-FU. Based on rate of DLTs, 2000 mg/m² was selected for part II.	Week 1: before and 2 hours after start of cetuximab infusion Weeks 2 and 3: before infusion Week 4: before infusion and 1, 2, 5, 24, 48 and 96 hours after start of infusion (a 72-h blood sample could be drawn instead of the 96-h sample at the discretion of the investigator) Week 5: before infusion
EMR 62 202-028 Previously treated CRC	Cetuximab (initial/weekly dose) Group A: 400/250 mg/m²; group B: 250/250 mg/m²; group C: 350/350 mg/m²	Weeks 1 and 2, just before and at end of cetuximab infusion Week 3, full profile: before, at end of, and 2, 6, 10, 24, 48, 96 and 168 h after start of infusion. Trough concentrations before every cetuximab infusion
EMR 62 202-047 Previously untreated CRC	Cetuximab (initial/weekly dose): 400/250 mg/m² Oxaliplatin: 85 mg/m² on day 1 of 2-week cycle FA: 200 mg/m² on days 1+2 of 2-week cycle	Week 1: just before and at end of cetuximab infusion Week 7: just before infusion Week 13: within 12 h after end of infusion
	5-FU: 400 mg/m² bolus followed by 22-h continuous infusion of 600 mg/m² on days 1+2 of 2-week cycle	Week 20: just before infusion
IMCL CP02-0144 Previously treated CRC	Cetuximab (initial/weekly dose): 400/250 mg/m²	Weeks 1, 4 and 6: before and at end of cetuximab infusion

DLT = dose-limiting toxicity, FA = folinic acid, 5-FU = 5-fluorouracil,

14 subjects in part II). Full PK profiles suitable for PK analysis following cetuximab administration were available from 34 subjects in week 4 (21 and 13 subjects for parts I and II) and from 32 subjects in week 5 (20 and 12 subjects).

Study EMR 62 202-018 was a multicentre, open-label, uncontrolled phase II study in 43 previously untreated subjects with EGFR-expressing metastatic CRC. Cetuximab (weekly) was administered in combination with oxaliplatin (85 mg/m²) and 5-FU/FA (every 2 weeks, FOLFOX-4 regimen) until occurrence of progressive disease or unacceptable toxicity. 5-FU (400 mg/m² bolus followed by 600 mg/m² continuous infusion and FA (200 mg/m²) were given on days 1 and 2 of each 2-week cycle. Multiple-dose PK data on cetuximab were determined from blood samples collected during week 5. Cetuximab concentration data were available for all subjects, with full PK profiles for 19 subjects.

Study EMR 62 202-021 was a multicentre, open-label, uncontrolled, phase I/II study in 49 previously untreated subjects with EGFR-expressing metastatic CRC. Cetuximab (weekly) was administered in combination with oxaliplatin and 5-FU/FA (every week for 4 weeks followed by 1 week of rest, FUFOX regimen). FUFOX was given on days 1, 8, 15, and 22 of each 5-week cycle: oxaliplatin 50 mg/m², FA 500 mg/m², and 5-FU at either a low dose (1500 mg/m²) or high dose (2000 mg/m²). Study medication was given until occurrence of progressive disease or unacceptable toxicity. Multiple-dose PK data on cetuximab were determined from blood samples collected during week 4. Cetuximab concentration data were available for all subjects, with full PK profiles for 20 subjects (5 with low-dose 5-FU and 15 with high-dose 5-FU).

Study EMR 62 202-028 was a multicentre, phase I study in subjects with EGFR-expressing, metastatic CRC after failure of standard therapy. A total of 49 subjects were recruited sequentially into 3 cetuximab dose groups. Cetuximab PK was evaluated in 45 subjects who received the following treatment regimens:

- Group A: initial/weekly dose of 400/250 mg/m² (N=11)
- Group B: initial/weekly dose of 250/250 mg/m² (N=17)
- Group C: initial/weekly dose of 350/350 mg/m² (N=17).

Blood samples for PK were taken before and after the first, second, and third cetuximab doses on days 1, 8, and 15, respectively.

Study EMR 62 202-047 was a randomised (1:1), open-label, multicentre, controlled phase II study in previously untreated subjects with unresectable, metastatic EGFR-expressing CRC. 169 subjects were treated with cetuximab + FOLFOX and 168 subjects were treated with FOLFOX. The FOLFOX regimen comprised a 2-week cycle of oxaliplatin (85 mg/m² on day 1), FA (200 mg/m² on days 1 and 2), and 5-FU (400 mg/m² bolus followed by a 22 h continuous infusion of 600 mg/m² on days 1 and 2). PK data were available from 139 cetuximab-treated subjects.

Study IMCL CP02-0144 was a multicentre, open-label, phase II study in 346 subjects with metastatic, EGFR-expressing CRC that was refractory to chemotherapy, which had to include irinotecan, oxaliplatin, and a fluoropyrimidine. Subjects received the cetuximab target dose regimen as monotherapy. Cetuximab serum concentrations were measured in 25 subjects.

Multiple-dose pharmacokinetic parameters in studies EMR 62 202-009, 010, 018, 021, 028

Multiple-dose pharmacokinetic (PK) parameters are available from studies in which cetuximab was administered at the target dose (initial dose of 400 mg/m², subsequent weekly

doses of 250 mg/m²) either as monotherapy (EMR 62 202-028, group A) or in combination with chemotherapy (EMR 62 202-009, 010, 018, 021). Descriptive statistics for selected PK parameters are displayed in Table 5.

Table 5: Multiple-dose PK parameters for the target dose of cetuximab in studies EMR 62 202-009, 010, 018, 021, and 028

Parameter (unit)	EMR 62 202-028 Week 3 (N=11, group A)	EMR 62 202-009 Week 4 (N=26)	EMR 62 202-010 Week 4 (N=34)	EMR 62 202-021 Week 4 (N=20)	EMR 62 202-010 Week 5 (N=32)	EMR 62 202-018 Week 5 (N=19)
C_{max} (µg/mL)						
Mean (S.D.)	158 (20)	177 (32)	220 (50)	211 (44)	204 (43)	256 (45.9)
Range	125 – 191	122 – 259	142 – 411	133 280	115 – 297	182 – 398
AUC_τ (µg/mL*h)						
Mean (S.D.)	13181 (2560)	15429 (4165)	17231 (4991)	16388 (5575)	17161 (5067)	20228 (5195)
Range	8265 – 17474	5071 – 22484	10363 – 30679	7306 30547	7493 – 27624	13897 – 32979
$t_{1/2}$ (h)						
Mean (S.D.)	97 (24)	112.2 (34.3)	114.0 (54.3)	108.4 (54.8)	123.1 (49.5)	100.5 (29.8)
Range	56 – 125	63.2 – 216.5	51.0 – 310.7	33.9 – 277.4	40.0 – 263.3	44 – 162.4
CL_{ss} (L/h)						
Mean (S.D.)	0.035 (0.010)	0.034 (0.017)	0.027 (0.0080)	0.032 (0.013)	0.028 (0.0097)	0.023 (0.006)
Range	0.024 – 0.059	0.021 – 0.106	0.013 – 0.043	0.016 0.068	0.014 – 0.054	0.014 – 0.035
V_{ss} (L)						
Mean (S.D.)	4.71 (0.46)	5.03 (1.7)	3.93 (1.03)	4.46 (2)	4.44 (1.46)	3.21 (0.95)
Range	3.95 – 5.3	3.43 – 11.17	2.35 – 6.18	2.15 11.43	2.53 – 8.63	1.98 – 4.87

S.D.=standard deviation

There was good agreement between the PK parameters for the target dose of cetuximab across studies EMR 62 202-009, 010, 018, 021, and 028. Results supported that concomitant administration of chemotherapy (5-FU/FA plus either irinotecan or oxaliplatin) did not have a clinically significant impact on the PK characteristics of cetuximab.

In studies EMR 62 202-009, 010, 018, and 021, mean values of PK parameters were similar between the 2 dose levels of 5-FU in each of these studies indicating that the various 5-FU regimens had no significant effects on the PK parameters of cetuximab.

In study EMR 62 202-028, the PK profile during week 3 was also analysed for the dose groups receiving weekly cetuximab doses of 250 mg/m² (group B, N=17) and 350 mg/m² (group C, N=17). In accordance with the higher cetuximab dose in group C (350/350 mg/m²), C_{max} for this group was higher than for group B (250/250 mg/m²): 272 µg/mL in group C vs 213 µg/mL in group B. The same was true for AUCτ: 22524 µg/mL*h in group C vs 14968 µg/mL*h in group B. PK was linear for the dose groups, as indicated by the dose-normalized mean AUC_τ values for groups B and C. Mean values for $t_{1/2}$, CL_{ss} and Vd_{ss} were similar across the 3 groups, indicating that these parameters were independent of the dosage regimen.

Comparison of peak and trough concentrations in studies EMR 62 202-009, 010, 021, and 028

The mean trough and peak serum concentrations obtained after the administration of the target dose of cetuximab (400/250 mg/m²) in studies EMR 62 202-009, 010, 021 and 028 are summarised in Table 6. Results for peak and trough concentrations were constant across the observed time periods, and similar across studies.

Table 6: Mean (SD) trough and peak serum concentrations of cetuximab in studies EMR 62 202-009, 010, 018, 021 and 028

Study	Timepoint	Trough concentration (µg/mL)			Peak concentration (µg/mL)		
		N	Mean	S.D.	N	Mean	S.D.
EMR 62 202-009	Week 1	31	0.1	0.2	29	122.2	44.7
	Week 4	28	53.8	18.2	27	166.4	38.9
EMR 62 202-010	Week 1	36	2.8	11.4	35	223.9	49.4
	Week 2	33	42.3	19.4	*	*	*
	Week 3	34	45.9	26.7	*	*	*
	Week 4	34	51.2	23.1	34	203.5	48.6
	Week 5	34	54.4	25.5	32	190.0	38.6
	Week 6	32	63.8	26.9	*	*	*
EMR 62 202-018	Week 1	40	12.4	75.5	40	253.0	65.3
	Week 2	19	41	17.2	*	*	*
	Week 3	20	50.7	24.2	*	*	*
	Week 4	20	58.9	23.2	*	*	*
	Week 5	19	66.1	27.6	*	*	*
	Week 6	19	64.8	28.2	*	*	*
EMR 62 202-021	Week 1	34	4.3	23.3	19	222.7	66.1
	Week 2	29	46.5	22.6	*	*	*
	Week 3	29	51.1	23.7	*	*	*
	Week 4	29	51.6	30.3	*	*	*
	Week 5	25	68.5	45.4	*	*	*
	Week 6	27	69.5	43.5	*	*	*
EMR 62 202-028	Week 1	14	0.5	1.9	13	201.3	55.5
	Week 2	12	44.0	29.3	12	155.4	29.4
	Week 3	11	55.1	38.1	11	147.3	23.5
	Week 4	11	42.2	15.5	*	*	*
	Week 5	11	57.6	20.0	*	*	*
	Week 6	11	56.0	22.5	*	*	*

*Not drawn as per protocol

S.D.=standard deviation

Pharmacodynamics

No new pharmacodynamic data were presented for evaluation.

Efficacy

Efficacy data to support the proposed new indication were primarily derived from three large, randomised, controlled studies: CA225025 for cetuximab as single agent and CA225006 and EMR 62 202-013 for cetuximab in combination with irinotecan-based therapy.

Efficacy data from Study EMR 62 202-047 supported cetuximab use in combination with oxaliplatin-based chemotherapy

Efficacy results from several minor supportive studies supplied in the dossier are not discussed in this AusPAR. When the studies submitted in this dossier were designed there was no conclusive evidence for potentially predictive biomarkers available, therefore analyses based on *K-RAS* status were not prospectively planned. Nevertheless, collection of tumour samples for analysis of *K-RAS* status (wild-type or mutant) was completed in 4 randomised, controlled phase III studies (CA225025, CA225006, EMR 62 202-013 and EMR 62 202-047). The statistical analyses of demographic, efficacy and safety data described in the original reports were repeated for each of these studies based on all subjects with an evaluable *K-RAS* status as well as for the subgroups of subjects with wild-type *K-RAS* and mutant *K-RAS* in their tumours.

Data to support efficacy in subjects undergoing treatment with cetuximab + chemotherapy (CTX) or CTX alone for recurrent/metastatic (R/M) SCCHN were based on one pivotal study (EMR 62 202-002) and two supporting studies (EMR 62 202-008 and ECOG E5397). Studies EMR 62 202-008 and ECOG E5397 were submitted and evaluated in a previous application to the TGA and data from these studies was not re-submitted in the current application, therefore these studies will not be discussed in this evaluation report.

Efficacy data relevant to the metastatic CRC indication will be presented firstly, followed by presentation of data in support of the R/M SCCHN indication.

Metastatic Colorectal Cancer

Study CA225025 was a multicentre, prospective, open-label, randomised phase III trial of cetuximab + best supportive care (BSC) vs BSC alone in subjects with pre-treated metastatic, EGFR-expressing CRC. BSC was defined as those measures designed to provide palliation of symptoms and improve quality of life as much as possible. Subjects were stratified by centre and Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 or 1 vs 2). Treatment of a subject continued until disease progressed, or until other conditions, including unacceptable toxicity, symptomatic disease progression, and need for standard radiation treatment for index lesions, led to discontinuation from protocol treatment.

All subjects received BSC. For subjects randomised to receive cetuximab, the initial cetuximab dose (Week 1) was an intravenous (IV) infusion of 400 mg/m^2, administered over 120 minutes. This was followed by weekly maintenance IV infusions of 250 mg/m^2, administered over 60 minutes.

The primary objective of this study was to compare overall survival (OS) in subjects with pre-treated metastatic, EGFR-expressing CRC treated with cetuximab and BSC to BSC only.

Secondary objectives were:

- To compare the progression-free survival (PFS) in subjects with pre-treated metastatic, EGFR-expressing, colorectal carcinoma treated with cetuximab and BSC to BSC only
- To compare the objective response rate in subjects with pre-treated metastatic, EGFR-expressing, colorectal carcinoma treated with cetuximab and BSC to BSC only
- To evaluate the safety profile of cetuximab administered weekly in subjects with pre-treated metastatic, EGFR-expressing colorectal carcinoma
- To compare the quality of life in subjects with pre-treated metastatic, EGFR-expressing colorectal carcinoma treated with cetuximab and BSC to BSC only
- To compare the health utilities of subjects with pre-treated metastatic, EGFR-expressing colorectal carcinoma treated with cetuximab and BSC to BSC only

- To conduct a comparative economic evaluation in subjects with pre-treated metastatic, EGFR-expressing colorectal carcinoma treated with cetuximab and BSC and subjects receiving BSC only.

Inclusion and exclusion criteria

Main inclusion criteria

Subjects of either sex, ≥16 years of age, who signed informed consent, had measurable or evaluable disease, and met all of the following disease criteria were eligible for the study:

- Histological proof of primary colorectal cancer that is metastatic
- EGFR expression of tumour tissue by immunohistochemistry
- Received a prior thymidylate synthase (TS) inhibitor (for example, 5-FU, capecitabine, raltitrexed, UFT) for adjuvant or metastatic disease; TS inhibitor may have been given in combination with oxaliplatin or irinotecan
- Received and failed irinotecan (CPT-11)-containing regimen (single agent or in combination) for treatment of metastatic disease, or relapsed within 6 months of unsuitability for an irinotecan-containing regimen
- Received and failed an oxaliplatin-containing regimen (that is, single agent or in combination) for treatment of metastatic disease, or relapsed within 6 months of completion of an oxaliplatin-containing adjuvant therapy, or have documented unsuitability for an oxaliplatin-containing regimen
- The only remaining standard available therapy as recommended by the investigator is BSC
- ECOG PS of 0, 1, or 2
- Adequate bone marrow, liver, and renal functions.

Main exclusion criteria

Subjects who met any of the following criteria were excluded from the study:

- History of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease ≥5 years
- Women who are pregnant or breastfeeding
- Any active pathological condition which would render the protocol treatment dangerous or impair the ability of the subject to receive protocol therapy
- Any condition that would not permit compliance with the protocol
- Significant history of uncontrolled angina, arrhythmias, cardiomyopathy, congestive heart failure (CHF), or documented myocardial infarction (MI) within the 6 months preceding registration (pre-treatment electrocardiogram (ECG) evidence only of MI will not exclude subject)
- Symptomatic metastases in the central nervous system
- A history of prior cetuximab or other therapy which targets the EGFR pathway
- A history of prior murine monoclonal antibody therapy
- Severe restrictive lung disease or radiological pulmonary findings of “interstitial lung disease” on the baseline chest x-ray which, in the opinion of the investigator, represents significant pathology
- Receipt of an experimental therapeutic agent within the past 30 days.

Efficacy variables

Overall survival was defined as the time from randomisation to the time of death due to any cause. Subjects who were alive at the time of OS analysis or who had been lost to follow-up

were censored at their last contact date. Survival was evaluated every 4 weeks post-progression.

Time to progression was defined per protocol as the time from randomisation to progressive disease or death due to any cause. Because deaths are included as events this variable is often more commonly referred to as progression-free-survival. For PFS, subjects who had not progressed or died at the time of analysis or who were lost to follow-up were censored at the date of their last disease assessment or at randomisation for subjects who did not have any post-baseline disease assessments.

The duration of overall response was assessed for subjects whose best response was either a PR or CR. It was defined as the number of months from when the measurement criteria are first met for a CR or PR, whichever is recorded first, until the first date of progressive disease or death. Tumour response was scored on the basis of measurable and evaluable criteria and classified by the investigator using the RECIST (Response Evaluation Criteria in Solid Tumours) criteria. Imaging studies of measurable and evaluable tumours were conducted pre-treatment, every 8 weeks during treatment, and at post-treatment visits (unless a subject discontinued for disease progression).

Demographics and baseline characteristics

The demographic and baseline characteristics for the full analysis set (FAS) and *K-RAS* populations (evaluable, wild-type, and mutant) are summarised in Table 7. In general, the *K-RAS* evaluable population of study CA225025 was similar to the FAS with respect to demographic variables, and the *K-RAS* wild-type and *K-RAS* mutant populations were also comparable. There were however slight imbalances with respect to age: the cetuximab + BSC group of the *K-RAS* wild-type and *K-RAS* mutant populations contained a lower proportion of elderly subjects than the BSC group. In the *K-RAS* wild-type population, the proportion of patients with an ECOG PS of 2 was lower in the cetuximab + BSC group than in the BSC group (13.0 vs 26.3%).

Disease characteristics at baseline were similar in both treatment groups. The median time from first histological diagnosis to randomisation in the study was 26.9 months. The distributions of EGFR staining intensity were similar in both treatment groups.

The extent of disease, including number of target lesions and disease sites, was similar in both treatment groups. The predominant metastatic disease sites were liver and lung.

Subjects in this study were heavily pre-treated. Per protocol, all subjects were to have received and failed prior therapy with 5-FU or equivalent, irinotecan, and oxaliplatin in the metastatic setting. Previous CRC treatments were similar between groups with a total of 97.7% of subjects received prior oxaliplatin therapy and 96.2% received irinotecan therapy. In the cetuximab + BSC group, 10 (3.5%) subjects did not receive prior irinotecan therapy and 6 (2.1%) subjects did not receive prior oxaliplatin therapy. In the BSC group, 12 (4.2%) subjects did not receive prior irinotecan therapy and 7 (2.5%) subjects did not receive prior oxaliplatin therapy. Most (82.9%) subjects received 2 to 4 prior chemotherapy regimens regardless of line of therapy. All subjects except for 1 in the BSC group had prior surgery for CRC. Prior radiotherapy was received by 202 (35.3%) of the 572 randomised subjects; therapy was adjuvant in 12.9%, palliative in 19.1%, and both in 3.3%.

Table 7: Baseline demographic variables for the FAS and *K-RAS* populations of study CA225025

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + BSC (N=287)	BSC (N=285)	Cmab + BSC (N=92)	BSC (N=96)	Cmab + BSC (N=54)	BSC (N=57)	Cmab + BSC (N=38)	BSC (N=39)
Gender, n (%)								
Male	186 (64.8)	182 (63.9)	64 (69.6)	62 (64.6)	37 (68.5)	37 (64.9)	27 (71.1)	25 (64.1)
Female	101 (35.2)	103 (36.1)	28 (30.4)	34 (35.4)	17 (31.5)	20 (35.1)	11 (29.0)	14 (35.9)
Age, years								
Median	63.0	63.6	62.4	65.1	63.7	64.9	60.1	65.8
Range	28.6–88.1	28.7–85.9	38.6–81.0	35.5–85.9	39.1–81.0	35.5–85.9	38.6–80.5	37.4–82.6
Age, n (%)								
<65 years	177 (61.7)	158 (55.4)	58 (63.0)	48 (50.0)	32 (59.3)	29 (50.9)	26 (68.4)	19 (48.7)
≥65 years	110 (38.3)	127 (44.6)	34 (37.0)	48 (50.0)	22 (40.7)	28 (49.1)	12 (31.6)	20 (51.3)
Ethnic origin, n (%)								
Caucasian	258 (89.9)	250 (87.7)	82 (89.1)	84 (87.5)	48 (88.9)	51 (89.5)	34 (89.5)	33 (84.6)
Black	5 (1.7)	4 (1.4)	4 (4.4)	2 (2.1)	3 (5.6)	1 (1.8)	1 (2.6)	1 (2.6)
Asian	20 (7.0)	25 (8.8)	4 (4.4)	6 (6.3)	2 (3.7)	4 (7.0)	2 (5.3)	2 (5.1)
Other	4 (1.4)	6 (2.1)	2 (2.2)	4 (4.2)	1 (1.9)	1 (1.8)	1 (2.6)	3 (7.7)
ECOG PS, n (%)								
0	72 (25.1)	64 (22.5)	26 (28.3)	17 (17.7)	16 (29.6)	11 (19.3)	10 (26.3)	6 (15.4)
1	148 (51.6)	154 (54.0)	51 (55.4)	57 (59.4)	31 (57.4)	31 (54.4)	20 (52.6)	26 (66.7)
2	67 (23.3)	67 (23.5)	15 (16.3)	22 (22.9)	7 (13.0)	15 (26.3)	8 (21.1)	7 (18.0)

BSC=best supportive care, Cmab=cetuximab, ECOG PS= Eastern Cooperative Oncology Group performance status, FAS=full analysis set, N=number of subjects

Study population

The majority of subjects in the cetuximab + BSC group discontinued the study due to progressive disease. Nine subjects in the randomised population discontinued for treatment-related toxicities (5 for hypersensitivity reactions (HSRs), 1 for rash/desquamation, 1 for petechiae/purpura, 1 for headache, and 1 for hypomagnesaemia). A tabular summary of the number of subjects in the overall (FAS) and *K-RAS* evaluable analysis populations is provided in Table 8.

Statistical methods

In order to calculate OS, with a 2-sided alpha of 5%, a total of 500 subjects with 445 events (deaths) were needed to provide 90% power to detect a 9.6% difference in 1-year survival (hazard ratio [HR] of 1.36) between the 2 treatment groups (assuming a 14.1% 1-year survival for the BSC group).

The primary method used to compare OS between the 2 groups was a 2-sided log-rank test stratified by PS (ECOG 0-1 versus 2) at randomisation. The HR of cetuximab + BSC over BSC and 2-sided 95% confidence interval (CI) were calculated based on a Cox regression model also stratified by PS (ECOG 0-1 versus 2) at randomisation. Kaplan- Meier (K-M) curves were presented to graphically display the survival distribution per group, the median survival times and their respective 95% CIs, and the percentage of subjects who died in each treatment group.

A stratified Cox regression model was fitted to the data in order to assess the impact of treatment group on OS after adjusting for pre-defined prognostic factors at baseline (gender

[male/female], age [< 65/≥65], LDH [> UNL/≤UNL], alkaline phosphatase [> UNL/≤UNL], haemoglobin [CTC Grade ≥1/CTC Grade 0], number of disease sites [> 2/≤2], number of previous chemotherapy drug classes [> 2/≤2], primary tumour site [rectum only/colon], and presence of liver metastases [yes/no]). The analyses for PFS were similar to those for OS.

Table 8: Numbers of subjects in overall (FAS) and *K-RAS* evaluable analysis populations in the randomised, controlled studies

Study / population	Control	Number (%) subjects in population					
		Cetuximab + control		Control		Total	
CA225025	BSC						
FAS		287		285		**572**	
KRAS evaluable		92	(100.0)	96	(100.0)	**188**	**(100.0)**
KRAS wild type		54	(58.7)	57	(59.4)	**111**	**(59.0)**
KRAS mutant		38	(41.3)	39	(40.6)	**77**	**(41.0)**
CA225006	Irinotecan						
FAS		648		650		**1298**	
KRAS evaluable		146	(100.0)	154	(100.0)	**300**	**(100.0)**
KRAS wild type		97	(66.4)	95	(61.7)	**192**	**(64.0)**
KRAS mutant		49	(33.6)	59	(38.3)	**108**	**(36.0)**
EMR 62 202-013	FOLFIRI						
FAS		599		599		**1198**	
KRAS evaluable		277	(100.0)	263	(100.0)	**540**	**(100.0)**
KRAS wild type		172	(62.1)	176	(66.9)	**348**	**(64.4)**
KRAS mutant		105	(37.9)	87	(33.1)	**192**	**(35.6)**
EMR 62 202-047	FOLFOX-4						
FAS		169		168		**337**	
KRAS evaluable		113	(100.0)	120	(100.0)	**233**	**(100.0)**
KRAS wild type		61	(54.0)	73	(60.8)	**134**	**(57.5)**
KRAS mutant		52	(46.0)	47	(39.2)	**99**	**(42.5)**
TOTAL							
FAS		1703		1702		**3405**	
KRAS evaluable		628	(100.0)	633	(100.0)	**1261**	**(100.0)**
KRAS wild type		384	(61.1)	401	(63.3)	**785**	**(62.3)**
KRAS mutant		244	(38.9)	232	(36.7)	**476**	**(37.7)**

BSC=best supportive care, FAS=full analysis set

Efficacy results

Analyses of progression-free survival

Table 9 summarises the results for PFS in study CA225025. Results are presented for the FAS as well as for the *K-RAS* populations (*K-RAS* evaluable, *K-RAS* wild-type, and *K-RAS* mutant). The treatment effect in terms of PFS time was notable in subjects with *K-RAS* wild-type tumours, with a hazard ratio of 0.456 in study CA225025.

Table 9: PFS for the FAS and *K-RAS* populations of study CA225 025

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control
CA225025 (cetuximab + BSC)								
Total subjects	287	285	92	96	54	57	38	39
No. (%) events	273 (95.1)	269 (94.4)	88 (95.7)	94 (97.9)	52 (96.3)	55 (96.5)	36 (94.7)	39 (100.0)
Hazard ratio*	0.676		0.594		0.456		0.877	
95% CI	0.568, 0.804		0.438, 0.806		0.301, 0.692		0.552, 1.391	
Log-rank p-value	<0.0001		0.0007		0.0002		0.5763	
Median PFS (months)	1.9	1.8	2.0	1.8	3.6	1.9	1.8	1.7
95% CI	1.8, 2.1	1.8, 1.9	1.8, 3.5	1.8, 1.9	2.7, 5.4	1.8, 2.0	1.8, 1.9	1.6, 1.9

* Hazard ratio for cetuximab + control over control

BSC=best supportive care, CI=confidence interval, Cmab=cetuximab, FAS=full analysis set, PFS=progression free survival time

Analyses of tumour response

Table 10 summarises the results for tumour response in study CA225025. Results are presented for the FAS as well as for the *K-RAS* populations (*K-RAS* evaluable, *K-RAS* wild-type, and *K-RAS* mutant. Statistics on odds ratios are not provided in cases of small cell sizes as they do not allow a clinically meaningful interpretation of treatment effects.

Table 10: Tumour response for the FAS and *K-RAS* populations of study CA225025

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control
CA225025 (cetuximab + BSC)								
Total subjects	287	285	92	96	54	57	38	39
Best overall response n (%)								
CR	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
PR	19 (6.6)	0 (–)	8 (8.7)	0 (–)	8 (14.8)	0 (–)	0 (–)	0 (–)
SD	84 (29.3)	29 (10.2)	29 (31.5)	11 (11.5)	24 (44.4)	8 (14.4)	5 (13.1)	3 (7.7)
PD	133 (46.3)	155 (54.4)	42 (45.7)	55 (57.3)	18 (33.3)	30 (52.6)	24 (63.2)	25 (64.1)
ORR, n (%)	19 (6.6)	0 (–)	8 (8.7)	0 (–)	8 (14.8)	0 (–)	0 (–)	0 (–)
95% CI	4.0, 10.2	–	3.8, 16.4	–	6.6, 27.1	–	–	–
p-value	<0.0001		0.004		0.005		–	

BSC=best supportive care, CI=confidence interval, Cmab=cetuximab, CR=complete response, FAS=full analysis set, n=number of subjects, ORR=objective response rate, PD=progressive disease, PR=partial response, SD=stable disease

p-values were determined by Fisher's exact test in studies CA225025 and CA225006 and by CMH in studies EMR 62 202-013 and 047

In subjects with *K-RAS* mutations in their tumours, the overall response rates (ORRs) in subjects who received cetuximab in combination with chemotherapy or BSC were similar to those in subjects who received chemotherapy or BSC alone. A notable treatment effect in terms of ORR was apparent in subjects without *K-RAS* mutations in their tumours. In study CA225025 the *K-RAS* wild-type subset showed a markedly enhanced response compared to the *K-RAS* evaluable sample.

Analyses of overall survival

Table 11 summarises the OS results for study CA225025. The median OS time was longer in subjects with *K-RAS* wild-type tumours than in subjects with *K-RAS* mutant tumours.

Table 11: Overall survival for the FAS and *K-RAS* populations of study CA225025

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control
CA225025 (cetuximab + BSC)								
Total subjects	287	285	92	96	54	57	38	39
No. (%) events	222 (77.4)	234 (82.1)	66 (71.7)	80 (83.3)	38 (70.4)	47 (82.5)	28 (73.7)	33 (84.6)
Hazard ratio	0.77*		0.75		0.74		0.79	
95% CI	0.64, 0.92		0.537, 1.036		0.479, 1.154		0.476, 1.322	
Log-rank p-value	0.0046**		0.0792		0.1852		0.3734	
Median OS (months)	6.1	4.6	6.6	5.1	8.0	5.4	5.0	4.0
95% CI	5.4, 6.7	4.2, 4.9	5.9, 8.3	4.0, 5.8	7.0, 10.1	4.5, 7.7	3.8, 6.4	3.2, 5.8

BSC=best supportive care, CI=confidence interval, Cmab=cetuximab, ECOG PS= Eastern Cooperative Oncology Group performance status, FAS=full analysis set, OS=overall survival time

* Adjusted for ECOG performance status

** Stratified by ECOG performance status

Study CA225006 was a randomised, open-label, multicentre phase III study conducted to assess the impact on overall survival of cetuximab in combination with irinotecan in subjects with EGFR-expressing, metastatic CRC who had failed a first line regimen containing oxaliplatin and a fluoropyrimidine and had not received prior irinotecan. Subjects were randomised (1:1) to receive cetuximab + irinotecan or irinotecan alone. Randomisation was stratified by study site and ECOG performance status (PS) (0 - 1, 2). Treatment continued until disease progression or unacceptable toxicity.

The first dose of study therapy was administered to each subject within 3 days of randomisation. Subjects randomised to cetuximab + irinotecan received IV cetuximab weekly. An initial dose of cetuximab 400 mg/m^2 infused over 120 minutes was administered at Week 1. A maintenance dose of 250 mg/m^2 was infused over 60 minutes each subsequent week. Subjects randomised to cetuximab + irinotecan or irinotecan alone received IV irinotecan once every 3 weeks. The first dose of irinotecan was administered as a 90-minute infusion on Day 1. Subsequent doses were administered every 3 weeks at the same infusion rate. For subjects in the cetuximab + irinotecan arm, the irinotecan dose was given 60 minutes after completion of the cetuximab infusion. Irinotecan was administered at a dose of 350 mg/m^2 for subjects < 70 years of age and 300 mg/m^2 for subjects ≥70 years of age, or who had a PS score of 2, or had prior pelvic or abdominal irradiation.

A cycle of therapy was defined as 3 weeks unless the start of a subsequent cycle was delayed, in which case the cycle length was longer than 3 weeks. Treatment was comprised of irinotecan administered on Day 1 of each 3-week cycle combined with weekly cetuximab infusions, or irinotecan alone every 3 weeks. For subjects randomised to cetuximab + irinotecan, if toxicities prevented the administration of irinotecan, the subject could continue to receive single-agent cetuximab. If toxicities prevented the administration of cetuximab, the subject could continue to receive single-agent irinotecan. Reductions of the cetuximab or irinotecan dose were allowed for management of haematological and non-haematological toxicities, acneiform rash, and infusion reaction.

The primary objective of this study was to determine whether overall survival is prolonged in subjects with EGFR-expressing mCRC treated with cetuximab in combination with irinotecan compared with irinotecan alone as second line therapy following treatment with a fluoropyrimidine- and oxaliplatin-based, non-irinotecan-containing regimen.

Secondary Objectives were:

- To compare progression-free survival (PFS) between the 2 treatment arms
- To compare tumour response rates between the 2 treatment arms
- To estimate duration of response within each treatment arm
- To estimate time to response within each treatment arm
- To compare the disease control rate between the 2 treatment arms
- To compare the safety profiles between the 2 treatment arms
- To compare the quality of life (QOL) between the 2 treatment arms
- To conduct an exploratory economic assessment comparing healthcare resource utilisation between the 2 treatment arms.

Inclusion and exclusion criteria

Main inclusion criteria

Eligible subjects were males or females at least 18 years of age who signed the informed consent form, had measurable disease, and met the following disease criteria:

- Histologically documented CRC that is metastatic
- EGFR positivity of tumour tissue by immunohistochemical evidence of EGFR Expression
- Prior fluoropyrimidine-containing regimen (5-FU, capecitabine, or UFT), for first line treatment of metastatic disease
- Prior oxaliplatin administered for first line treatment of mCRC
- Failed an oxaliplatin regimen for metastatic disease. Failure was defined as either progression of disease (clinical or radiologic) within 6 months of the last dose of any agent of an oxaliplatin-based regimen, or intolerance to an oxaliplatin regimen. Intolerance to an oxaliplatin regimen was defined as discontinuation due to any of the following: severe allergic reaction, persistent severe neurotoxicity, or delayed recovery from toxicity preventing retreatment.
- Adequate recovery from recent surgery, chemotherapy, or radiation therapy ECOG PS of 0, 1, or 2.

Main exclusion criteria

Subjects who met any of the following criteria were excluded from the study:

- Any concurrent malignancy. The following were exceptions and were permitted: non-melanoma skin cancer, in-situ cancer of the cervix, and other malignancy with no evidence of disease ≥ 3 years
- More than one prior chemotherapy regimen for the treatment of mCRC; prior irinotecan for the treatment of mCRC; prior cetuximab or other therapy which targets the epidermal growth factor (EGF) pathway
- Prior hypersensitivity reaction (HSR) to chimerised or murine monoclonal antibody therapy

- Any concurrent chronic systemic immune therapy, chemotherapy not indicated in the study protocol, radiation therapy, hormonal therapy (except for physiological replacement), or any other investigational agent
- Inadequate haematologic, hepatic, or renal function
- History of uncontrolled congestive heart failure, uncontrolled angina, or uncontrolled arrhythmias.

Efficacy variables

Survival time was defined as the time from randomisation to the date of death. Subjects were evaluated every 3 months following completion of therapy for survival follow-up. If the subject had not died at the time of follow-up, survival was censored on the last date the subject was known to be alive. Tumour response was assessed every 6 weeks until disease progression.

Demographics and baseline characteristics

The demographic and baseline characteristics for the FAS and *K-RAS* populations are summarised in Table 12. In study CA225006, the majority of the demographic variables were comparable between the FAS and the *K-RAS* evaluable population. The exception was ethnic origin where there were a higher proportion of black subjects in the *K-RAS* evaluable, due to the fact that the *K-RAS* evaluable population consisted only of subjects from the United States.

Table 12: Baseline demographic variables for the FAS and *K-RAS* populations of study CA225006

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + irinotecan (N=648)	Irinotecan (N=650)	Cmab + irinotecan (N=146)	Irinotecan (N=154)	Cmab + irinotecan (N=97)	Irinotecan (N=95)	Cmab + irinotecan (N=49)	Irinotecan (N=59)
Gender, n (%)								
Male	405 (62.5)	411 (63.2)	79 (54.1)	91 (59.1)	52 (53.6)	59 (62.1)	27 (55.1)	32 (54.2)
Female	243 (37.5)	239 (36.8)	67 (45.9)	63 (40.9)	45 (46.4)	36 (37.9)	22 (44.9)	27 (45.8)
Age, years								
Median	61.0	62.0	59.5	62.5	60.0	60.0	59.0	65.0
Range	23.0–85.0	21.0–90.0	23.0–85.0	25.0–90.0	23.0–85.0	25.0–87.0	34.0–78.0	29.0–90.0
Age, n (%)								
<65 years	393 (60.6)	375 (57.7)	91 (62.3)	88 (57.1)	57 (58.8)	60 (63.2)	34 (69.4)	28 (47.5)
≥65 years	255 (39.4)	275 (42.3)	55 (37.7)	66 (42.9)	40 (41.2)	35 (36.8)	15 (30.6)	31 (52.5)
Ethnic origin, n (%)								
Caucasian	589 (90.9)	600 (92.3)	109 (74.7)	123 (79.9)	73 (75.3)	76 (80.0)	36 (73.5)	47 (79.7)
Black	29 (4.5)	24 (3.7)	25 (17.1)	21 (13.6)	15 (15.5)	15 (15.8)	10 (20.4)	6 (10.2)
Asian	19 (2.9)	16 (2.5)	5 (3.4)	5 (3.2)	3 (3.1)	2 (2.1)	2 (4.1)	3 (5.1)
Other	11 (1.7)	10 (1.5)	7 (4.8)	5 (3.2)	6 (6.2)	2 (2.1)	1 (2.0)	3 (5.1)
ECOG PS, n (%)								
0	348 (53.7)	316 (48.6)	64 (43.8)	64 (41.6)	42 (43.3)	39 (41.1)	22 (44.9)	25 (42.4)
1	260 (40.1)	295 (45.4)	77 (52.7)	83 (53.9)	50 (51.5)	53 (55.8)	27 (55.1)	30 (50.8)
2	35 (5.4)	35 (5.4)	5 (3.4)	6 (3.9)	5 (5.2)	3 (3.2)	0 (–)	3 (5.1)

Cmab=cetuximab, ECOG PS= Eastern Cooperative Oncology Group performance status, FAS=full analysis set, N=number of subjects

Treatment arms were balanced based on subjects' histories of CRC, median time from metastatic disease to randomisation, baseline signs and symptoms, and EGFR expression. The maximum staining intensity was 1+ to 2+ for 74% of subjects in both treatment arms.

More than 99% of subjects in both arms received prior chemotherapy for metastatic disease, as required by eligibility criteria. Neo-adjuvant chemotherapy was reported for 6.8% and 5.5% of subjects in the cetuximab + irinotecan and irinotecan arms, respectively. Oxaliplatin was reported as prior chemotherapy for 99.5% subjects in both arms; fluorouracil for 83% and 85% of subjects in the cetuximab + irinotecan and irinotecan arms, respectively; and bevacizumab for 13% of subjects in both arms. Disease progression was the most common reason for coming off previous first line therapy (66% and 64% in the cetuximab + irinotecan and irinotecan arms, respectively). Treatment arms were balanced for index lesions at baseline and common disease sites. More than two thirds of subjects had lesions at 2 or more disease sites, indicating relatively advanced disease at baseline.

Study population

All 1267 treated subjects (638 cetuximab + irinotecan; 629 irinotecan) received their assigned treatment as randomised. As of the last follow-up, all but 19 subjects (10 cetuximab + irinotecan, 9 irinotecan) were off treatment. Disease progression was the most frequent reason for discontinuation of study therapy in both treatment arms. Study drug toxicity led to discontinuation of study therapy in similar proportions of subjects in each arm (6.5% cetuximab + irinotecan; 4.8% irinotecan). In the cetuximab + irinotecan arm, 2.4% discontinued cetuximab prior to discontinuing irinotecan and 9.1% discontinued irinotecan prior to discontinuing cetuximab. A tabular summary of the number of subjects in the overall (FAS) and *K-RAS* evaluable analysis populations is provided in Table 8.

Statistical methods

An independent Data Safety Monitoring Board (DSMB) was convened to conduct a single safety review based on the first 400 randomised subjects. This analysis was restricted to safety and had no bearing on the sample size calculations for assessment of the primary endpoint (OS). Following the DSMB meeting to discuss results of the first interim analysis, the board requested a second interim analysis, this time on survival as well as safety. The DSMB asked that this analysis be based on data from the first 800 randomised subjects and that it encompass the period from the start of study until 6 weeks after the randomisation of the 800th subject. The interim analysis of survival was comprised of a log-rank test, an estimate of and CI for the hazard ratio of the experimental arm to the control arm, and Kaplan-Meier curves.

Efficacy results

Progression-free survival

Table 13 summarises the results for PFS in study CA225006. Results are presented for the FAS as well as for the *K-RAS* populations (*K-RAS* evaluable, *K-RAS* wild-type, and *K-RAS* mutant). The treatment effect in terms of PFS time was notable in subjects with *K-RAS* wild-type tumours, with a hazard ratio of 0.773 in study CA225006.

Table 13: PFS for the FAS and *K-RAS* populations of study CA225 006

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control

CA225006 (cetuximab + irinotecan)								
Total subjects	648	650	146	154	97	95	49	59
No. (%) events	610 (94.1)	598 (92.0)	134 (91.8)	142 (92.2)	**87 (89.7)**	**88 (92.6)**	47 (95.9)	54 (91.5)
Hazard ratio*	0.692		0.838		**0.773**		0.996	
95% CI	0.617, 0.776		0.659, 1.065		**0.572, 1.044**		0.668, 1.485	
Log-rank p-value	<0.0001		0.1526		**0.0954**		0.9853	
Median PFS (months)	4.0	2.6	3.5	2.8	**4.0**	**2.8**	2.6	2.7
95% CI	3.2, 4.1	2.1, 2.7	2.7, 4.0	2.4, 3.0	**2.8, 5.4**	**2.4, 3.3**	1.5, 3.6	1.5, 2.8

Analyses of tumour response

Table 14 summarises the results for tumour response in study CA225006. Results are presented for the FAS as well as for the *K-RAS* populations (*K-RAS* evaluable, *K-RAS* wild-type, and *K-RAS* mutant). Compared to the *K-RAS* evaluable sample the *K-RAS* wild-type subsets showed similar results in the two patient populations.

Table 14: Tumour response for the FAS and *K-RAS* populations of study CA225006

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control
CA225006 (cetuximab + irinotecan)								
Total subjects	648	650	146	154	97	95	49	59
Best overall response n (%)								
CR	9 (1.4)	1 (0.2)	2 (1.4)	0 (–)	1 (1.0)	0 (–)	1 (2.0)	0 (–)
PR	97 (15.0)	26 (4.0)	14 (9.6)	10 (6.5)	9 (9.3)	7 (7.4)	5 (10.2)	3 (5.1)
SD	292 (45.1)	271 (41.7)	70 (48.0)	70 (45.5)	49 (50.5)	44 (46.3)	21 (42.9)	26 (44.1)
PD	174 (26.9)	243 (37.4)	39 (26.7)	55 (35.7)	22 (22.7)	33 (34.7)	17 (34.7)	22 (37.3)
ORR, n (%)	106 (16.4)	27 (4.2)	16 (11.0)	10 (6.5)	10 (10.3)	7 (7.4)	6 (12.2)	3 (5.1)
95% CI	13.6, 19.4	2.8, 6.0	6.4, 17.2	3.2, 11.6	5.1, 18.1	3.0, 14.6	4.6, 24.8	1.1, 14.2
p-value *	<0.0001		0.22		0.61		0.29	

BSC=best supportive care, CI=confidence interval, Cmab=cetuximab, CR=complete response, FAS=full analysis set, n=number of subjects, ORR=objective response rate, PD=progressive disease, PR=partial response, SD=stable disease

p-values were determined by Fisher's exact test in studies CA225025 and CA225006 and by CMH in studies EMR 62 202-013 and 047

Analyses of overall survival

Table 15 summarises the OS results for study CA225006. The median OS time was longer in subjects with *K-RAS* wild-type tumours than in subjects with *K-RAS* mutant tumours.

Table 15: OS for the FAS and *K-RAS* populations of study CA225006

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control
CA225006 (cetuximab + irinotecan)								
Total subjects	648	650	146	154	97	95	49	59
No. (%) events	445 (68.7)	429 (66.0)	105 (71.9)	93 (60.4)	66 (68.0)	53 (55.8)	39 (79.6)	40 (67.8)
Hazard ratio	0.98*		1.25		1.29		1.28	
95% CI	0.85, 1.11		0.947, 1.660		0.894, 1.846		0.813, 2.005	
Log-rank p-value	0.7115**		0.1133		0.1755		0.2874	
Median OS (months)	10.7	10.0	9.3	11.3	10.9	11.6	8.4	10.7
95% CI	9.6, 11.3	9.1, 11,3	7.7, 11.2	9.5, 12.3	7.8, 13.2	9.5, 18.6	6.1, 11.0	8.4, 14.0

BSC=best supportive care, CI=confidence interval, Cmab=cetuximab, ECOG PS= Eastern Cooperative Oncology Group performance status, FAS=full analysis set, OS=overall survival time

* Adjusted for ECOG performance status

** Stratified by ECOG performance status

Comment: The *K-RAS* wild-type subset did not show a markedly enhanced response rate in this study.

Study EMR 62 202-013 was an open, randomised, controlled, multicentre, phase III study comparing 5-FU/FA plus irinotecan plus cetuximab versus 5-FU/FA plus irinotecan as first line treatment for EGFR-expressing metastatic CRC (mCRC).

The primary objective of the study was to assess whether the PFS time under 5-FU/FA plus irinotecan plus cetuximab was longer than that under 5-FU/FA plus irinotecan as first line treatment for EGFR-expressing mCRC.

Secondary objectives were to compare the 2 treatment groups in relation to:

- Overall survival time

- Response rate (modified World Health Organization [WHO] criteria)
- Disease control rate
- Duration of response
- QoL
- Safety.

The screening (baseline) visit was to be performed no more than 21 days prior to randomisation. EGFR-expressing subjects were to complete the second informed consent form to participate in the study. After screening, eligible subjects were randomised in a 1:1 ratio to 1 of the 2 treatment regimens; group A (cetuximab plus irinotecan and 5-FU/FA) or group B (irinotecan and 5-FU/FA only).

The planned treatment duration per subject was until demonstration of PD by computed tomography (CT) or magnetic resonance imaging (MRI), occurrence of unacceptable AEs, or withdrawal of consent. Groups A and B both received the same chemotherapy regimen every 14 days. The regimen was based on the simplified de Gramont regimen plus irinotecan (modified FOLFIRI regimen). In addition to the chemotherapy regimen, the subjects in group A were to receive cetuximab every 7 days. Cetuximab was to be administered 1 hour before chemotherapy at a dose of 400 mg/m² IV for the first infusion and 250 mg/m² IV for subsequent infusions.

The ideal treatment cycle in study EMR 62 202-013 lasted 14 days and was determined by the chemotherapy dosage interval. Treatment cycles were defined as follows:

Group A: 1 treatment cycle consisted of dosing with cetuximab, irinotecan and 5-FU/FA on day 1 of the cycle, and of dosing with cetuximab on day 8 of the cycle, with follow-up through day 14 of the cycle.

Group B: 1 treatment cycle consisted of dosing with irinotecan and 5-FU/FA on day 1 of the cycle, with follow-up through day 14 of the cycle.

Inclusion and exclusion criteria

Main inclusion criteria

The following inclusion criteria had to be fulfilled:

General

- Signed written informed consent (first and second)
- Effective contraception for both male and female subjects if the risk of conception existed.

Demographic characteristics

- Inpatient or outpatient ≥18 years of age
- Disease-related characteristics
- Diagnosis of histologically confirmed adenocarcinoma of the colon or rectum
- First occurrence of metastatic disease (not curatively resectable) (modified from ‘inoperable metastatic disease’ by amendment 1)
- Immunohistochemical evidence of EGFR expression in tumour tissue
- Life expectancy of at least 12 weeks
- Presence of at least 1 bi-dimensionally measurable index lesion, whereby index lesions could not lie in an irradiated area
- ECOG performance status of ≤ 2 at study entry

- White blood cell count (WBC) $\geq 3 \times 10^9$/L with neutrophils $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, haemoglobin ≥ 5.6 mmol/L (9 g/dL)
- Total bilirubin $\leq 1.5 \times$ upper reference range
- Aspartate aminotransferase (AST) $\leq 2.5 \times$ upper reference range, or $\leq 5 \times$ upper reference range in case of liver metastasis
- Serum creatinine $\leq 1.5 \times$ upper reference range
- Recovery from relevant toxicity to previous treatment before study entry.

Main exclusion criteria

Subjects were not eligible for this study if any of the following exclusion criteria applied:

General

- Pregnancy (absence to be confirmed by ß-hCG test) or lactation period.

Medical history

- Previous exposure to EGFR-targeting therapy
- Previous irinotecan-based chemotherapy
- Previous chemotherapy for CRC except adjuvant treatment if terminated >6 months before the start of treatment in this study
- Radiotherapy, surgery (excluding prior diagnostic biopsy), or any investigational drug in the 30 days before the start of treatment in this study
- Concurrent chronic systemic immune therapy or hormone therapy not indicated in the study protocol, except for physiologic replacement (clarification regarding physiologic replacement provided by amendment 1)
- Known hypersensitivity reaction to any of the components of study treatments
- Clinically relevant coronary artery disease or history of myocardial infarction in the last 12 months, or high risk of uncontrolled arrhythmia
- Acute or sub-acute intestinal occlusion or history of inflammatory bowel disease
- Previous malignancy other than CRC in the last 5 years except basal cell cancer of the skin or pre-invasive cancer of the cervix
- Known alcohol or drug abuse
- Medical or psychological conditions that would not have permitted the subject to complete the study or sign informed consent
- Participation in another clinical study within the past 30 days
- Significant disease which, in the investigator's opinion, would have excluded the subject from the study
- Legal incapacity or limited legal capacity.

Disease-related characteristics

- Brain metastasis and leptomeningeal disease (known or suspected) (leptomeningeal disease added as an exclusion criterion by amendment 1).

Efficacy variables

The primary efficacy variable was the PFS time. All dates related to PD used in the calculation of the PFS time (progression date, last known tumour assessment) were to be determined by an independent committee. A subject's PFS time was defined as the time in months from randomisation until PD was first observed or death occurred due to any cause within 60 days of the last tumour assessment or randomisation. In subjects without a progression date or death date more than 60 days after the last tumour assessment or

randomisation, the PFS time was censored on the date of last tumour assessment or randomisation.

Secondary efficacy variables assessed included OS, tumour response, best overall response (confirmed as CR, PR, stable disease [SD], or PD), duration of response time to response, disease control rate (defined as the proportion of subjects having achieved confirmed CR, PR or SD as best overall response), rate of surgery with curative intent and QoL (determined using the EORTC QLQ-C30 [version 3.0]).

Demographics and baseline characteristics

The demographic and baseline characteristics for the FAS and *K-RAS* populations in study EMR 62 202 -013 are provided in Table 16. Disease characteristics at baseline were similar in both treatment groups with respect to gender, age and ECOG performance status.

Table 16: Baseline demographic variables for the FAS and *K-RAS* populations of study EMR 62 202-013 (M2.7.3, v2, p14)

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + FOLFIRI (N=599)	FOLFIRI (N=599)	Cmab + FOLFIRI (N=277)	FOLFIRI (N=263)	Cmab + FOLFIRI (N=172)	FOLFIRI (N=176)	Cmab + FOLFIRI (N=105)	FOLFIRI (N=87)
Gender, n (%)								
Male	369 (61.6)	356 (59.4)	172 (62.1)	140 (53.2)	105 (61.0)	96 (54.5)	67 (63.8)	44 (50.6)
Female	230 (38.4)	243 (40.6)	105 (37.9)	123 (46.8)	67 (39.0)	80 (45.5)	38 (36.2)	43 (49.4)
Age, years								
Median	61.0	61.0	61.0	62.0	61.0	60.5	62.0	63.0
Range	22.0–82.0	19.0–84.0	22.0–79.0	22.0–79.0	24.0–79.0	22.0–79.0	22.0–79.0	32.0–79.0
Age, n (%)								
<65 years	374 (62.4)	377 (62.9)	174 (62.8)	170 (64.4)	109 (63.4)	120 (68.2)	65 (61.9)	50 (57.5)
≥65 years	224 (37.4)	222 (37.1)	102 (36.8)	93 (35.4)	63 (36.6)	56 (31.8)	39 (37.1)	37 (42.5)
Ethnic origin, n (%)								
Caucasian	513 (85.6)	514 (85.8)	263 (94.9)	258 (98.1)	161 (93.6)	172 (97.7)	102 (97.1)	86 (98.9)
Black	2 (0.3)	5 (0.8)	1 (0.4)	1 (0.4)	1 (0.6)	1 (0.6)	0 (–)	0 (–)
Asian	75 (12.5)	75 (12.5)	9 (3.2)	3 (1.1)	6 (3.5)	2 (1.1)	3 (2.9)	1 (1.1)
Other/missing	9 (1.5)	5 (0.8)	4 (1.5)	1 (0.4)	4 (2.3)	1 (0.6)	0 (–)	0 (–)
ECOG PS, n (%)								
0	330 (55.1)	318 (53.1)	153 (55.2)	144 (54.8)	99 (57.6)	104 (59.1)	54 (51.4)	40 (46.0)
1	248 (41.4)	260 (43.4)	113 (40.8)	112 (42.6)	66 (38.4)	65 (36.9)	47 (44.8)	47 (54.0)
2	21 (3.5)	21 (3.5)	11 (4.0)	7 (2.7)	7 (4.1)	7 (4.0)	4 (3.8)	0 (–)

Cmab=cetuximab, ECOG PS= Eastern Cooperative Oncology Group performance status, FAS=full analysis set, N=number of subjects

The median (range) duration of CRC for subjects at randomisation was 2.3 months (0 to 239 months). For duration of metastatic CRC, a median (range) of 1.6 months (0 to 92 months) was reported. The location of the primary tumour was in the colon for 720 (60.1%) subjects, in the rectum for 453 (37.8%) subjects, and in both the colon and rectum for 23 (1.9%) subjects. Disease staging at diagnosis was IV for the majority of subjects (943 [78.7%]). 1015 (84.7%) subjects had at least 2 index lesions identified for evaluation of progression status; for almost half of the subjects (585 [48.8%]) this assessment was based on 4 or more index lesions.

Study population

In total, 1221 subjects were either randomised or treated: 1217 subjects (608 in the cetuximab pus FOLFIRI group and 609 in the FOLFIRI alone group) were randomised and 4 subjects (2 in each group) were treated erroneously without being randomized. At the clinical cut-off date (27 July 2006), 201 subjects were still receiving study treatment: 118 in the cetuximab plus FOLFIRI group and 84 in the FOLFIRI group.

Progressive disease was the most frequent main reason for discontinuation in both treatment groups. AEs were the main reason for discontinuation in 7.9% of subjects in the cetuximab plus FOLFIRI group and in 5.4% of subjects in the FOLFIRI alone group. A tabular summary of the number of subjects in the overall (FAS) and *K-RAS* evaluable analysis populations is provided in Table 8.

Statistical methods

For the primary analysis, the PFS hazard ratio of FOLFIRI in combination with cetuximab to FOLFIRI alone, and an associated 95% confidence interval, was computed using a univariate Cox proportional hazards model (log-rank test) with treatment as single covariate and the randomisation strata ECOG performance status (0–1, 2) and region as strata. For exploratory analyses of PFS time and overall survival time, a Cox proportional hazards model was employed to assess and adjust the treatment comparison for these factors.

Efficacy results

Analyses of progression-free survival

Table 17 summarises the results for PFS in study EMR 62 202-013. Results are presented for the FAS as well as for the *K-RAS* populations. The treatment effect in terms of PFS time was pronounced in subjects with *K-RAS* wild-type tumours with a hazard ratio of 0.684 in EMR 62 202- 013. Results supported that cetuximab treatment in patients metastatic CRC with *K-RAS* wild-type status was efficacious.

Table 17: PFS for the FAS and *K-RAS* populations of study EMR 62 202-013

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control
EMR 62 202-013 (cetuximab + FOLFIRI)								
Total subjects	599	599	277	263	172	176	105	87
No. (%) events	298 (49.7)	322 (53.8)	134 (48.4)	138 (52.5)	76 (44.2)	95 (54.0)	58 (55.2)	43 (49.4)
Hazard ratio*	0.851		0.822		0.684		1.069	
95% CI	0.726, 0.998		0.645, 1.048		0.501, 0.934		0.710, 1.610	
Log-rank p-value	0.0479		0.1141		0.0167		0.7496	
Median PFS (months)	8.9	8.0	9.2	8.7	9.9	8.7	7.6	8.1
95% CI	8.0, 9.5	7.6, 9.0	8.0, 11.0	7.6, 9.4	8.7, 14.6	7.4, 9.9	6.7, 9.4	7.5, 9.4

Analyses of tumour response

Table 18 summarises the results for tumour response in study EMR 62 202-013. In subjects with *K-RAS* mutations in their tumours, the ORRs in subjects who received cetuximab in combination with chemotherapy or BSC were similar to those in subjects who received chemotherapy or BSC alone. A relevant treatment effect in terms of ORR was apparent in subjects without *K-RAS* mutations in their tumours. Compared to the *K-RAS* evaluable sample, the *K-RAS* wild-type subsets showed an enhanced response rate.

Table 18: Tumour response for the FAS and *K-RAS* populations of study CA202-013

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control
EMR 62 202-013 (cetuximab + FOLFIRI)								
Total subjects	599	599	277	263	**172**	**176**	105	87
Best overall response n (%)								
CR	3 (0.5)	2 (0.3)	2 (0.7)	0 (–)	**2 (1.2)**	**0 (–)**	0 (–)	0 (–)
PR	278 (46.4)	230 (38.4)	138 (49.8)	111 (42.2)	**100 (58.1)**	**76 (43.2)**	38 (36.2)	35 (40.2)
SD	224 (37.4)	280 (46.7)	102 (36.8)	117 (44.5)	**53 (30.8)**	**77 (43.8)**	49 (46.7)	40 (46.0)
PD	53 (8.8)	54 (9.0)	19 (6.9)	23 (8.7)	**9 (5.2)**	**16 (9.1)**	10 (9.5)	7 (8.0)
ORR, n (%)	281 (46.9)	232 (38.7)	140 (50.5)	111 (42.2)	**102 (59.3)**	**76 (43.2)**	38 (36.2)	35 (40.2)
95% CI	42.9, 51.0	34.8, 42.8	44.5, 56.6	36.2, 48.4	**51.6, 66.7**	**35.8, 50.9**	27.0, 46.2	29.9, 51.3
p-value	0.0038		0.0624		**0.0025**		0.46	

BSC=best supportive care, CI=confidence interval, Cmab=cetuximab, CR=complete response, FAS=full analysis set, n=number of subjects, ORR=objective response rate, PD=progressive disease, PR=partial response, SD=stable disease

p-values were determined by Fisher's exact test in studies CA225025 and CA225006 and by CMH in studies EMR 62 202-013 and 047

Analyses of overall survival

Mature OS data were not available for study EMR 62 202-013 at the time of the submission.

Study EMR 62 202-047 was an open, randomised, controlled, multicentre phase II study comparing 5-FU/FA plus oxaliplatin (FOLFOX-4) plus cetuximab with 5-FU/FA plus oxaliplatin as first line therapy for EGFR-expressing mCRC. Subjects at 87 centres were screened for EGFR-expressing tumours to identify a minimum of 292 subjects eligible for 1:1 randomisation: 146 in each group. The study started in July 2005 and recruitment was closed in March 2006. All subjects in both treatment groups received the same chemotherapy regimen. In addition, the subjects in the cetuximab plus FOLFOX-4 group were treated with cetuximab every week. Cetuximab was administered 1 hour before chemotherapy. The weekly cetuximab regimen was cetuximab 400 mg/m² for the first infusion and thereafter 250 mg/m².

Inclusion and exclusion criteria

Main inclusion criteria

Men and women had to fulfil all the following criteria to be eligible for inclusion:

General

- Signed written informed consents (first and second)
- Effective contraception for both male and female subjects if conception was possible.
- ≥18 years.

Disease-related characteristics

- Presence of histologically confirmed adenocarcinoma of the colon or rectum
- First occurrence of metastatic disease (not curatively resectable)
- EGFR-expressing disease
- Life expectancy of at least 12 weeks
- Presence of at least 1 bidimensionally measurable index lesion not in an irradiated area
- ECOG PS ≤ 2 at study entry
- Laboratory levels: white blood cell count (leukocytes)≥ $3x10^{9}$/L; neutrophils

≥1.5x10^9/L; platelet count ≥100 x10^9/L; haemoglobin ≥ 6.21 mmol/L (10 g/dL); AST and alanine aminotransferase (ALT)≤ 2.5 x upper reference range, or ≤5 x upper reference range in case of liver metastasis; serum creatinine≤1.5 x upper reference range

- Recovery from relevant toxicity to previous treatment before study.

Main exclusion criteria

Subjects were not eligible for this study if any of the following exclusion criteria applied:

Disease-related characteristics

- Brain metastasis and/or leptomeningeal disease (known or suspected).

Previous and concurrent treatment

- Previous exposure to EGFR-targeting therapy
- Previous oxaliplatin-based chemotherapy
- Previous chemotherapy for CRC except adjuvant treatment with PD documented > 6 months after the end of adjuvant treatment
- Radiotherapy, surgery (excluding prior diagnostic biopsy) or any investigational drug in the 30 days before randomisation
- Concurrent chronic systemic immune therapy or hormone therapy not indicated in this study protocol except physiologic replacement.

Medical history

- Clinically relevant coronary artery disease, history of myocardial infarction in the last 12 months, or high risk of uncontrolled arrhythmia
- Acute or sub-acute intestinal occlusion or history of inflammatory bowel disease
- Previous malignancy other than CRC in the last 5 years, except basal cell cancer of the skin or pre-invasive cancer of the cervix
- Known alcohol or drug abuse
- Significant disease which, in the investigator's opinion, would exclude the subject from the study
- Peripheral neuropathy > grade 1
- Medical or psychological conditions that would not permit the subject to complete the study or sign informed consent.

Other

- Known hypersensitivity reaction to any of the components of study treatments
- Pregnancy (absence to be confirmed by β-hCG test) or lactation period
- Participation in another clinical study within the 30 days before randomization
- Legal incapacity or limited legal capacity.

Demographics and baseline characteristics

The demographic and baseline characteristics for the FAS and *K-RAS* populations in study EMR 62 202-047 are shown in Table 19. The *K-RAS* evaluable population was similar to the FAS population with respect to gender, age, ethnic origin, and ECOG PS. All subjects except 1 (336 of 337) had adenocarcinoma. The majority of subjects (236 [70.0%]) had stage IV CRC at primary diagnosis, with the colon as the primary site for 181 (53.7%) subjects, rectum for 154 (45.7%) subjects, and both the colon and rectum for 2 (0.6%). There were no major differences between the treatment groups.

All subjects except 1 had at least one other organ involved: 143 (42.4%) subjects with 1 other organ and 123 (36.5%) subjects with 2 other organs involved. These organs were most frequently either the liver (295 [87.5%] subjects) or the lung (129 [38.3%] subjects). 280 (83.1%) subjects had not received prior adjuvant chemotherapy.

Study population

629 subjects attended a pre-screening visit for this study of whom 607 were tested for the presence of EGFR-expressing disease. Of the 629 subjects who underwent pre-screening, 265 were not eligible for screening. 341 subjects were actually eligible for the study, and 3 were randomised in error. Of these 344, 338 actually received treatment. A tabular summary of the number of subjects in the overall (FAS) and *K-RAS* evaluable analysis populations is provided in Table 8. PD was the most frequent reason for study discontinuation in both treatment groups. AEs led to study discontinuation in 12 (7.1%) subjects in the cetuximab plus FOLFOX-4 group and 26 (15.5%) subjects the FOLFOX-4 group. Death was the reason for discontinuation in 9 (5.3%) subjects in the cetuximab plus FOLFOX-4 group and 5 (3.0%) in the FOLFOX-4 alone group.

Table 19: Baseline demographic variables for the FAS and *K-RAS* populations of study EMR 62 202-047

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + FOLFOX (N=169)	FOLFOX (N=168)	Cmab + FOLFOX (N=113)	FOLFOX (N=120)	Cmab + FOLFOX (N=61)	FOLFOX (N=73)	Cmab + FOLFOX (N=52)	FOLFOX (N=47)
Gender, n (%)								
Male	89 (52.7)	92 (54.8)	57 (50.4)	66 (55.0)	30 (49.2)	44 (60.3)	27 (51.9)	22 (46.8)
Female	89 (47.3)	76 (45.2)	56 (49.6)	54 (45.0)	31 (50.8)	29 (39.7)	25 (48.1)	25 (53.2)
Age, years								
Median	62.0	60.0	59.0	59.5	59.0	59.0	59.5	61.0
Range	24–82	30–82	24–82	30–82	24–74	36–82	41–82	30–75
Age, n (%)								
<65 years	96 (56.8)	109 (64.9)	70 (61.9)	77 (64.2)	39 (63.9)	46 (63.0)	31 (59.6)	31 (66.0)
≥65 years	73 (43.2)	59 (35.1)	43 (38.1)	43 (35.8)	22 (36.1)	27 (37.0)	21 (40.4)	16 (34.0)
Ethnic origin, n (%)								
Caucasian	169 (100)	167 (99.4)	113(100.0)	119 (99.2)	61 (100.0)	72 (98.6)	52 (100.0)	47 (100.0)
Other	0 (–)	1 (0.6)	0 (–)	1 (0.8)	0 (–)	1 (1.4)	0 (–)	0 (–)
ECOG PS, n (%)								
0	65 (38.5)	75 (44.6)	34 (30.1)	50 (41.7)	19 (31.1)	27 (37.0)	15 (28.8)	23 (48.9)
1	89 (52.7)	76 (45.2)	70 (61.9)	56 (46.7)	37 (60.7)	37 (50.7)	33 (63.5)	19 (40.4)
2	15 (8.9)	17 (10.1)	9 (8.0)	14 (11.7)	5 (8.2)	9 (12.3)	4 (7.7)	5 (10.6)

Cmab=cetuximab, ECOG PS= Eastern Cooperative Oncology Group performance status, FAS=full analysis set, N=number of subjects

Efficacy results

Analyses of progression-free survival

Table 20 summarises the results for PFS in study EMR 62 202-047. Results are presented for the FAS as well as for the *K-RAS* populations.

Table 20: PFS for the FAS and *K-RAS* populations of study EMR 62 202-047

EMR 62 202-047 (cetuximab + FOLFOX)								
Total subjects	169	168	113	120	61	73	52	47
No. (%) events	102 (60.4)	102 (60.7)	69 (61.1)	74 (61.7)	30 (49.2)	48 (65.8)	39 (75.0)	26 (55.3)
Hazard ratio*	0.931		0.928		0.570		1.830	
95% CI	0.705, 1.230		0.665, 1.295		0.358, 0.907		1.095, 3.056	
Log-rank p-value	0.6170		0.6609		0.0163		0.0192	
Median PFS (months)	7.2	7.2	7.3	7.2	7.7	7.2	5.5	8.6
95% CI	5.6, 7.7	6.0, 7.8	5.6, 8.1	6.0, 7.9	7.1, 12.0	5.6, 7.4	4.0, 7.4	6.5, 9.5

* Hazard ratio for cetuximab + control over control

BSC=best supportive care, CI=confidence interval, Cmab=cetuximab, FAS=full analysis set, PFS=progression free survival time

The treatment effect in terms of PFS time was notable in subjects with *K-RAS* wild-type tumours with a hazard ratio of 0.570 in EMR 62 202-047. A statistically significant difference between the treatment groups was established at the 5% significance level. The hazard ratio supports the hypothesis that the *K-RAS* wild-type status can be considered as a predictive marker for the efficacy of cetuximab treatment in metastatic CRC.

Analyses of tumour response

Table 21 summarises the results for tumour response in study EMR 62 202-047. The *K-RAS* wild-type subsets showed a superior response rate.

Table 21: Tumour response for the FAS and *K-RAS* populations of study EMR 62 202-047

Characteristic	FAS		KRAS evaluable		KRAS wild type		KRAS mutant	
	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control	Cmab + control	Control
EMR 62 202-047 (cetuximab + FOLFOX)								
Total subjects	169	168	113	120	61	73	52	47
Best overall response n (%)								
CR	3 (1.8)	3 (1.8)	2 (1.8)	3 (2.5)	**2 (3.3)**	**1 (1.4)**	0 (–)	2 (4.3)
PR	75 (44.4)	64 (38.1)	52 (46.0)	47 (39.2)	**35 (57.4)**	**26 (35.6)**	17 (32.7)	21 (44.7)
SD	65 (38.5)	70 (41.7)	46 (40.7)	47 (39.2)	**19 (31.1)**	**30 (41.1)**	27 (51.9)	17 (36.2)
PD	18 (10.7)	21 (12.5)	10 (8.8)	17 (14.2)	**3 (4.9)**	**12 (16.4)**	7 (13.5)	5 (10.6)
ORR, n (%)	78 (46.2)	67 (39.9)	54 (47.8)	50 (41.7)	**37 (60.7)**	**27 (37.0)**	17 (32.7)	23 (48.9)
95% CI	38.5, 54.0	32.4, 47.7	38.3, 57.4	32.7, 51.0	**47.3, 72.9**	**26.0, 49.1**	20.3, 47.1	34.1, 63.9
p-value	0.243		0.390		**0.011**		0.106	

BSC=best supportive care, CI=confidence interval, Cmab=cetuximab, CR=complete response, FAS=full analysis set, n=number of subjects, ORR=objective response rate, PD=progressive disease, PR=partial response, SD=stable disease

p-values were determined by Fisher's exact test in studies CA225025 and CA225006 and by CMH in studies EMR 62 202-013 and 047

Analyses of overall survival

Mature OS data were not available for study EMR 62 202-047 at the time of the submission.

Head and Neck Cancer

Study EMR 62 202-002 examined cetuximab in combination with cisplatin and 5-FU or carboplatin and 5-FU in the treatment of subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) (study also known as the "EXTREME" study).

The study was an open-label, randomised, controlled, multicentre phase III study in R/M SCCHN comparing cetuximab + cisplatin or carboplatin + 5-FU versus cisplatin or carboplatin + 5-FU as first line therapy for R/M SCCHN. Subjects were randomised 1:1 and stratified according to previous chemotherapy (CTX) (defined as neoadjuvant or induction CTX, adjuvant CTX or CTX in combination with concomitant radiotherapy as therapy for locally advanced disease) (yes/no) and Karnofsky performance score (KPS) (<80≥80). Treatment was continued until PD or symptomatic deterioration, or unacceptable toxicity occurred. CTX was given for a maximum of 6 cycles and cetuximab was continued in subjects without PD as monotherapy after the end of CTX in subjects in the cetuximab + CTX group. Subjects with unacceptable toxicity on cisplatin could be switched to carboplatin. Tumour response assessments using modified World Health Organization (WHO) criteria were based on CT or MRI every 6 weeks.

The primary objective of study EMR 62 202-002 was to assess whether OS time on cetuximab + cisplatin or carboplatin + 5-FU was longer than in subjects receiving cisplatin or carboplatin + 5-FU in the first line treatment of R/M SCCHN. Secondary objectives were to compare the following between the two treatment groups: PFS time, best overall response and disease control, duration of response, time to treatment failure, safety, and QoL.

Study treatment and duration were as follows:

- Cetuximab (initial dose 400 mg/m²; subsequent weekly doses 250 mg/m²) + 3-weekly cycles of CTX, i.e. cisplatin (100 mg/m² on Day 1) or carboplatin (area under the curve [AUC] 5 on Day 1) + 5-FU (1000 mg/m²/day continuous infusion Day 1–4).

or

- Cisplatin or carboplatin + 5-FU alone at the same dosages.

CTX was given for a maximum of 6 cycles; in subjects in the cetuximab + CTX group, cetuximab was continued as monotherapy after CTX discontinuation until PD, symptomatic deterioration or unacceptable toxicity occurred.

Inclusion and Exclusion Criteria

Inclusion criteria

All of the following criteria had to be fulfilled for inclusion in the study:

General

- Signed written informed consent before any study-related activities.
- Men or women aged ≥18 years.

History of SCCHN

- Histologically or cytologically confirmed diagnosis of SCCHN
- Recurrent and/or metastatic SCCHN, not suitable for local therapy
- At least 1 bi-dimensionally measurable lesion either by CT scan or MRI
- KPS of ≥70 at study entry.

Laboratory investigations

- Neutrophils ≥ 1500/mm³, platelet count ≥ 100000/mm³, and haemoglobin ≥ 9 g/dL
- Total bilirubin ≤ 2 × upper limit of normal (ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × ULN
- Creatinine clearance > 60 mL/min
- Tumour tissue available for immunohistochemical evaluation of EGFR expression.

Safety considerations

- Effective contraception for both male and female subjects if risk of conception exists.

Exclusion Criteria

Subjects who fulfilled one or more of the following criteria were not eligible for the study:

Previous treatment for SCCHN

- Prior systemic CTX, except if given as part of a multimodal treatment for locally advanced disease which was completed more than 6 months prior to study entry
- Surgery (excluding prior diagnostic biopsy), or irradiation within 4 weeks before study entry.

Medical history, previous and concomitant treatment

- Presence of nasopharyngeal carcinoma
- Active infection (infection requiring IV antibiotics), including active tuberculosis, and known and declared human immunodeficiency virus infection

- Uncontrolled hypertension defined as systolic blood pressure≥180 mmHg and/or diastolic blood pressure ≥130 mmHg under resting conditions
- Pregnancy (absence confirmed by serum β-human chorionic gonadotropin test) or lactation period
- Concomitant chronic systemic immune therapy, or hormonal therapy as cancer therapy
- Other concomitant anticancer therapies
- Documented or symptomatic brain or leptomeningeal metastasis
- Clinically relevant coronary artery disease or history of myocardial infarction in the last 12 months or high risk of uncontrolled arrhythmia or uncontrolled cardiac insufficiency
- Previous treatment with monoclonal antibody therapy, or other signal transduction inhibitors or EGFR targeting therapy
- Previous or current other squamous cell carcinoma
- Evidence of previous other malignancy within the last 5 years
- Any investigational medication within 30 days before study entry.

General

- Medical or psychological condition that would not permit the subject to complete the study or sign informed consent
- Known drug abuse (except alcohol abuse).

Safety issues

- Known allergic reaction against any of the components of the study treatment.

442 subjects were enrolled between December 2004 and 30 December 2005: 222 to cetuximab + CTX and 220 to CTX alone. In general the groups were well balanced with regard to demographic characteristics. 219 (98.6%) subjects in the cetuximab + CTX group and 213 (96.8%) subjects in the CTX group were Caucasian, and about 90% of subjects in each group were male. The mean age of subjects was 57.1 years in the cetuximab + CTX group and 56.7 in the CTX group. More than 80% of subjects in each group were less than 65 years. Medical history and concomitant disorders at study entry were similar in the two treatment groups. Baseline physical examination and the number of subjects with abnormal and normal baseline findings for ECG, chest X-ray and ejection fraction were similar in the two groups. The groups were also similar in terms of previous treatment and response to precious treatment. The groups were also balanced with regard to EGFR-detectable cells at baseline. Less than 2% had non-detectable EGFR in the cetuximab + CTX group (CTX: 2.5%). More than 80% of subjects in the two groups showed ≥ 40% EGFR-detectable cells.

Efficacy results

Overall survival time

OS time was defined as the time in months from randomisation to the date of death (date of death minus date of randomisation + 1). If a subject had not died, the survival time was censored at the last date the subject was known to be alive or if this date was after data cut-off, the date of data cut-off. The median time of follow-up was similar between the two groups: 19.1 months in the cetuximab + CTX group and 18.2 in the CTX group, and the event rate (number of deaths) was 75.2% in the cetuximab + CTX group and 80.0% in the CTX group. These indicated that follow-up was sufficiently long to allow for adequate accuracy in the estimation of the OS time curve. Results of the primary analysis of OS time in the ITT population are provided in Table 26. The HR for cetuximab + CTX over CTX of

0.797 [95% CI: 0.644, 0.986] showed a statistically significant reduction of about 20% in the risk of death for a subject randomised to the cetuximab + CTX group (p=0.036; stratified log-rank test). Median [95% CI] OS time was 10.1 [8.6, 11.2] months under cetuximab + CTX and 7.4 [6.4, 8.3] months under CTX alone.

A sensitivity analysis of OS time was conducted consisting of a Cox regression analysis with stepwise selection of potential prognostic baseline factors. Stratification factors were previous CTX and KPS. Whereas previous CTX appeared not to have prognostic relevance (HR of 0.999), a KPS ≥80 notably reduced the risk of death by 49.2% (HR=0.508, 95% CI: [0.374, 0.689]) compared to KPS <80. Subjects with metastatic, including recurrent, SCCHN had a lower risk of death than those with recurrent, non-metastatic SCCHN (HR: 0.814, 95% CI: [0.656, 1.009]). Adjustment for the most important prognostic variables confirmed the primary analysis on OS time. The estimated risk reduction of death in the cetuximab + CTX group was 21% (HR=0.786, 95% CI: [0.636, 0.973]; p=0.027).

Table 26: Summary of primary analysis of overall survival time in study EMR 62 202-002 (ITT Population)

Response variable	**Cetuximab + CTX N=222**		**CTX N=220**	
Hazard ratio, stratified [95% CI] [a, b]	0.797 [0.644, 0.986]			
Log rank p value, stratified[a]	0.036			
Number of deaths (%)	167	(75.2)	176	(80.0)
Overall survival time, *months, median [95% CI]* [c]	10.1 [8.6, 11.2]		7.4 [6.4, 8.3]	
Number (%) of subjects at risk/survival rates up to [95% CI] [c]				
3 months	184	84% [79, 89]	173	81% [75, 86]
6 months	153	71% [65, 77]	127	60% [53, 66]
12 months	82	39% [32, 45]	65	31% [24, 37]
18 months	30	24% [18, 30]	19	16% [10, 21]

Source: *see Table 14.2-1.1 in Section 5.3.5.1.1-HN2*

[a] Stratification based on previous chemotherapy and Karnofsky Performance Status

[b] Hazard ratio of cetuximab + CTX over CTX

[c] Product-limit (Kaplan-Meier) estimates

CI=confidence interval, CTX=chemotherapy, ITT=intention-to-treat, N=number of subjects

After the end of study, 91 (41.0%) subjects in the cetuximab + CTX group and 85 (38.6%) in the CTX group received anticancer treatments given after the study; 6 (2.7%) and 14 (6.4%) subjects were treated with cetuximab in the second line setting. The most frequent anticancer post-treatment was CTX in 74 (33.3%) subjects in the cetuximab + CTX group and 71 (32.3%) subjects in the CTX group. The next most frequent treatments were radiotherapy (11.3% cetuximab + CTX vs 9.1% CTX) and surgery (4.5% cetuximab + CTX vs 1.8% CTX). The anticancer treatments given after the study were evenly distributed between the treatment groups, and were not likely to have had any effect on OS time.

Progression-free survival time

PFS time was defined as the duration from randomisation until the first observation of radiologically confirmed PD or death due to any cause when death occurred within 60 days of the last tumour response assessment or randomisation, whichever was later. Table 27 summarises results of the analysis of PFS time in the ITT population. The HR for cetuximab + CTX over CTX of 0.538 [95% CI: 0.431, 0.672] showed a statistically significant reduction

of about 46% in the risk of PD for a subject randomised to the cetuximab + CTX group ($p<0.0001$; stratified log-rank test). Median [95% CI] PFS time was 5.6 [5.0, 6.0] months under cetuximab + CTX and 3.3 [2.9, 4.3] months under CTX alone.

Table 27: Summary of analysis of progression-free survival time in study EMR 62 202-002 (ITT Population) (M2.7.3, v9, p19)

Response variable	Cetuximab + CTX N=222		CTX N=220	
Hazard ratio, stratified [95% CI][a, b]	0.538 [0.431, 0.672]			
Log rank p value, stratified[a]	<0.0001			
Number of PDs and deaths (%)	168 (75.7)		173 (78.6)	
Progression-free survival time, *months, median [95% CI]* [c]	5.6 [5.0, 6.0]		3.3 [2.9, 4.3]	
Number of subjects (%) at risk/survival rates up to [95% CI] [c]				
3 months	138 (74%)	[68, 80%]	103 (56%)	[49, 63%]
6 months	72 (42%)	[35, 49%]	29 (20%)	[14, 26%]
12 months	12 (10%)	[5, 14%]	3 (3%)	[0, 5%]
18 months	3 (5%)	[1, 8%]	0 (1%)	[0, 3%]

Source: *see Table 14.2-2.1 in Section 5.3.5.1.1-HN2*

[a] Stratification based on previous chemotherapy and Karnofsky Performance Status as per IVRS

[b] Hazard ratio of cetuximab + CTX over CTX

[c] Product-limit (Kaplan-Meier) estimates

CI=confidence interval, CTX=chemotherapy, ITT=intention-to-treat, IVRS=interactive voice response system, N=number of subjects; PD=progressive disease

Best overall response rate and disease control rate

Table 28 summarises the response rates in the ITT population. In the ITT population, a complete response (CR) was achieved in 15 (6.8%) subjects in the cetuximab + CTX group and 2 (0.9%) in the CTX group. A partial response (PR) was achieved in 64 (28.8%) and 41 (18.6%) subjects. Stable disease (SD) was achieved in 101 (45.5%) and 89 (40.5%) subjects, and the best response was PD in 12 (5.4%) and 45 (20.5%) subjects.

The best overall response rate was 35.6% [95% CI: 29.3, 42.3] in the cetuximab + CTX group and 19.5% [95% CI: 14.5, 25.4] in the CTX group. This difference was statistically significant (CMH test: p=0.0001), with an odds ratio of 2.326 [95% CI: 1.504, 3.600]. The odds for a CR or PR were 2.3 times higher for subjects randomised to cetuximab + CTX group than in those randomised to CTX.

The disease control rate was 81.1% [95% CI: 75.3, 86.0] in the cetuximab + CTX group and 60.0% [95% CI: 53.2, 66.5] in the CTX group, and the difference was statistically significant (CMH test: p<0.0001), with an odds ratio of 2.881 [95% CI: 1.870, 4.441].

Table 28: Summary of best overall confirmed response and disease control in study EMR 62 202-002 (ITT Population) (M2.7.3, v9, p21)

Response variable	Cetuximab + CTX N=222	CTX N=220
Best overall response, N (%)		
Complete response	15 (6.8)	2 (0.9)
Partial response	64 (28.8)	41 (18.6)
Stable disease	101 (45.5)	89 (40.5)
Progressive disease	12 (5.4)	45 (20.5)
Not evaluable	30 (13.5)	43 (19.5)
Best overall response rate, % [95% CI][a]	35.6 [29.3, 42.3]	19.5 [14.5, 25.4]
CMH test[b]		
p value	0.0001	
Odds ratio [95% CI][b]	2.326 [1.504, 3.600]	
Disease control rate, % [95% CI][a]	81.1 [75.3, 86.0]	60.0 [53.2, 66.5]
CMH test[b]		
P value	<0.0001	
Odds ratio [95% CI][b]	2.881 [1.870, 4.441]	

Source: *see Table 14.2-3.1 in Section 5.3.5.1.1-HN2*

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

[b] Stratification based on previous chemotherapy and Karnofsky Performance Status as per IVRS

CMH=Cochran-Mantel-Haenszel (test), CI=confidence interval, CR=complete response, CTX=chemotherapy, ITT=intention-to-treat, IVRS=interactive voice response system, N=number of subjects, PR=partial response, SD=stable disease

Time to treatment failure

The time to treatment failure was defined as the time in months from randomisation until the date of the first occurrence of one of the events defining treatment failure: PD assessed by the investigator, discontinuation of treatment due to PD, discontinuation of treatment due to an AE, start of any new anticancer therapy, or withdrawal of consent or death within 60 days of the final tumour assessment or randomisation. If a subject was still responding to treatment, i.e. had neither progressed nor died (still on randomised treatment), the time to treatment failure was censored on the date of the final tumour assessment. A tabular summary of results for time to treatment failure in the ITT population is provided in Table 29. Treatment failed at a given time after the start of treatment in 199 (89.6%) subjects in the cetuximab + CTX group and 203 (92.3%) in the CTX group. The HR for cetuximab + CTX over CTX of 0.593 [95% CI: 0.484, 0.727]; a statistically significant reduction of about 41% in the risk of treatment failure for a subject randomised to the cetuximab + CTX group (p<0.0001; stratified log-rank test). The median time to treatment failure was 4.8 months [95% CI: 4.0, 5.6] and 3.0 months [95% CI: 2.8, 3.4].

Table 29: Time to treatment failure in study EMR 202-002 (ITT Population)

Response variable	Cetuximab + CTX N=222		CTX N=220	
Hazard ratio, stratified [95% CI][a, b]	0.593 [0.484, 0.727]			
Log rank p value, stratified[a]	<0.0001			
Number of events (%)[c]	199	(89.6)	203	(92.3)
Time to treatment failure, *months, median [95% CI]*[d]	4.8 [4.0, 5.6]		3.0 [2.8, 3.4]	
Number of subjects (%) at risk/treatment failure rates up to [95% CI][d]				
3 months	138	66% [60, 72]	103	50% [44, 57]
6 months	73	36% [29, 43]	34	17% [12, 23]
12 months	15	9% [5, 13]	5	3% [0, 5]

Source: *see Table 14.2-5.1 in Section 5.3.5.1.1-HN2*

[a] Hazard ratio of cetuximab + CTX over CTX

[b] Stratification based on previous chemotherapy and Karnofsky Performance Status as per IVRS

[c] Event defined by disease progression, discontinuation due to disease progression or adverse event, start of any new anticancer therapy, withdrawal of consent or death within 60 days of the last tumor assessment or randomization

[d] Product-limit (Kaplan-Meier) estimates

CI=confidence interval, CTX=chemotherapy, ITT=intention-to-treat, IVRS=interactive voice response system, N=number of subjects

Subgroup analyses

The subgroup analyses of best overall response were consistently in favour of the addition of cetuximab to CTX. Once again caution is required when interpreting the results of the subgroup analyses as the sample size of the study was not powered to establish significant differences. Subgroup analyses tended to indicate that patients with a good prognosis as indicated by tumour stage, baseline KPS and age (<65 years vs >65 years) had a more pronounced benefit when cetuximab was added to platinum-based chemotherapy. No overall benefit in terms of overall survival could be demonstrated in patients with KPS≤ 80 and aged 65 years or older.

Supportive studies

Two studies were nominated as supportive studies; however these have been submitted in previous applications to the TGA and were not re-submitted for evaluation in this submission.

Summary and discussion of efficacy results

Metastatic colorectal cancer

Cetuximab as single agent

Cetuximab administered as a single agent demonstrated statistically significant and clinically meaningful efficacy benefits in comparison with BSC in the overall population of patients who had failed all standard treatment options in study CA225025. These benefits were even more pronounced in the *K-RAS* wild-type subset. In the *K-RAS* evaluable population there was an imbalance with respect to ECOG PS favouring the experimental arm. Tumour response was assessed by the investigator rather than an independent assessor; however this is acceptable given that survival was the primary endpoint. PFS data are critical to assessment of efficacy and the results for PFS in study CA225025 do support benefit of cetuximab in patients with wild-type *K-RAS* tumours.

Single agent cetuximab therefore can be considered as appropriate therapy for patients with *K-RAS* wild-type tumours who have failed multiple lines of standard chemotherapy and who are not eligible for treatment with cetuximab in combination with irinotecan.

Cetuximab in combination with chemotherapy

In study CA225006 cetuximab was used second line with add-on irinotecan. This study was open-label and tumour response was not independently assessed. PFS is a recognised and well-established endpoint for the assessment of efficacy for agents given as early treatment in patients with metastatic CRC because PFS time measures the direct impact of the study treatment and is not affected by follow-up treatments. It is often the most meaningful endpoint for settings where effective follow-up treatments are available that have an impact on survival time. In this study there was the potential for investigator bias in assessment of PFS.

In study CA225006 no effect was seen for the primary endpoint, overall survival, with a HR of 0.98. There was however a treatment effect in terms of PFS with a HR of 0.7. The number of patients in this study with *K-RAS* wild-type was small, and tumour response data were inconsistent, making interpretation of the efficacy of cetuximab difficult. Efficacy data from study CA 225006 were inconclusive.

In study EMR 62 202-013 cetuximab was used first line as add-on to FOLFIRI, and efficacy was demonstrated in patients with *K-RAS* wild-type tumours. There was an increase in response rate, and a notable difference in PFS of about two months, which can be considered clinically relevant. Further evidence of efficacy was provided by the observation of an increased percentage of patients treated with cetuximab being able to undergo surgery with curative intent.

In study EMR 62 202-047 cetuximab was used first line as add-on to FOLFOX-4. In the overall population there was an increased response rate, however results were not impressive in the KRAS wild-type evaluable population. This may have been due to imbalances at baseline, particularly the fact that the control group had better performance status at baseline.

Overall, given the results across the studies, the evaluator considered that cetuximab in combination with chemotherapy and as a single agent was efficacious in treatment of patients with *K-RAS* wild-type metastatic CRC. The requested proposed indication for cetuximab was considered appropriate.

Head and Neck Cancer

Study EMR 62 202-002, the pivotal randomised controlled study, met its primary endpoint and demonstrated a statistically significant increase in OS for cetuximab in combination with standard platinum-based CTX in the first line treatment of subjects with R/M SCCHN. The addition of cetuximab to standard CTX led to a clinically meaningful reduction in the risk of death (HR 0.797) and an increase of 2.7 months in the median OS time. In addition, cetuximab + CTX showed significant advantages over CTX alone in median PFS time, time to treatment failure, and best overall response rate. The risk of disease progression was reduced by 46% and the risk of treatment failure by 41%. The response rate in the cetuximab + CTX group was significantly higher than in the CTX group.

The median OS time of over 10 months achieved with the addition of cetuximab is highly relevant clinically in this patient population that has a poor prognosis with few effective treatments available. Subgroup analyses showed some beneficial effects on OS, PFS, and response of adding cetuximab to platinum/5-FU; however results of subgroup analyses should be interpreted with caution.

Overall the evaluator considered that efficacy of cetuximab in treatment of patients with head and neck cancer was demonstrated by the data submitted for evaluation.

Safety

Metastatic Colorectal Cancer

The main exposure data for cetuximab in the 3 randomised, controlled studies conducted in patients with mCRC are summarised in Table 31. The proportion of subjects who received more than 80% of the planned dose intensity of cetuximab ranged from 78% to 87%.

Table 31: Key exposure data to cetuximab in studies CA225025, CA225006, and EMR 62 202-013

Characteristic	Statistic	CA225025 N=288 (+ BSC)	CA225006 N=638 (+ irinotecan)	EMR 62 202-013 N=600 (+ FOLFIRI)
Duration, weeks	Median	8.0	14.0	25.0
	Range	1 to 60	1 to 98	1 to 92
Cumulative dose per subject, mg/m²	Median	2156	3170	5912
	Range	391 to 15216	3 to 22086	8 to 22532
Dose intensity per subject, mg/m²/week	Median	247	234	236
	Range	117 to 283	67 to 293	59 to 267
Subjects with >80% of planned dose intensity	% subjects	86.5	77.7	81.2

Progressive disease (PD) was the most frequent reason for discontinuation in all studies. In study CA225025, a total of 271 (94%) subjects had discontinued cetuximab at the data cut-off. In study CA225006 the proportions of subjects who discontinued the study at the data cut-offs were cetuximab + irinotecan 98%, and irinotecan 99%. In study EMR 62 202-013 the proportions of subjects who discontinued were cetuximab + FOLFIRI 81%, and FOLFIRI 86%.

Most common adverse events (AEs) (any grade and grade 3 or 4)

Common adverse events

In the 3 randomised, controlled studies more than 95% of the subjects experienced at least one AE. The profile of most frequent AEs associated with the underlying disease is probably best reflected by the group of subjects who received BSC only in study CA225025: fatigue, anorexia, abdominal pain, nausea, dyspnoea, constipation, neuropathy-sensory and “pain other” were reported in ≥ 30% subjects in the BSC group. A tabular summary of the most frequent AEs reported in study CA225025 is provided in Table 32.

Skin reactions were among the most common AEs in cetuximab-treated subjects, with the highest incidences being reported for rash/desquamation (NCI-CTC AE) in about 90% of subjects in study CA225025 and for rash (MedDRA preferred term) in about 50% of subjects in the other 2 studies. Skin reactions are an expected AE known to be associated with cetuximab therapy.

The other most common AEs occurring in ≥30% subjects in both treatment groups included diarrhoea, vomiting, and alopecia in studies CA225006 and EMR 62 202-013 and neutropenia in study EMR 62 202-013 only. These are all known side effects of irinotecan as single agent or in combination with 5-FU/FA.

For most of the AEs, frequencies were comparable between the treatment groups within the respective study. Table 33 lists the AEs that were more common in the cetuximab group than in the control group in one or more of the 3 randomized, controlled studies (difference

between treatment groups ≥5% of subjects for studies CA225006 and EMR 62 202-013, ≥10% of subjects for the smaller study CA225025). The majority of these AEs were graded mild to moderate in intensity.

All of the AEs that were more common in the cetuximab groups than in the control groups of all 3 randomised, controlled studies were known side effects of cetuximab: skin reactions, pyrexia, and stomatitis. Furthermore, other known side effects of cetuximab (acne, conjunctivitis, dermatitis acneiform, exfoliative rash, mucosal inflammation, nail disorders, paronychia, and skin fissures) were also observed to be common in the cetuximab groups of studies CA 225025 and CA 225006. Diarrhoea and fatigue were both more frequent in the cetuximab groups of studies CA225025 and CA225006.

The following AEs that were more common in the cetuximab group of at least one study are also known to be associated with cetuximab: headache, various skin disorders, hypomagnesaemia, and hypokalaemia. Other AEs observed with a higher incidence in one study were abdominal pain, anorexia, asthenia, back pain, cough, epistaxis, infection without neutropenia, insomnia, "pain other", palmar-plantar erythrodysesthesia (PPE) syndrome, and weight decreased. The frequencies of dyspnoea were comparable between treatment groups in all three studies.

Grade 3 or 4 AEs

Grade 3 or 4 AEs were reported in approximately 70–85% of subjects in the cetuximab-treated groups and about 55–60% subjects in the control groups. Incidences reported were as follows:

- study CA225025 - cetuximab + BSC 82.6%, BSC 60.9%
- study CA225006 - cetuximab + irinotecan 73.2%, irinotecan 57.9%
- study EMR 62 202-013 - cetuximab + FOLFIRI 78.0%, FOLFIRI 59.5%.

Frequencies of individual grade 3 or 4 AEs were generally comparable between treatment groups within each study, and the most common grade 3 or 4 AEs were typical of the underlying disease or would be expected to occur with the study treatments.

Table 32: Most frequent AEs (≥10%) in study CA225025

NCI-CTC AE	% of subjects	
	Cetuximab + BSC (N=288)	BSC (N=274)
Any	99.7	91.6
Fatigue	89.2	75.5
Rash/desquamation	88.5	16.1
Anorexia	67.0	64.6
Abdominal pain	58.7	52.2
Nausea	56.9	47.8
Pain other	50.7	33.6
Dry skin	49.0	10.9
Dyspnea	48.3	43.4
Constipation	45.8	37.6
Pruritus	40.3	8.4
Diarrhea	38.9	20.1
Neuropathy-sensory	38.5	36.1
Vomiting	37.2	29.2
Infection w/o neutropenia	35.1	16.8
Headache	33.0	10.6
Edema	30.9	26.6
Fever	29.5	17.5
Insomnia	29.5	15.0
Cough	29.2	19.0
Other skin	27.4	5.8
Stomatitis	25.3	9.5
Other gastrointestinal	22.6	17.9
Nail changes	21.2	3.6
Confusion	14.9	9.1
Bone pain	14.6	6.9
Anxiety	14.2	8.4
Dyspepsia/heart burn	14.2	14.2
Depression	13.2	5.8
Rigors, chills	13.2	4.0
Mouth dryness	10.8	4.4
Dizziness	10.1	6.9

Individual NCI-CTC AEs classified in the category 'hypersensitivity reaction' were also classified in other categories e.g. dyspnea in the category 'pulmonary'. However all of the NCI-CTC AEs in the category 'hypersensitivity reaction' occurred in <10% subjects in either treatment group and are consequently not included in the above table.

Note: Cancer deaths have not been included in this table, although they were in the original source table. The reasons are discussed in *2.7.4.2.1.1.1 CRC2*.

AE=adverse event, BSC=best supportive care, NCI-CTC=National Cancer Institute-Common Toxicity Criteria

Table 33: AEs with higher frequency in the cetuximab group vs control group of study CA225025, CA225006, or EMR 62 202-013

NCI-CTC AE (CA225025)	Cetuximab	Cetuximab + irinotecan-based regimen	
MedDRA preferred term (CA225006, EMR 62 202-013)	CA225025 (N=562)	CA225006 (N=1267)	EMR 62 202-013 (N=1202)
More common in 3 studies			
Dry skin	X	X	X
Pruritus	X	X	X
Pyrexia	X (fever*)	X	X
Rash	X (rash/desquamation*)	X	X
Stomatitis	X	X	X
More common in 2 studies			
Acne		X	X
Conjunctivitis		X	X
Dermatitis acneiform		X	X
Diarrhea	X	X	
Exfoliative rash		X	X
Fatigue	X	X	
Mucosal inflammation		X	X
Nail disorder	X (nail changes*)		X
Paronychia		X	X
Skin fissures		X	X
More common in 1 study			
Cough	X		
Headache	X		
Infection w/o neutropenia	X		
Insomnia	X		
"Pain other"	X		
Other skin	X		
Abdominal pain		X	
Anorexia		X	
Asthenia		X	
Back pain		X	
Epistaxis		X	
Hypokalemia		X	
Neutropenia		X	
Skin chapped		X	
Hypomagnesemia			X
PPE syndrome			X
Skin toxicity			X
Weight decreased			X

* NCI-CTC AE

PPE = palmar-plantar erythrodysesthesia

"X" denotes that there was a higher frequency of the specified AE in the cetuximab group vs the control group (difference between treatment groups: ≥10% subjects for CA225025; ≥5% subjects for CA225006 and EMR 62 202-013).

A tabular summary of grade 3 and 4 AEs reported in ≥10% of subjects in study CA225025 is provided in Table 34. In study CA225025, fatigue, abdominal pain, and dyspnoea were reported in ≥10% subjects who received cetuximab + BSC or BSC only and are expected events in heavily pre-treated patients with metastatic CRC. "Pain other", infection without neutropenia and rash/desquamation were also reported in ≥10% subjects of the cetuximab + BSC group.

Table 34: Grade 3 or 4 AEs occurring in ≥5% of subjects or Grade 4 AEs occurring in ≥1% subjects in any treatment group in study CA225025

NCI-CTC AEs	Number (%) of subjects			
	Cetuximab + BSC (N=288)		BSC (N=274)	
	Grade 3 or 4	Grade 4	Grade 3 or 4	Grade 4
Any	238 (82.6)	113 (39.2)	167 (60.9)	65 (23.7)
Fatigue	96 (33.3)	16 (5.6)	72 (26.3)	14 (5.1)
Dyspnea (pulmonary)	47 (16.3)	10 (3.5)	34 (12.4)	6 (2.2)
Pain-Other	45 (15.6)	7 (2.4)	20 (7.3)	0 –
Abdominal pain	41 (14.2)	8 (2.8)	43 (15.7)	6 (2.2)
Infection w/o neutropenia	39 (13.5)	3 (1.0)	16 (5.8)	1 (0.4)
Rash/desquamation	34 (11.8)	0 –	1 (0.4)	0 –
Other (gastrointestinal)	28 (9.7)	5 (1.7)	24 (8.8)	7 (2.6)
Anorexia	24 (8.3)	1 (0.3)	16 (5.8)	4 (1.5)
Nausea	17 (5.9)	0 –	16 (5.8)	0 –
Vomiting	17 (5.9)	2 (0.7)	15 (5.5)	1 (0.4)
Confusion	16 (5.6)	4 (1.4)	6 (2.2)	0 –
Edema	15 (5.2)	2 (0.7)	16 (5.8)	2 (0.7)
Constipation	10 (3.5)	2 (0.7)	14 (5.1)	2 (0.7)
Other (hepatic)	10 (3.5)	5 (1.7)	6 (2.2)	2 (0.7)
Thrombosis/embolism	9 (3.1)	2 (0.7)	14 (5.1)	6 (2.2)
Dyspnea (hypersensitivity reaction)	8 (2.8)	5 (1.7)	0 –	0 –
Other (neurology)	8 (2.8)	3 (1.0)	2 (0.7)	0 –
Bilirubin	6 (2.1)	2 (0.7)	3 (1.1)	3 (1.1)
Liver dysfunction	3 (1.0)	2 (0.7)	5 (1.8)	4 (1.5)
Ureteral obstruction	3 (1.0)	3 (1.0)	2 (0.7)	2 (0.7)
Renal failure	1 (0.3)	0 –	3 (1.1)	3 (1.1)

Note: Grade 4 includes all toxicities that are grade 4 or 5.

Note: Cancer deaths have not been included in this table, although they were in the original source table. The reasons are discussed in *2.7.4.2.1.1.1 CRC2*.

AE=adverse events, BSC=best supportive care, NCI-CTC=National Cancer Institute-Common Toxicity Criteria

Tabular summaries of grade 3 and 4 AEs reported in ≥5% of subjects in studies CA225025 and EMR 62 202-013 are provided in Tables 35 and 36 respectively. In studies CA225006 and EMR 62 202-013, grade 3 or 4 diarrhoea and neutropenia were reported in ≥5% of subjects of both treatment groups. These AEs are commonly reported in patients treated with concomitant irinotecan-based regimens.

Table 35: Grade 3 or 4 AEs occurring in ≥5% of subjects or grade 4 AEs occurring in ≥1% of subjects in any treatment group in study CA225006

MedDRA preferred term	Number (%) of subjects			
	Cetuximab + irinotecan (N=638)		Irinotecan (N=629)	
	Grade 3 or 4	Grade 4	Grade 3 or 4	Grade 4
Any	467 (73.2)	176 (27.6)	364 (57.9)	135 (21.5)
Diarrhea	184 (28.8)	10 (1.6)	102 (16.2)	11 (1.7)
Neutropenia	112 (17.6)	58 (9.1)	85 (13.5)	43 (6.8)
Fatigue	59 (9.2)	4 (0.6)	31 (4.9)	5 (0.8)
Febrile neutropenia	53 (8.3)	23 (3.6)	40 (6.4)	16 (2.5)
Abdominal pain	52 (8.2)	1 (0.2)	37 (5.9)	1 (0.2)
Vomiting	39 (6.1)	0 –	40 (6.4)	2 (0.3)
Asthenia	38 (6.0)	2 (0.3)	35 (5.6)	3 (0.5)
Nausea	36 (5.6)	0 –	33 (5.2)	0 –
Rash	34 (5.3)	1 (0.2)	1 (0.2)	0 –
Leukopenia	29 (4.5)	13 (2.0)	22 (3.5)	10 (1.6)
Neutrophil count decreased	12 (1.9)	7 (1.1)	10 (1.6)	5 (0.8)

Note: Grade 4 includes all toxicities that are grade 4 or 5. Disease progression, metastases to central nervous system and malignant neoplasm progression have not been included in this table, although they were in the original source tables. The reasons are discussed in *2.7.4.2.1.1.1 CRC2*. Detailed analyses of deaths are provided in *2.7.4.2.1.2 CRC2*

MedDRA=Medical Dictionary for Regulatory Affairs

Table 36: Grade 3 or 4 AEs occurring in ≥5% of subjects or grade 4 AEs occurring in ≥1% of subjects in any treatment group in study EMR 62 202-013

MedDRA preferred term	Number (%) of subjects			
	Cetuximab + FOLFIRI (N=600)		FOLFIRI (N=602)	
	Grade 3 or 4	Grade 4	Grade 3 or 4	Grade 4
Any	468 (78.0)	149 (24.8)	358 (59.5)	97 (16.1)
Neutropenia	160 (26.7)	55 (9.2)	140 (23.3)	46 (7.6)
Diarrhea	91 (15.2)	3 (0.5)	63 (10.5)	2 (0.3)
Rash	46 (7.7)	0 –	0 –	0 –
Leukopenia	42 (7.0)	9 (1.5)	29 (4.8)	6 (1.0)
Dermatitis acneiform	30 (5.0)	0 –	0 –	0 –
Fatigue	30 (5.0)	1 (0.2)	27 (4.5)	3 (0.5)
Vomiting	27 (4.5)	1 (0.2)	30 (5.0)	3 (0.5)
Pulmonary embolism	23 (3.8)	20 (3.3)	16 (2.7)	6 (1.0)
Hypomagnesemia *	11 (1.8)	9 (1.5)	1 (0.2)	1 (0.2)

* Serum magnesium was only measured in a limited number of subjects.

FOLFIRI=folinic acid + 5-fluorouracil + irinotecan, MedDRA=Medical Dictionary for Regulatory Affairs

Deaths

Tabular summaries of deaths occurring up to 30 days after the last dose of study treatment in studies CA 225025, CA 225006 and EMR 62 202-013 are provided in Tables 37, 38 and 39 respectively. In the 3 randomised, controlled studies, 215 subjects died within 30 days after the last dose of study medication: 59/288 (20.5%) treated with cetuximab + BSC, 90/1238 (7.3%) treated with cetuximab + an irinotecan-based regimen, and 66/1231 (5.4%) treated with an irinotecan-based regimen. A treatment period including 30 days follow up could not be defined in the BSC group of study CA225025 due to the absence of study medication. Most of the deaths were considered to be due to the underlying disease.

Table 37: Number (%) of deaths up to 30 days after last dose of cetuximab in study CA225025

Primary reason for death	Cetuximab + BSC (N=288)
All reasons	59 (20.5)
Colorectal cancer	58 (20.1)
Other	1 (0.3)

Note: For the BSC group, no information could be provided for this time period as no study drug was given. For the overall number of deaths in both treatment groups, see *Table S.6.1 in 5.3.5.1.1 CRC2*.

BSC=best supportive care

The higher death rate in study CA225025 may be attributed to the more advanced disease status of the heavily pre-treated subjects; none of the deaths in this study were assessed as related to cetuximab.

Table 38: Number (%) of deaths up to 30 days after last dose of cetuximab in study CA225006

Primary reason for death	Cetuximab + irinotecan (N=638)	Irinotecan (N=629)
All reasons	57 (8.9)	40 (6.4)
Tumor related disease	37 (5.8)	29 (4.6)
Study drug toxicity	5 (0.8)*	2 (0.3)**
Other	11 (1.7)	7 (1.1)
Unknown	4 (0.6)***	2 (0.3)

* 5 were considered study treatment related, of these 1 related to cetuximab+ irinotecan and 4 to irinotecan.
** Both were irinotecan related.
*** 1 death was considered related to cetuximab + irinotecan.

In subjects treated with irinotecan-based regimens, the higher death rate (all reasons) in the group that also received cetuximab was probably related to an imbalance of deaths in study CA225006: cetuximab + irinotecan 57 (8.9%) subjects vs irinotecan 40 (6.4%) subjects. In the subjects treated with cetuximab + irinotecan-based regimens, none of the deaths were assessed as being due to events related specifically and solely to cetuximab.

Table 39: Number (%) of deaths up to 30 days after last dose of cetuximab in study EMR 62 202-013 (M2.7.4, v2, p53)

Primary reason for death	Cetuximab + FOLFIRI (N=600)	FOLFIRI (N=602)
All reasons	33 (5.5)	26 (4.3)
Disease progression	7 (1.2)	8 (1.3)
Disease-related complication	7 (1.2)	7 (1.2)
Intercurrent or unrelated illness/event	11 (1.8)	3 (0.5)
Events related to cetuximab	0 –	0 –
Events related to chemotherapy	3 (0.5)	5 (0.8)
Unknown	5 (0.8)	3 (0.5)

FOLFIRI=folinic acid + 5-fluorouracil + irinotecan

In the other supportive studies submitted in the dossier, 250/1716 (14.6%) subjects died within 30 days after the last dose of study medication: 94/456 (20.6%) subjects treated with cetuximab as single agent, 156/1260 (12.4%) subjects treated with cetuximab + an irinotecan-based regimen. Almost all of the deaths were due to the underlying cancer or cancer-related complications.

Special AE categories

The following categories of special AEs were examined in the randomised, controlled MedDRA-coded studies CA225006 and EMR 62 202-013: acne-like rash, mucositis, infusion-related reactions (IRRs), haemorrhage, cardiac events, thromboembolic events, cerebrovascular accidents (CVAs) / ischaemia, and eye disorders. Frequencies of relevant NCI-CTC terms or categories in study CA225025 were also reviewed. Time to first onset of diarrhoea (any grade and grade 3 or 4) and association between diarrhoea and electrolyte disturbances were also analysed.

Acne-like rash and mucositis**.** Incidences and severities of acne-like rash and mucositis were consistent with the known safety profile of cetuximab as reflected in the current product information.

Infusion-related reactions (IRRs). Incidences of IRRs in the 2 MedDRA-coded studies were consistent with incidences reported in earlier clinical trials. A higher incidence of hypersensitivity reactions (HSRs) in study CA225025 was probably due to the broader definition and inclusion of additional clinical symptoms for reporting these events in the case report form.

Analyses on first occurrence, intervention, outcome, and re-exposure were performed on cetuximab-treated subjects who experienced grade 3 or 4 IRRs (26/1238 [2.1%] subjects in studies CA225006 and EMR 62 202-013) or HSR/allergic reactions (13 [4.5%] subjects in study CA225025). Treatment of the reactions using parasympatholytics, sympathomimetics, corticosteroids, antihistamines, methylxanthines, infusion solutions, oxygen, and/or reduction of infusion rate led to resolution of the events in all but 2 subjects where the outcome is unknown.

In studies CA225006 and EMR 62 202-013, cetuximab therapy was discontinued permanently in 21 subjects following a grade 3 or 4 IRR. 5 subjects were re-exposed. One of these subjects experienced a second grade 3 IRR and was then permanently discontinued. The 4 remaining subjects continued cetuximab treatment without experiencing any subsequent IRRs.

In study CA225025, 14 subjects experienced a grade 3 or 4 AE classified as HSR/allergic reaction. Cetuximab therapy was discontinued permanently in 2 subjects and treatment was continued in the remaining 12 subjects. Four of these subjects experienced a second HSR with a subsequent cetuximab infusion (1 grade 4, 3 grade 2) leading to permanent discontinuation of cetuximab treatment in 2 subjects.

Haemorrhage**.** The data from the 3 randomised, controlled studies indicate that cetuximab increases the incidence of mild to moderate epistaxis which is a known symptom of mucositis.

Cardiac events. Administration of cetuximab as a single agent with BSC in study CA225025 did not result in any clinically relevant imbalances with respect to BSC in cardiac events.

Thromboembolic events. In study CA225025, the incidences of the NCI-CTC AE "thrombosis/embolism" were comparable in the cetuximab + BSC and BSC groups. The frequencies of AEs of "thromboembolic events" in the randomised, controlled studies CA225006 and EMR 62 202-013 were comparable between treatment groups within each of the 2 studies.

Eye disorders**.** The incidence of conjunctivitis with cetuximab as a single agent (3.8% in study CA225025) and in combination with irinotecan (7.7% in study CA225006) were similar to incidences described in the current product information (5%). A higher incidence of conjunctivitis was observed with cetuximab in combination with FOLFIRI (13.5% in study EMR 62 202-013). These findings may suggest that the incidence of conjunctivitis may increase with longer exposure of subjects to cetuximab.

Time to event analysis of diarrhoea and association between diarrhoea and electrolyte disturbances***:*** The cumulative risk of developing diarrhoea under cetuximab + BSC in study CA225025 was significantly higher than under BSC (at 6 weeks 16.8 vs 5.1%). In both studies (CA225006 and EMR 62 202-013) in which cetuximab was given in combination with irinotecan-based regimens, results indicated that cetuximab increased the risk of

diarrhoea. The highest risk was for the 350 mg/m² irinotecan regimen every 3 weeks (or 300 mg/m² in subjects aged≥70 years, with ECOG PS 2, or who had previously received abdominal or pelvic radiation according to the irinotecan prescribing information) in study CA225006. A plateau for the development of first-time diarrhoea grade ≥1 or grade ≥3 was reached within 3 to 6 months. A potential association between electrolyte disturbances and diarrhoea was investigated; however no conclusions could be drawn.

Laboratory findings

Overall, laboratory findings reflected the known safety profiles of cetuximab, the concomitant chemotherapy, and the underlying disease. Mild to moderate increases in liver enzyme values and decreases of magnesium are known and included in the current product information for cetuximab. Higher frequencies of these laboratory abnormalities for these parameters were observed in the cetuximab-treated groups of the 3 randomised, controlled studies.

In the current product information, hypomagnesaemia is listed as occurring at an unknown frequency. Laboratory data from the 3 randomised, controlled studies indicate that hypomagnesaemia can now be classified as a very common side effect of cetuximab. Decreases in serum levels of potassium and calcium are already included in the product information for cetuximab, and imbalances in these electrolytes were also observed in the 3 randomised, controlled studies.

Other imbalances with higher frequencies in the cetuximab groups were as follows:

- Low platelet counts (mainly grade 1) in study CA225025. In the BSC group a bias due to less frequent assessments in end-stage disease may be possible because there were fewer subjects with laboratory assessments in this group compared to the cetuximab group.
- The frequency of low absolute neutrophil count (grade 3 or 4) was higher in the cetuximab + irinotecan group compared to the irinotecan group in study CA225006 (23.8% vs 17.3%).
- A higher incidence of low serum albumin (mainly grade 1 or 2) was observed in the cetuximab treatment groups of studies CA225006 and EMR 62 202-013.

Head and neck cancer

Cetuximab was given as weekly infusions until disease progression (PD) or unacceptable toxicity. CTX was given in cycles of 21 days and subjects could receive up to 6 cycles of CTX provided that they did not show PD or unacceptable toxicity. Subjects in the cetuximab + CTX group received a median of 17 cetuximab infusions. A total of 100 subjects continued to receive cetuximab as monotherapy after CTX; the median number of cetuximab monotherapy infusions was 10 (interquartile range: 6–23, range: 1–71).

Overall, the median cumulative cetuximab dose was 4,139 mg/m². The median dose intensity for the initial dose was 399 mg/m². The median dose intensity for the weekly treatment was 241 mg/m² and was very close to the target dose of 250 mg/m². 75.2% of subjects achieved a relative dose intensity of ≥ 90%.

Most common AEs (any grade and grade 3 or 4) in study EMR 62 202-002

99.5% subjects in the cetuximab + CTX group and 96.7% subjects in the CTX group of study EMR 62 202-002 experienced at least one AE (any grade). This high incidence of AEs is not unexpected in this subject population with advanced cancer.

The most frequent AEs occurring in more than 25% of the 219 subjects treated with cetuximab + CTX were nausea, anaemia, vomiting, neutropenia, rash, asthenia, diarrhoea, and anorexia. Rash, acne, acneiform dermatitis, dry skin and anorexia were more common in the cetuximab + CTX group than in the CTX group (difference between treatment groups ≥10%), and these are known side effects of cetuximab. The following AEs were also more frequent in the cetuximab + CTX group, however differences were less pronounced: nausea, diarrhoea, pyrexia, hypocalcaemia, hypomagnesaemia, and conjunctivitis.

A tabular summary of the most frequent AEs of grade 3 or 4 in intensity reported in study EMR 62 202 -002 is provided in Table 40. Grade 3 or 4 AEs were reported in 81.7% subjects in the cetuximab + CTX group and 76.3% in the CTX group. The proportions of subjects who experienced grade 4 AEs were similar (30.6 and 30.7%, respectively).

Table 40: Most common Grade 3 or 4 AEs occurring in ≥5% subjects in either treatment group of study EMR 62 202-002

Preferred term	Number (%) of subjects[a]			
	Grade 3 or 4 events		Grade 4 events	
	Cetuximab+CTX N=219	CTX N=215	Cetuximab+CTX N=219	CTX N=215
Any event	179 (81.7)	164 (76.3)	67 (30.6)	66 (30.7)
Neutropenia	49 (22.4)	50 (23.3)	9 (4.1)	18 (8.4)
Anemia	29 (13.2)	41 (19.1)	2 (0.9)	2 (0.9)
Thrombocytopenia	24 (11.0)	24 (11.2)	0 –	3 (1.4)
Leukopenia	19 (8.7)	19 (8.8)	4 (1.8)	5 (2.3)
Hypokalemia	16 (7.3)	10 (4.7)	2 (0.9)	1 (0.5)
Vomiting	12 (5.5)	6 (2.8)	0 –	0 –
Anorexia	11 (5.0)	3 (1.4)	2 (0.9)	1 (0.5)
Asthenia	11 (5.0)	12 (5.6)	1 (0.5)	1 (0.5)
Hypomagnesemia	11 (5.0)	3 (1.4)	8 (3.7)	1 (0.5)
Rash	11 (5.0)	0 –	0 –	0 –
Dyspnea	9 (4.1)	17 (7.9)	2 (0.9)	5 (2.3)

For grade 3 or 4 AEs that occurred in <5% of subjects, higher frequencies in the cetuximab + CTX group (relative increase >2) were seen for dehydration, diarrhoea, hypocalcaemia, pneumonia, sepsis, and septic shock (see Table 41 for a tabular summary of results).

Table 41: Grade 3 or 4 AEs in <5% subjects of study EMR 62 202-002 with higher frequencies in the cetuximab + CTX group (relative increase >2)

Preferred term	Number (%) of subjects[a]			
	Grade 3 or 4 events		Grade 4 events	
	Cetuximab+CTX N=219	CTX N=215	Cetuximab+CTX N=219	CTX N=215
Dehydration	8 (3.7)	3 (1.4)	1 (0.5)	1 (0.5)
Diarrhea	10 (4.6)	2 (0.9)	0 –	0 –
Hypocalcemia	9 (4.1)	2 (0.9)	5 (2.3)	0 –
Pneumonia	9 (4.1)	4 (1.9)	3 (1.4)	1 (0.5)
Sepsis	6 (2.7)	1 (0.5)	3 (1.4)	1 (0.5)
Septic shock	3 (1.4)	0 –	3 (1.4)	0 –

Source: *see Table 2.7.4-HN2–11; Table 14.3.1-3.3 in Section 5.3.5.1.1-HN2*

CTX=chemotherapy, N=number of subjects

Deaths

In both treatment groups a similar proportion of subjects died on treatment or in the 30 days after last study treatment: 19.2% in the cetuximab + CTX group vs 18.6% in the CTX group. The profile of primary reasons for death differed slightly between the two treatment groups, in that there was a lower frequency of deaths due to disease progression in the cetuximab + CTX group than in the CTX group (4.6 vs 7.0% subjects). In the cetuximab + CTX group frequencies were higher for deaths due to intercurrent or unrelated illnesses (5.5 vs 2.8%) and deaths due to unknown causes (4.6 vs 0.9%). The primary reason for death was not considered to be due to cetuximab-related events in any of the subjects. nine deaths were considered to be due to an AE related to CTX (2 in the cetuximab + CTX group, 7 in the CTX group).

Serious adverse events

SAEs were reported in both treatment groups in a similar proportion of subjects: 50.2% in the cetuximab + CTX group and 47.4% in the CTX group. The profile of SAEs was typical of the underlying disease and the concomitant CTX. Frequencies for most SAEs were comparable between treatment groups.

The following SAEs were more frequent in the cetuximab + CTX group than in the CTX group (relative increase >2): pneumonia (4.6 vs 1.9%), dehydration (4.1 vs 1.4%), sepsis (2.7 vs 0.5%), and septic shock (1.4 vs 0%). The combined incidence of sepsis and septic shock was 4.1 vs 0.5%. It is possible that the longer treatment duration in the cetuximab + CTX group may have contributed to these imbalances.

Withdrawals due to AEs

Cetuximab was discontinued due to AEs in 44 (20.1%) of the 219 subjects in the cetuximab + CTX group; in 28 (12.8%) of these subjects, CTX was also discontinued. The most frequent reason for discontinuation of cetuximab was hypersensitivity (1.8% subjects). The proportion of subjects in whom AEs led to discontinuations of CTX was higher in the cetuximab + CTX group compared to the CTX group: 22.8 vs 17.7% subjects. The most frequent AEs leading to discontinuation of CTX were neutropenia (2.7 vs 0.9%), mucosal inflammation (1.8 vs 0.9%), and general physical health deterioration (1.8 vs 0%).

Special AE categories

Incidences and severities of skin reactions, acne-like rash, IRRs, thrombosis and pulmonary embolism, and cardiac events were consistent with previous findings and the current product information of cetuximab. Severe cardiac AEs occurred more often in the cetuximab + CTX group than in the CTX group (7.3 vs 4.2%). This was mainly due to AEs of 'infarction/ischaemia' occurring primarily during the first 5-FU infusion, as well as 'congestive heart failure' and 'sudden death' due to unknown causes.

In study EMR 62 202-002 the frequency of mucositis was not increased by the addition of cetuximab to CTX, which is in contrast to findings reported in other studies.

The frequency of 'haemorrhages' was not increased by the combination of cetuximab with platinum-based CTX as compared to platinum-based CTX alone.

Laboratory findings

Overall, the changes in laboratory parameters (all grades) observed in study EMR 62 202-002 were consistent with the underlying disease and the administration of cisplatin or carboplatin and 5-FU with or without cetuximab. The addition of cetuximab to the combination of cisplatin or carboplatin with 5-FU did not appear to worsen the known haemotoxicity of

platinum-based CTX but led to a mild to moderate increase in liver enzymes and enhanced the depletion of magnesium and calcium. All these abnormalities except for hypocalcaemia are included in the current product information. Low calcium values were reported in 22.9% subjects of the cetuximab + CTX group and 9.0% of the CTX group, with grade 3 or 4 values in 6.5 vs 1.6% subjects, respectively. The sponsor proposes to include hypocalcaemia in the proposed product information.

Summary of Safety

Analysis of safety data from the randomised, controlled studies conducted in patients with mCRC showed that the safety profile of cetuximab when given as a single agent or in combination with chemotherapy was consistent with the known safety profile of cetuximab. The majority of the most frequent AEs were typical of the underlying cancer disease and/or study medications. With the exception of neutropenia, the AEs that were more common in the cetuximab groups were consistent with the known safety profile of cetuximab as described either in the current product information or in the labelling changes that are proposed by the sponsor.

Nausea, vomiting, and headache have so far been regarded as symptoms of an IRR with expected frequencies of about 15%. However, these AEs occurred at considerably higher frequencies in the cetuximab + BSC group compared to the BSC group of the randomised, controlled study CA225025: nausea 56.9 vs 47.8%, vomiting 37.2 vs 29.2%, headache 33.0 vs 10.6% patients (see Table 42). These findings indicate that nausea, vomiting, and headache should be considered as general side effects of cetuximab treatment and are therefore reassigned to the respective MedDRA SOCs in the proposed product information.

Table 42: Incidences of AEs in the cetuximab groups of studies CA225025, CA225006, and EMR 62 202-013 and frequency categories for the proposed product information

AE category / preferred term	Frequency category for proposed product labeling	% subjects with AE					
		CA225025		CA225006		EMR 62 202-013	
		Cetuximab + BSC	BSC	Cetuximab +irinotecan	Irinotecan	Cetuximab +FOLFIRI	FOLFIRI
Eye disorders							
Blepharitis	Uncommon	0.3	0.0	0.8	0.0	1.7	0.0
Keratitis	Uncommon	0.0	0.0	0.0	0.0	0.3	0.0
Gastrointestinal disorders							
Diarrhea	Common	38.9	20.1	83.9	74.2	62.2	59.1
Nausea	Common	56.9	47.8	58.2	57.4	53.8	59.5
Vomiting	Common	37.2	29.2	42.2	38.5	32.5	38.9
General disorders							
Epistaxis as symptom of mucositis	Common	7.6	1.5	8.8	3.0	7.8	4.5
Fatigue	Common	89.2	75.5	47.2	41.8	31.5	30.7
Weight decrease	Common	3.8	5.1	11.9	7.2	15.2	8.5
Metabolism and nutrition disorders							
Anorexia	Common	67.0	64.6	34.0	25.0	27.8	24.6
Hypomagnesemia *	Very common	53.3	15.2	33.8	8.4	21.5	2.5
Nervous system disorders							
Headache	Common	33.0	10.6	9.7	8.7	9.7	9.1
Respiratory, thoracic and mediastinal disorders							
Pulmonary embolism	Uncommon	NA	NA	1.1	0.2	3.8	2.7
Vascular disorders							
Deep vein thrombosis	Uncommon	NA	NA	1.1	0.2	3.8	2.0

* Data are based on analyses of laboratory assessments performed at scheduled study visits.

NA = not available

Previously, hypomagnesaemia was listed in the Product Information as occurring at an unknown frequency. Further laboratory data from these new randomised, controlled studies indicate that hypomagnesaemia can now be classified as a very common side effect of cetuximab. The proposed product information included this update.

Furthermore, review of AE data from controlled studies revealed that the frequencies of cardiac ischaemia (including myocardial infarction and CHF) and palmar-plantar erythrodysaesthesia syndrome were increased when cetuximab was added to regimens containing infusional 5-FU. These findings are also included in the proposed product information. The product information has been updated to include increased incidence of severe leukopenia or neutropenia in combination with platinum-based chemotherapy. In contrast to the current product information, there were no relevant imbalances in frequencies of dyspnoea between the treatment groups of the randomised, controlled studies. It is therefore proposed to remove dyspnoea as a side effect of cetuximab from the product information.

In study EMR 62 202-002 conducted in patients with head and neck cancer, the profile of AEs, SAEs and the pattern of AEs leading to discontinuation of cetuximab or CTX were consistent with the underlying disease and the known side effects of cetuximab and the chemotherapeutic agents. The higher frequency of individual SAEs and AEs leading to discontinuation in the cetuximab + CTX group in study EMR 62 202- 002 is likely to be related to the longer treatment duration in this group.

Clinical Summary and Conclusions

In this application the sponsor is proposing a new indication for cetuximab in metastatic CRC as follows:

Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, K-RAS wild-type metastatic colorectal cancer

- *in combination with chemotherapy*
- *as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.*

Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck

- *in combination with radiation therapy for locally advanced disease*
- *in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.*

Metastatic colorectal cancer

Cetuximab as single agent

Cetuximab administered as a single agent demonstrated statistically significant and clinically meaningful efficacy benefits in comparison with BSC in the overall population of patients who had failed all standard treatment options in study CA225025. These benefits were more pronounced in the *K-RAS* wild-type subset. Efficacy data supported that single agent cetuximab therefore could be considered as appropriate therapy for patients with *K-RAS* wild-type tumours who have failed multiple lines of standard chemotherapy and who are not eligible for treatment with cetuximab in combination with irinotecan.

Cetuximab in combination with chemotherapy

In study CA225006 cetuximab was used second line with add-on irinotecan. In study CA225006 no effect was seen for the primary endpoint, overall survival. There was however

a treatment effect in terms of PFS. The number of patients in this study with *K-RAS* wild-type was small, and tumour response data were inconsistent making interpretation of the efficacy of cetuximab difficult. Efficacy data from study CA 225006 were inconclusive.

In study EMR 62 202-013 cetuximab was used first line as add-on to FOLFIRI, and efficacy was demonstrated in patients with *K-RAS* wild-type tumours. There was an increase in response rate, and a notable difference in PFS of about two months, which can be considered clinically relevant.

In study EMR 62 202-047 cetuximab was used first line as add-on to FOLFOX-4. In the overall population there was an increased response rate, however results were not impressive in the KRAS wild-type evaluable population. This may have been due to imbalances at baseline, particularly the fact that the control group had better performance status at baseline.

Overall, given the results across the studies, the evaluator considered that cetuximab in combination with chemotherapy and as a single agent has been shown to be efficacious in treatment of patients with *K-RAS* wild type metastatic CRC. The requested proposed indication for cetuximab in this application was considered appropriate.

Head and neck cancer

Study EMR 62 202-002, the pivotal randomised controlled study, met its primary endpoint and demonstrated a statistically significant increase in OS for cetuximab in combination with standard platinum-based CTX in the first line treatment of subjects with R/M SCCHN. The addition of cetuximab to standard CTX led to a clinically meaningful reduction in the risk of death, and an increase of 2.7 months in the median OS time. In addition, cetuximab + CTX showed significant advantages over CTX alone in median PFS time, time to treatment failure, and best overall response rate.

The median OS time of over 10 months achieved with the addition of cetuximab is highly relevant clinically in this patient population that has a poor prognosis with few effective treatments available. Subgroup analyses showed some beneficial effects on OS, PFS, and response of adding cetuximab to platinum/5-FU; however results of subgroup analyses should be interpreted with caution.

Overall the evaluator considered that efficacy of cetuximab in treatment of patients with head and neck cancer had been adequately demonstrated by the data submitted for evaluation.

Analysis of safety data from the randomised, controlled studies conducted in patients with mCRC showed that the safety profile of cetuximab when given as a single agent or in combination with chemotherapy was consistent with the known safety profile of cetuximab. The majority of the most frequent AEs were typical of the underlying cancer disease and/or study medications.

Laboratory data from the randomised, controlled studies indicate that hypomagnesaemia can now be classified as a very common side effect of cetuximab.

Furthermore, a review of AE data from controlled studies revealed that the frequencies of cardiac ischaemia (including myocardial infarction and CHF) and palmar-plantar erythrodysaesthesia syndrome were increased when cetuximab was added to regimens containing infusional 5-FU. These findings are also included in the proposed product information.

It was the opinion of the evaluator that the data presented in this application provided evidence of efficacy of cetuximab for the treatment of mCRC and head and neck cancer. In

addition, considering the safety profile reported in the clinical studies, the risk/benefit ratio for treatment with cetuximab was considered favourable in both therapeutic settings.

The evaluator recommended that the extension of indication for cetuximab should be approved.

V. Pharmacovigilance Findings

A risk management plan was included in the dossier but was not evaluated for this submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality assessment in this submission.

Nonclinical

The submitted published literature provided *in vitro* evidence to support the extension of indications.

An embryofetal development study in monkeys showed increased embryofetal loss at doses six times clinical exposure; however, teratogenicity was not observed.

There were no nonclinical objections to the extension of indications.

Clinical

Colorectal Cancer, EGFR – expressing, Metastatic

Monotherapy

In a randomised open-label controlled trial (CA225025) in patients with EGFR-expressing metastatic CRC who had failed or were intolerant of fluorouracil, irinotecan and oxaliplatin, addition of cetuximab to best supportive care significantly increased progression-free (PFS) and overall survival (OS) by small amounts – 0.1 months for PFS and 1.5 months for OS (Tables 9, 11). The standard cetuximab dose of 400 mg/m^2 initially and then 250 mg/m^2 weekly IV was given. Treatment continued until disease progression. The median age of subjects was 63 years (range 29-88), with most being male (64%).

The impact of *K-RAS* status was evaluated retrospectively in about a third of subjects in each treatment group. In the *K-RAS* evaluable population, cetuximab significantly increased PFS but not OS. The improvement was confined to the wild type *K-RAS* subgroup (59% of *K-RAS* evaluable subjects), median PFS increasing from 1.9 months to 3.6 months (Table 9).

Combination with Chemotherapy (first line)

Concomitant administration of chemotherapy (fluorouracil/folinic acid plus either irinotecan or oxaliplatin) did not significantly affect the pharmacokinetics of cetuximab.

In trial 62 202-013, the addition of cetuximab to FOLFIRI, a standard 1st line regimen consisting of irinotecan, fluorouracil and folinic acid, increased PFS by a small amount (median 0.9 months) at marginal statistical significance (Table 17). Results for OS were not available at the time of submission. The standard cetuximab dose of 400 mg/m^2 initially and

then 250 mg/m^2 weekly IV was given. Treatment continued until disease progression. The median age of subjects was 61 years (range 19-84), with most being male (61%).

The impact of *K-RAS* status was evaluated retrospectively in 30% of subjects in each treatment group. Cetuximab did not significantly affect PFS in the *K-RAS* evaluable population; however, in wild type *K-RAS* (64% of *K-RAS* evaluable subjects), cetuximab increased PFS significantly by a small amount (Table 17). In view of marginal significance overall, this result needs confirmation.

In trial EMR 62 202-047, the addition of cetuximab to FOLFOX4, a standard 1st line regimen consisting of oxaliplatin, fluorouracil and folinic acid, had no effect on PFS (Table 20). Results for OS were not available at the time of submission. The standard cetuximab dose of 400 mg/m^2 initially and then 250 mg/m^2 weekly IV was given. Treatment continued until disease progression. The median age of subjects was 61 years (range 24-82), with most being male (54%).

The impact of *K-RAS* status was evaluated retrospectively in 70% of subjects in each treatment group. Cetuximab did not significantly affect PFS in the *K-RAS* evaluable population; however, in wild type *K-RAS* (58% of *K-RAS* evaluable subjects), cetuximab significantly increased PFS by a small amount (Table 20). In view of lack of effect overall, this result needs confirmation.

Combination with Chemotherapy (second line)

In a randomised open-label trial (CA225006) in subjects with EGFR-expressing metastatic CRC in whom oxaliplatin and a fluoropyrimidine had failed or were not tolerated, the addition of cetuximab to irinotecan monotherapy, a standard 2nd line treatment, did not significantly increase OS (the primary endpoint) but did significantly increase PFS by a small amount (median 1.4 months) (Tables 13, 15). OS was confounded by treatment crossover on progression. The standard cetuximab dose of 400 mg/m^2 initially and then 250 mg/m^2 weekly IV was given. Irinotecan IV was administered every three weeks at 350 mg/m^2 for subjects < 70 years of age and 300 mg/m^2 for subjects ≥ 70 years of age or who had performance status of 2 or had prior pelvic or abdominal irradiation. Treatment continued until disease progression. The median age of subjects was 61 years (range 21-90), with most being male (63%).

The impact of *K-RAS* status was evaluated retrospectively in about a quarter of subjects in each treatment group. Cetuximab did not significantly affect PFS or OS in the *K-RAS* evaluable population or in wild type *K-RAS* (64% of *K-RAS* evaluable subjects).

In study EMR 62 202-013, the addition of cetuximab to FOLFIRI in the first-line treatment of metastatic CRC demonstrated statistically significant and clinical meaningful improvements in median OS time (increase from 20.0 to 23.5 months). In study EMR 62c 202-047, addition of cetuximab to FOLFOX4 increased objective response rate as the primary endpoint but did not reach statistical significance in the overall study population. In patients with *K-RAS* wild-type tumours, cetuximab significantly improved overall response rate and progression-free survival. Addition of cetuximab to FOLFOX led to a clinically meaningful improvement in OS time of over 4 months (i.e. an increase from 18.5 to 22.8 months); the study was not powered to demonstrate significant survival differences.

Safety

The major safety analysis was from trials CA225025, EMR 62 202-013 and CA225006 of 1,526 subjects receiving cetuximab (alone n=288, with irinotecan n=638 and with FOLFIRI

n=600). The median durations of treatment were 8, 14 and 25 weeks for cetuximab alone, with irinotecan and with FOLFIRI respectively.

The incidence of the following events was substantially higher with cetuximab (Tables 32-33):

- General: fatigue, insomnia, pain, headache, fever, infection, asthenia (in combination with irinotecan).
- Gastrointestinal: diarrhoea, anorexia, stomatitis, mucositis, abdominal pain (in combination with irinotecan).
- Metabolism & Nutrition: hypokalaemia (in combination with irinotecan), hypomagnesaemia, weight decrease (the last two in combination with FOLFIRI).
- Respiratory: cough.
- Skin & Subcutaneous: rash, exfoliative rash, dry skin, pruritus, acne, acneiform dermatitis, nail changes, paronychia, skin fissures, palmar-plantar erythrodysaesthesia (in combination with FOLFIRI).
- Haematological: epistaxis, neutropenia (both in combination with irinotecan).
- Eye*:* conjunctivitis.
- Musculoskeletal: back pain (in combination with irinotecan).

There was an increased incidence of cardiac and thrombotic events with cetuximab in trials CA225006 (combination with irinotecan) and EMR 62 202-013 (combination with FOLFIRI); however, the numbers were small.

In the other major CRC trial EMR 62 202-047, 170 subjects received cetuximab in combination with FOLFOX4 for a median duration of 22 weeks. The incidence of following events was higher with cetuximab:

- General: fatigue, fever.
- Gastrointestinal: diarrhoea, anorexia, vomiting, constipation, stomatitis, mucositis.
- Metabolism & Nutrition: weight decrease.
- Neurological: paraesthesia (difference in incidence ≥ 10% between Cetuximab+FOLFOX4 and FOLFOX4 groups).
- Skin & Subcutaneous: rash (52% vs 2%), dry skin, acneiform dermatitis, paronychia (in all cases, difference in incidence≥ 10% between Cetuximab+FOLFOX4 and FOLFOX4 groups), palmar-plantar erythrodysaesthesia.
- Eye*:* conjunctivitis.

A pooled analysis of safety in the *K-RAS* wild type population of trials CA225025 (monotherapy), EMR 62 202-013 (combination with FOLFIRI), EMR 62 202-047 (combination with FOLFOX4) and CA225006 (combination with irinotecan 2nd line) representing about one-third of the total safety population provided safety information for the proposed *K-RAS* wild type metastatic CRC indication.

Generally, adverse event profiles were similar in the *K-RAS* wild type population and the overall safety population. However, a higher incidence of neutropenia was noted in the *K-RAS* wild type population given cetuximab in combination with chemotherapy compared with chemotherapy alone. This higher incidence was explained by longer treatment duration and greater exposure in view of better efficacy in the *K-RAS* wild type population.

Head and Neck Cancer, Recurrent or Metastatic

Combination with Platinum-Based Chemotherapy

There was one trial of cetuximab in combination with platinum-based chemotherapy for first line treatment of recurrent and/or metastatic SCCHN – trial EMR 62 202-002 or EXTREME. In this randomised open-label trial, the addition of cetuximab to platinum-based chemotherapy, the standard of care, significantly increased PFS and OS by a median 2.3 and 2.7 months respectively (Tables 26, 27). The standard cetuximab dose of 400 mg/m^2 initially and then 250 mg/m^2 weekly IV was given. Platinum-based chemotherapy consisted of either cisplatin or carboplatin in combination with fluorouracil in 3-week cycles for up to six cycles. Cetuximab treatment continued until disease progression. The median age of subjects was 56 years (interquartile range 51-62), with most being male (90%).

Safety

In trial EMR 62 202-002, 219 subjects received cetuximab in combination with platinum-based chemotherapy for a median 17 weeks and then cetuximab alone for another 10 weeks. Safety data were provided only for severe adverse events. The incidence of the following severe events was at least two percent higher with cetuximab (Tables 40, 41):

- General: sepsis, septic shock.
- Gastrointestinal: vomiting, diarrhoea, anorexia.
- Metabolism & Nutrition: dehydration, hypokalaemia, hypomagnesaemia, hypocalcaemia.
- Respiratory: pneumonia.
- Skin & Subcutaneous: rash.

Although no severe cardiac adverse events were listed in Tables 40 and 41, as a group these events increased after the addition of cetuximab to chemotherapy (7.3% vs 4.2%). Events included infarction, ischaemia, congestive cardiac failure and sudden death.

The evaluator recommended approval.

Risk-Benefit Analysis

Trial CA225025 supports third line for monotherapy in metastatic CRC and restriction to patients with wild type *K-RAS*.

Trial 62 202-013 supports combination with FOLFIRI in first line treatment of wild type *K-RAS* metastatic CRC based on progression-free survival and overall survival. In the wild type *K-RAS* subgroup, progression-free survival was increased by a statistically significant median 1.2 months. In view of marginal statistical significance in the overall population, the benefit in wild type *K-RAS* needs confirmation. The sponsor was requested to provide results for overall survival if available in their Pre-ADEC Response. Trial 62 202-047 supports combination with FOLFOX4 in first line treatment of wild type *K-RAS* metastatic CRC based on progression-free survival. The benefit was 0.5 months increase in median progression-free survival in the *K-RAS* wild-type population in the original submitted data. and needs confirmation in view of the lack of benefit in the overall population. The sponsor was requested to provide results for overall survival if available in their pre-ADEC Response. Updated data reviewed by the Delegate and ADEC revealed a 1.1 month increase in median PFS.

Updated analyses for the studies were provided by the sponsor and reviewed by the Delegate and ADEC. These data included overall survival (OS) data for the pivotal studies in this dossier as presented at the recent European Society for Medical Oncology meeting. The OS data are supportive of the results seen with progression-free survival (PFS) and objective response rate (ORR) data included in the dossier. The addition of cetuximab to FOLFIRI prolonged median OS time from 20.0 to 23.5 months (HR 0.796, p=0.0094) compared with

patients receiving FOLFIRI alone. The sponsor further noted that this was the first time in 1st line mCRC that the addition of an EGFR antibody therapy to a standard continuous 5-FU-based regimen resulted in an overall survival benefit. In the smaller randomised phase II trial EMR 62 202-047, median OS time was prolonged by more than four months (18.5 to 22.8 months) compared to patients receiving FOLFOX alone in the K-RAS wild-type population. The clinical trials section of the proposed Product Information document was updated with these new data.

Two uncontrolled trials of cetuximab with irinotecan-based regimens were supportive of benefit in progression-free survival. In the controlled second line trial of cetuximab with irinotecan (CA225006), it was noteworthy that no significant effect was seen in wild-type *K-RAS* subjects. This was most likely due to imbalances in confounders in the treatment groups as a result of loss of randomisation in the *K-RAS* analysis.

In monotherapy, adverse effects were consistent with the known cetuximab profile. In combination therapy, the incidence of adverse effects was increased with additive effects seen for specific adverse effects. For example, the incidence of cardiac (myocardial ischemia, infarction and CHF) and thrombotic events (DVT and pulmonary embolism) was increased when cetuximab was used in combination with irinotecan or FOLFIRI, palmar-plantar erythrodysaesthesia was increased with cetuximab and FOLFIRI and paraesthesia was substantially increased with cetuximab and FOLFOX4. The Delegate recommended improvements to the description of the adverse effects of combination treatment in the product information.

If there is support from the overall survival data of trials 62 202-013 and 62 202-047, the Delegate was inclined to allow the general "with chemotherapy" first line indication. Even though cetuximab has only been tested with FOLFIRI and FOLFOX4 in controlled trials for the first line indication, it is likely to add benefit to other chemotherapy regimens. The product information warns prescribers to consider respective product information when use of cetuximab with other chemotherapy is being considered. This is important in predicting the toxicity of the proposed drug combination. The general indication will allow flexibility with frequently changing chemotherapy regimens.

Trial EMR 62 202-002 supports extension of cetuximab to recurrent and/or metastatic SCCHN in combination with platinum-based therapy and fluorouracil. The incidence of adverse effects was increased after the addition of cetuximab, notably increased severe gastrointestinal and metabolic events. Cardiac toxicity also appeared to be increased with cetuximab and is most likely related to combination with fluorouracil. An appropriate statement has been included in the proposed product information.

During the evaluation, the sponsor notified the TGA of a safety issue in a trial of cetuximab in combination with capecitabine and cisplatin in advanced gastric adenocarcinoma. The cardiac events in this trial appear similar to those experienced in trial EMR 62 202-002 in SCCHN and most likely relate to use of capecitabine in combination with cetuximab. Currently, the product information only mentions cetuximab with infusional 5-fluorouracil as being responsible for increased cardiac events. The Delegate recommended that capecitabine also be mentioned. The sponsor included the most recent follow-up safety issue report with their pre-ADEC response. The report indicated that the Data Safety Monitoring Board recommended continuation of the trial with additional cardiac monitoring of both treatment arms to be implemented.

The Delegate recommended approval of the extension of indications to:

Treatment of patients with epidermal growth factor receptor (EGFR)-expressing, K-RAS

wild-type metastatic colorectal cancer

- *In combination with chemotherapy*
- *As a single agent in patients who have failed or are intolerant to oxaliplatin-based therapy and irinotecan-based therapy and*

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,*

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

In making this recommendation, the ADEC noted that the studies submitted for evaluation demonstrated statistically significant improvements in PFS for first and third line treatment for patients with EGFR expressing K- RAS wild type CRC, although there was inconsistent improvement in overall survival (OS). In second line treatment, the improvement in progression free survival (PFS) was in favour of cetuximab but not statistically significant. The Committee further noted that the incidence of adverse effects was worse for combination therapy, therefore endorsed the recommendation by the Delegate to improve descriptions of the adverse effects of combination treatment in the product information.

The Committee agreed with the Delegate that the Trial EMR 62 202-002 supports the extension of indication to SCCHN in combination with platinum based chemotherapy for recurrent/metastatic disease. The study revealed a 2.3 (3.3 to 5.6) and 2.7 (7.4 to 10.1) month improvement in PFS and OS, respectively that were statistically significant and favoured the cetuximab patients. The ADEC noted that there were mild increases in toxicity associated with the addition of cetuximab.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Erbitux solution for injection vial containing cetuximab 50mg/10mL, 100mg/20mL, 250mg/50mL and 500mg/100mL for the new indication for

the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, K-RAS wild-type metastatic colorectal cancer (CRC)

- *in combination with chemotherapy*
- *as a single agent in patients who have failed or are intolerant to oxaliplatin based therapy and irinotecan-based therapy.*

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.*

Attachment 1. Product Information

Erbitux®5 mg/mL

cetuximab (rmc)

PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient in Erbitux is cetuximab (rmc).

DESCRIPTION

Cetuximab is a chimaeric monoclonal antibody of the immunoglobulin G_1 (IgG_1) subclass, produced in mammalian cell culture by mouse myeloma cells (Sp2/0). It is obtained by attaching the variable regions of the murine monoclonal antibody M225 against epidermal growth factor receptor (EGFR) to constant regions of the human IgG_1. The molecular weight is approximately 152 kDa.

Erbitux 5 mg/mL is a sterile, preservative-free, colourless solution that is intended for intravenous infusion. The pH of the solution is in the range of 5.3 – 5.7 and the osmolality is between 280 and 350 mOsm/kg.

Erbitux 5 mg/mL contains 5 mg cetuximab per millilitre of solution. Erbitux 5mg/mL is available in the following vial sizes: 10 ml, 20 mL, 50 mL or 100 mL of solution. The solution also contains the following inactive ingredients: sodium chloride, glycine, polysorbate 80, citric acid monohydrate, sodium hydroxide and water for injections.

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC Code: L01XC06.

PHARMACOLOGY

Cetuximab binds to the EGFR with an affinity that is approximately 5 to 10 fold higher than that of endogenous ligands. Cetuximab blocks binding of endogenous EGFR ligands resulting in inhibition of the function of the receptor. It induces the internalisation of the EGFR, which could lead to down-regulation of EGFR.

Cetuximab does not bind to other receptors belonging to the HER family (Erb B2, Erb B3, Erb B4).

The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicles. Over-expression of EGFR is also detected in many human cancers, including those of the colon and rectum. The contribution of the EGFR signalling pathways in the development of malignancy of certain tumours has been extensively documented in *in vitro* and *in vivo* studies. EGFR signalling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis. Expression of EGFR and its cognate ligands in tumours has been correlated with poor prognosis, decreased survival, and/or increased metastases.

The protein product of the proto-oncogene *K-RAS* (Kirsten rat sarcoma 2 viral oncogene homologue) is a central down-stream signal-transducer of EGFR. In tumours, activation of K-RAS by EGFR contributes to EGFR-mediated increased proliferation, survival and the production of pro-angiogenic factors.

K-RAS is one of the most frequently activated oncogenes in human cancers. Mutations of the *K-RAS* gene at certain hot-spots (mainly codons 12 and 13) result in constitutive activation of the K-RAS protein independently of EGFR signalling.

Pharmacodynamics

In both *in vitro* and *in vivo* assays, cetuximab inhibits the proliferation and induces apoptosis of human tumour cells that express EGFR, but it has no anti-tumour effects in human tumour xenografts that do not express EGFR. *In vitro* cetuximab inhibits the production of angiogenic factors by tumour cells and blocks endothelial cell migration. *In vivo* cetuximab inhibits expression of angiogenic factors by tumour cells and causes a reduction in tumour neo-vascularisation and metastasis.

Cetuximab is a mediator of antibody-dependent cellular cytotoxicity *in vitro*, eliciting increased cytotoxicity of EGFR-expressing tumour cells in the presence of immune effector cells. Therefore, in addition to its inhibitory function on receptor signalling, patients with EGFR-expressing tumours may also benefit from this immune stimulatory effect of cetuximab.

Immunogenicity

The development of human anti-chimeric antibodies (HACA) is a class-specific effect of monoclonal chimeric antibodies. Measurable HACA titres developed in 3.4% of the patients studied. No conclusive data on the neutralising effect of HACAs on cetuximab is available to date. The appearance of HACA did not correlate with the occurrence of hypersensitivity reactions or any other undesirable effects of cetuximab.

Pharmacokinetics

Cetuximab pharmacokinetics were studied in clinical studies where cetuximab was administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy. Intravenous infusions of cetuximab exhibited non-linear pharmacokinetics at weekly doses ranging from 5 to 500 mg/m^2 body surface area. Cetuximab clearance decreased with increasing doses to 200 mg/m^2, then appeared to plateau.

When cetuximab was administered at an initial dose of 400 mg/m^2 body surface area, the mean volume of distribution was approximately equivalent to the vascular space (2.9 L/m^2 with a range of 1.5 to 6.2 L/m^2). The mean C_{max} (± SD) was 185±55 microgram/mL. The mean clearance was 0.022 L/h per m^2 body surface area. Cetuximab has a long elimination half-life with values ranging from 70 to 100 hours at the target dose.

Cetuximab serum concentrations reached stable levels after 3 weeks of cetuximab monotherapy. Mean peak cetuximab concentrations were 155.8 microgram/mL in week 3 and 151.6 microgram/mL in week 8, whereas the corresponding mean trough concentrations were 41.3 and 55.4 microgram/mL, respectively. In a study of cetuximab administered in combination with irinotecan, the mean cetuximab trough levels were 50.0 microgram/mL in week 12 and 49.4 microgram/mL in week 36.

Several pathways have been described that may contribute to the metabolism of antibodies. All of these pathways involve the biodegradation of the antibody to smaller molecules, *i.e.*, small peptides or amino acids.

An integrated analysis across all clinical studies showed that the pharmacokinetic characteristics of cetuximab are not influenced by race, age, gender, renal or hepatic status. However, only patients with adequate renal and hepatic function have been investigated to date (serum creatinine £ 1.5 fold, transaminases £ 5 fold and bilirubin £ 1.5 fold the upper limit of normal).

CLINICAL TRIALS

Colorectal Cancer

A diagnostic assay (EGFR pharmDx^{TM}) was used for immunohistochemical detection of EGFR expression in tumour material. Approximately 75% of the patients with metastatic colorectal cancer screened for clinical studies had an EGFR-expressing tumour and were therefore considered eligible for cetuximab treatment.

In metastatic colorectal cancer, the incidence of *K-RAS* mutations is in the range of 30 - 50%. Recent data demonstrate that patients with *K-RAS* wild-type metastatic colorectal cancer have a significantly higher chance of benefiting from treatment with cetuximab or a combination of cetuximab and chemotherapy.

Cetuximab as a single agent or in combination with chemotherapy was investigated in 5 randomised controlled clinical studies and several supportive studies. The 5 randomised studies investigated a total of 3734 patients with metastatic colorectal cancer, in whom EGFR expression was detectable and who had an ECOG performance status of≤ 2. The majority of patients included had an ECOG performance status of≤ 1. In all studies, cetuximab was administered as described in DOSAGE AND ADMINISTRATION.

The *K-RAS* status was recognised as a predictive factor for treatment with cetuximab in 4 of the randomised controlled studies. *K-RAS* mutational status was available for 2072 patients. Only in study EMR 62 202-007 was an analysis not possible.

Cetuximab in combination with chemotherapy

EMR 62 202-013 (CRYSTAL): This randomised, open-label, Phase III study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of cetuximab and irinotecan plus infusional fluorouracil/folinic acid (5-FU/FA) (599 patients) to the same chemotherapy alone (599 patients). The chemotherapy regimen was the FOLFIRI regimen. The median age of subjects was 61 years (range 19-84), with most being male (61%).

Addition of cetuximab to FOLFIRI increased median progression-free survival by 0.9 months - hazard ratio 0.85, p=0.05 - in the overall population. The impact of *K-RAS* status was evaluated subsequently in 89% of patients. The significant effect in terms of progression-free survival was more pronounced in patients with *K-RAS* wild type tumours (increase by 1.5 months, hazard ratio 0.70; p = 0.001). This effect translated into an increase of median overall survival in the *K-RAS* wild type population of 3.5 months. Cetuximab significantly increased objective response rate (see Table 1).

Table 1: Study EMR 62 202-013: Efficacy Results

Variable/ statistic	Overall population		*K-RAS* wild-type population	
	Cetuximab plus FOLFIRI	FOLFIRI	Cetuximab plus FOLFIRI	FOLFIRI
	(N=599)	(N=599)	(N=316)	(N=350)
OS				
Hazard Ratio (95% CI)	0.88 (0.77, 0.10)		0.80 (0.67, 0.95)	
p-value	0.04		0.01	
Median (months), (95% CI)	19.9 (16.7, 19.8)	18.6 (18.5, 21.3)	23.5 (21.2, 26.3)	20.0 (17.4, 21.7)
ORR				
% (95% CI)	46.9 (42.9, 51.0)	38.7 (34.8, 42.8)	57.3 (51.6, 62.8)	39.7 (34.6, 45.1)
p-value	0.004		< 0.0001	
PFS				
Hazard Ratio (95% CI)	0.85 (0.73, 0.10)		0.70 (0.56, 0.87)	
p-value	0.05		0.001	
Median (months, 95% CI)	8.9 (8.0, 9.5)	8.0 (7.6, 9.0)	9.9 (9.0, 11.3)	8.4 (7.4, 9.2)

CI = confidence interval, FOLFIRI = irinotecan plus infusional 5-FU/FA, ORR = objective response rate (patients with complete response or partial response), OS = overall survival, PFS = progression-free survival.

EMR 62 202-047 (OPUS): This randomised, open-label study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of cetuximab and oxaliplatin plus infusional fluorouracil/folinic acid (5-FU/FA) (169 patients) to the same chemotherapy alone (168 patients). The chemotherapy regimen was the FOLFOX4 regimen. The median age of subjects was 61 years (range 24-82), with most being male (54%).

Addition of cetuximab to FOLFOX4 increased objective response rate as the primary endpoint, but did not reach statistical significance in the overall study population. The impact of *K-RAS* status was evaluated subsequently in 93% of patients. In patients with *K-RAS* wild-type tumours (57% of *K-RAS* evaluable patients), cetuximab significantly improved overall response rate and progression-free survival. Overall survival was also improved but not significantly (see Table 2).

Table 2: Study EMR 62 202-047: Efficacy Results

Variable/ statistic	Overall population		*K-RAS* wild-type population	
	Cetuximab plus FOLFOX4	FOLFOX4	Cetuximab plus FOLFOX4	FOLFOX4
	(N=169)	(N=168)	(N=82)	(N=97)
OS				
Hazard Ratio (95% CI)	1.02 (0.79, 1.30)		0.86 (0.60, 1.22)	
p-value	0.91		0.39	
Median (months, 95% CI	18.3 (14.8, 20.4)	18.0 (16.7, 21.8)	22.8 (19.3, 25.9)	18.5 (16.4, 22.6)
ORR				
% (95% CI)	46.2 (38.5, 54.0)	39.9 (32.4, 47.7)	57.3 (45.9, 68.2)	34.0 (24.7, 44.3)
p-value	0.24		0.003	
PFS				
Hazard Ratio (95% CI)	0.93 (0.70, 1.23)		0.57 (0.38, 0.86)	
p-value	0.62		0.006	
Median (months, 95% CI)	7.2 (5.6, 7.7)	7.2 (6.0, 7.8)	8.3 (7.2, 12.0)	7.2 (5.6, 7.4)

CI = confidence interval, FOLFOX4 = oxaliplatin plus infusional 5-FU/FA, ORR = objective response rate (patients with complete response or partial response), OS = overall survival, PFS = progression-free survival

· CA225006 (EPIC): This randomised, open-label study in patients with metastatic colorectal cancer who had received initial combination treatment with oxaliplatin plus fluoropyrimidine for metastatic disease compared the combination of cetuximab and irinotecan (648 patients) with irinotecan alone (650 patients).

A significant difference in overall survival time could not be shown in this study. Following disease progression, treatment with EGFR-targeting agents was initiated in 50% of patients in the irinotecan-alone arm, which most likely impacted survival results. Objective response rate and progression free survival time were significantly improved with cetuximab. However, as no independent review of imaging data was conducted, these results have to be interpreted with caution. The impact of *K-RAS* status was evaluated retrospectively in 23% of subjects. Unlike in the other trials, cetuximab did not have a significant impact on either progression-free survival or overall survival in wild-type *K-RAS* disease. However, the results should be treated with caution due to the small number of subjects.

· EMR 62 202-007 (BOND): This randomised study in patients with metastatic colorectal cancer after failure of irinotecan-based treatment for metastatic disease as the last treatment before study entry compared the combination of cetuximab and irinotecan (218 patients) with cetuximab monotherapy (111 patients).

Addition of irinotecan to cetuximab increased median progression-free survival from 1.5 months to 4.1 months – hazard ratio 0.54, 95% CI [0.42, 0.71] - and significantly increased the objective response rate. The improvement in overall survival time did not reach statistical significance; however, in the follow-up treatment, nearly 50% of patients in the cetuximab only arm received a combination of cetuximab and irinotecan after progression of disease, which may have influenced overall survival time.

Cetuximab as a single agent

· CA225025 (NCIC CTG CO.17): This randomised, open-label study in patients with metastatic colorectal cancer who had received prior oxaliplatin-, irinotecan- and fluoropyrimidine-based treatment for metastatic disease compared the addition of cetuximab as a single agent to best supportive care (BSC) (287 patients) with BSC alone (285 patients). The median age of subjects was 63 years (range 29-88), with most being male (64%).

Addition of cetuximab to BSC (best supportive care) increased overall survival time significantly by 1.5 months from 4.6 to 6.1 months - hazard ratio 0.77, 95% CI [0.64, 0.92]) - while median progression-free survival increased from 1.8 months to 1.9 months - hazard ratio 0.676, 95% CI [0.57, 0.80], in the overall population. The impact of *K-RAS* status was evaluated subsequently in 69% of patients. The benefits of cetuximab were enhanced in the *K-RAS* wild-type population (Table 3).

Table 3: Study CA225025: Efficacy Results

Variable/ statistic	Overall population		*K-RAS* wild-type population	
	Cetuximab plus BSC (N=287)	BSC (N=285)	Cetuximab plus BSC (N=117)	BSC (N=113)
OS				
Median (months, 95% CI	6.1 (5.4, 6.7)	4.6 (4.2, 4.9)	9.5 (7.7, 10.3)	4.8 (4.2, 5.5)
Hazard Ratio (95% CI)	0.77 (0.64, 0.92)		0.55 (0.41, 0.75)	
p-value	0.005		<0.0001	
ORR				
% (95% CI)	6.6 (4.0, 10.2)	0 (-) (-)	12.8 (7.4, 20.3)	0 (-) (-)
p-value	<0.0001		<0.0001	
PFS				
Median (months, 95% CI	1.9 (1.8, 2.1)	1.8 (1.8, 1.9)	3.7 (3.1, 5.1)	1.9 (1.8, 2.0)
Hazard Ratio (95% CI)	0.68 (0.57, 0.80)		0.40 (0.30, 0.54)	
p-value	<0.0001		<0.0001	

CI = confidence interval, BSC = best supportive care, ORR = objective response rate (patients with complete response or partial response), OS = overall survival, PFS = progression-free survival

Squamous cell cancer of the head and neck

Immunohistochemical detection of EGFR expression was not performed at study entry since more than 90% of patients with squamous cell cancer of the head and neck have tumours that express EGFR.

Cetuximab in combination with radiation therapy for locally advanced disease

· EMR 62 202-006: This randomised study compared the combination of cetuximab and radiation therapy (211 patients) with radiation therapy alone (213 patients) in patients

with locally advanced squamous cell carcinoma of the head and neck. Cetuximab was started one week before radiation therapy and administered at the doses described in the DOSAGE AND ADMINISTRATION section until the end of the radiation therapy period.

The efficacy data generated in this study are summarised in the table below:

Table 4: Study EMR 62 202-006: Efficacy Results

Variable/ statistic	**Radiation therapy alone**		**Radiation therapy + cetuximab**		*Treatment comparison*	
	(N=213)		(N=211)		p-value	Hazard ratio (95% CI)
Locoregional control*, months						
Median (95% CI)	14.9	(11.8, 19.9)	24.4	(15.7, 45.1)	0.005	0.68 (0.52, 0.89)
Overall Survival time, months						
Median (95% CI)	29.3	(20.6, 42.8)	49.0	(32.8, 62.6+)	0.032	0.74 (0.56, 0.97)

CI = confidence interval; a'+' denotes that the upper bound limit had not been reached at cut-off.

*Locoregional control = absence of disease recurrence/progression or death.

Subgroup analyses indicated that patients with a good prognosis as indicated by tumour stage (stage II/III vs stage IV), baseline Karnofsky performance status (KPS: 90 – 100% vs 50 – 80%) and age (<65 years vs ≥65 years) had a more pronounced benefit when cetuximab was added to radiation therapy. No clinical benefit could be demonstrated in patients with KPS ≤ 80 and aged 65 years or older.

The use of cetuximab in combination with chemo-radiotherapy has so far not been adequately investigated. Thus, a benefit-risk ratio has not been established.

Cetuximab in combination with platinum-based chemotherapy in recurrent and/or metastatic disease

- EMR 62 202-002 (EXTREME): This randomised, open-label study in patients with recurrent and/or metastatic squamous cell cancer of the head and neck who had not received prior chemotherapy for recurrent and/or metastatic disease compared the combination of cetuximab and cisplatin or carboplatin plus infusional fluorouracil (222 patients) to the same chemotherapy alone (220 patients). Patients may have received prior chemotherapy for locally advanced disease. The median age of subjects was 56 years (interquartile range 51-62), with most being male (90%). Treatment in the cetuximab arm consisted of up to 6 cycles of platinum-based chemotherapy in combination with cetuximab followed by cetuximab as maintenance therapy until disease progression.

  Addition of cetuximab to platinum-based chemotherapy significantly increased progression-free and overall survival by a median 2.3 and 2.7 months, respectively (Table 5).

Table 5: Study EMR 62 202-002: Efficacy Results

Variable/ statistic	Cetuximab + CTX (N=222)		CTX (N=220)
OS			
months, median (95% CI)	10.1 (8.6, 11.2)		7.4 (6.4, 8.3)
Hazard Ratio (95% CI)		0.80 (0.64, 0.99)	
p-value		0.036	
PFS			
months, median (95% CI)	5.6 (5.0, 6.0)		3.3 (2.9, 4.3)
Hazard Ratio (95% CI)		0.54 (0.43, 0.67)	
p-value		<0.0001	
ORR			
% (95% CI)	35.6 (29.3, 42.3)		19.5 (14.5, 25.4)
p-value		0.0001	

CI = confidence interval, CTX = platinum-based chemotherapy, ORR = objective response rate, OS = overall survival time, PFS = progression-free survival

Patients with a good prognosis as indicated by tumour stage, baseline Karnofsky performance status (KPS) and age (< 65 years vs ≥ 65 years) had a more pronounced benefit when cetuximab was added to platinum-based chemotherapy. In contrast to progression-free survival time, no benefit in overall survival time could be demonstrated in patients with KPS ≤ 80 who were 65 years of age or older.

INDICATIONS

Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, *K-RAS* wild-type metastatic colorectal cancer

- in combination with chemotherapy
- as a single agent in patients who have failed or are intolerant to oxaliplatin-based therapy and irinotecan-based therapy.

Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck

- in combination with radiation therapy for locally advanced disease
- in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.

CONTRAINDICATIONS

Erbitux is contraindicated in patients with known severe (grade 3 or 4) hypersensitivity reactions to cetuximab.

Before initiation of combination treatment, contraindications for concomitantly used chemotherapeutic agents (refer to their product information documents) or radiation therapy must be considered.

PRECAUTIONS

Infusion-related reactions

Prior to the first infusion, patients must receive premedication with an antihistamine and a corticosteroid. Similar premedication is recommended for all subsequent infusions. Cetuximab infusion must be carried out in an area where resuscitation equipment and agents are available.

If a patient experiences mild to moderate infusion-related reactions, the infusion rate should be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions (see DOSAGE AND ADMINISTRATION).

Severe infusion-related reactions have been reported in patients treated with cetuximab (see ADVERSE EFFECTS). Symptoms usually occurred during the initial infusion and up to 1 hour after the end of infusion, but may occur after several hours or with subsequent infusions. It is recommended to warn patients of the possibility of such a late onset and instruct them to contact their physician if symptoms of an infusion-related reaction occur. Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment.

Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease.

Respiratory Disorders

If patients develop dyspnoea during the course of cetuximab treatment, it is recommended to investigate them for signs of progressive pulmonary disorders as appropriate. In the event of acute onset or worsening dyspnoea, cetuximab therapy should be interrupted.

Individual cases of interstitial lung disorders of unknown causal relationship to cetuximab have been reported. If interstitial lung disease is diagnosed, cetuximab must be discontinued and the patient treated appropriately.

Skin Reactions

If a patient experiences a severe skin reaction (≥ grade 3; US National Cancer Institute – Common Toxicity Criteria, NCI-CTC), cetuximab therapy should be interrupted. Treatment may be resumed if the reaction has resolved to grade 2 (see ADVERSE EFFECTS and DOSAGE AND ADMINISTRATION sections for further information on handling skin reactions).

Electrolyte Disturbances

Progressively decreasing serum magnesium levels occur frequently and may lead to severe hypomagnesaemia. Hypomagnesaemia is reversible following discontinuation of cetuximab. In addition, hypokalaemia may develop sometimes as a consequence of diarrhoea. Hypocalcaemia may also occur; in particular, in combination with platinum-based chemotherapy, the frequency of severe hypocalcaemia may be increased.

Measurement of serum electrolyte levels is recommended prior to and periodically during cetuximab treatment. Electrolyte replacement is recommended, as appropriate.

Hepatic and Renal Impairment

Only patients with adequate hepatic and renal function have been investigated to date (serum creatinine £ 1.5 fold, transaminases £ 5 fold and bilirubin £ 1.5 fold the upper limit of normal).

Haematological

Cetuximab has not been studied in patients presenting with an abnormal haematological profile as defined by one or more of the following:

haemoglobin < 90 g/L

leukocyte count < 3 x 10^9/L

absolute neutrophil count < 1.5 x 10^9/L

platelet count < 100 x 10^9/L

Carcinogenicity

No long term animal studies have been performed to establish the carcinogenic potential of cetuximab.

Genotoxicity

Cetuximab was not genotoxic in an *in vitro* microbial assay or an *in vivo* rat micronucleus assay.

Effects on Fertility

Fertility has not been specifically examined in animal studies. However, female cynomolgus monkeys given IV maintenance doses of 7.5 - 75 mg/kg/week (approx. 1-17 times the recommended maintenance dose in humans based on serum AUC values) showed impairment of menstrual cycling.

Wound Healing

To date, no data on the effect of cetuximab on wound healing is available. However, in preclinical wound healing models, EGFR selective tyrosine kinase inhibitors were shown to retard wound healing.

Use in Pregnancy

Pregnancy Category D

The epidermal growth factor receptor (EGFR) is involved in foetal development. Observations in animals are indicative of a placental transfer of cetuximab, and other IgG_1 antibodies have been found to cross the placental barrier. An embryo-foetal toxicity study in cynomolgus monkeys revealed no evidence of teratogenicity at exposures (AUC) up to 16 times that anticipated clinically. However, a dose-dependent, increased incidence of abortion was observed, with a NOAEL of 7.5 mg/kg/week (exposure (AUC) similar to clinical exposure). No data regarding use in pregnant women are available. It is recommended that Erbitux should not be administered during pregnancy. Adequate contraception should be maintained in women of child-bearing potential during treatment with Erbitux and for 2 months after the last dose.

Use in Lactation

Studies in animals or sufficient data from lactating women are not available. It is recommended that women do not breast-feed during treatment with Erbitux and for 2 months after the last dose.

Paediatric Use

The safety and effectiveness of cetuximab in paediatric patients have not been established.

Use in the Elderly

No dose adjustment is required in the elderly but experience is limited in patients 75 years of age and above. However, elderly patients, especially those with a history of cardiac disease, are at greater risk of adverse effects than younger patients and patients without a history of cardiac disease (see ADVERSE EFFECTS).

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

Interactions with Other Medicines

Physicians are advised to consider the toxicities of the individual components of therapy and to monitor patients receiving cetuximab in combination with other therapies closely.

When cetuximab is used in combination with chemo- or radiotherapy, patients may experience an increased incidence of specific adverse reactions (see also ADVERSE EFFECTS - Combination Treatment):

In combination with infusional fluorouracil or capecitabine, the frequency of cardiac ischaemia including myocardial infarction and congestive heart failure as well as the frequency of hand-foot syndrome (palmar-plantar erythrodysaesthesia) were increased compared to that with infusional fluorouracil.

In combination with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia may be increased, and thus may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia and sepsis compared to platinum-based chemotherapy alone. Patients with skin lesions, mucositis or diarrhoea that may facilitate the development of infections are at particular risk.

In combination with local radiation therapy of the head and neck area, additional undesirable effects were those typical of radiation therapy (such as mucositis, radiation dermatitis, dysphagia or leukopenia, mainly presenting as lymphocytopenia), see ADVERSE EFFECTS – Combination treatment.

In squamous cell cancer of the head and neck, use of cetuximab in combination with chemoradiotherapy has not been adequately investigated. Therefore benefits and risks of this combination are not known.

There is limited experience in the use of cetuximab in combination with radiation therapy in colorectal cancer.

ADVERSE EFFECTS

The following definitions apply to the frequency terminology used hereafter:

Very common (³ 1/10)
Common (³ 1/100 to < 1/10)
Uncommon (³ 1/1,000 to < 1/100)
Rare (³ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Frequency not known (cannot be estimated from the available data)

An asterisk (*) indicates that additional information on the respective undesirable effect is provided below the table.

Nervous system disorders

Common: Headache

Eye disorders

Common: Conjunctivitis
Uncommon: Blepharitis, keratitis

Respiratory, thoracic and mediastinal disorders

Uncommon: Pulmonary embolism

Gastrointestinal disorders

Common:	Diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders

Very common:	Skin reactions*
Common:	Hand-foot syndrome in combination with fluorouracil (see Combination Treatment)
Frequency not known:	Superinfection of skin lesions*

Metabolism and nutrition disorders

Very common:	Hypomagnesaemia (see PRECAUTIONS)
Common:	Dehydration, in particular, secondary to diarrhoea or mucositis; hypocalcaemia (see PRECAUTIONS); anorexia which may lead to weight decrease; hypokalaemia (in combination with irinotecan or platinum/fluorouracil combinations)

Vascular disorders

Uncommon:	Deep vein thrombosis

General disorders and administration site conditions

Very common:	Mild or moderate infusion-related reactions*; mild to moderate mucositis which may lead to epistaxis
Common:	Severe infusion-related reactions*, fatigue; Increased infections in combination with platinum-based regimens and increased radiation-related effects in combination with radiotherapy (see Combination Treatment)

Hepatobiliary disorders

Very common:	Increase in liver enzyme levels (AST, ALT, AP)

Cardiac

Uncommon:	Ischaemia in combination with fluorouracil or capecitabine (see Combination Treatment)

Haematological

Frequency	
Not known:[1]	Increased severe neutropenia and leukopenia in combination with platinum and fluorouracil

Additional information

Overall, no clinically relevant difference between genders was observed.

[1] Not to be estimated from the available data set in patients with recurrent and/or metastatic squamous cell cancer of the head and neck because patient numbers were too small to provide meaningful frequency estimation.

Infusion-related reactions

Mild or moderate infusion-related reactions are very common comprising symptoms such as fever, chills, dizziness, or dyspnoea that occur in a close temporal relationship mainly to the first cetuximab infusion.

Severe infusion-related reactions may commonly occur, in rare cases with fatal outcome. They usually develop during or within 1 hour of the initial cetuximab infusion, but may occur after several hours or with subsequent infusions. Although the underlying mechanism has not been identified, some of these reactions may be anaphylactoid/anaphylactic in nature and may include symptoms such as bronchospasm, urticaria, increase or decrease in blood pressure, loss of consciousness or shock. In rare cases, angina pectoris, myocardial infarction or cardiac arrest has been observed.

For clinical management of infusion-related reactions, see PRECAUTIONS.

Skin reactions

Skin reactions may develop in more than 80% of patients and mainly present as acne-like rash and/or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis, or nail disorders (e.g. paronychia). Approximately 15% of the skin reactions are severe, including single cases of skin necrosis. The majority of skin reactions develop within the first three weeks of therapy. They generally resolve, without sequelae, over time following cessation of treatment if the recommended adjustments in dose regimen are followed (see DOSAGE AND ADMINISTRATION section). According to NCI-CTC, grade 2 skin reactions are characterised by rash up to 50% of body surface area, while grade 3 reactions affect equal or more than 50% of body surface area.

Skin lesions induced by cetuximab may predispose patients to superinfections (e.g. with *S. aureus*), which may lead to subsequent complications, e.g. cellulitis, erysipelas, or, potentially with fatal outcome, staphylococcal scalded skin syndrome or sepsis.

Combination treatment

When cetuximab is used in combination with chemotherapeutic agents, also refer to their respective product information.

In combination with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia may be increased, and thus may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia and sepsis compared to platinum-based chemotherapy alone.

In combination with infusional fluorouracil or capecitabine, the frequency of cardiac ischaemia including myocardial infarction and congestive heart failure as well as the frequency of hand-foot syndrome (palmar-plantar erythrodysaesthesia) were increased compared to that with infusional fluorouracil.

In combination with local radiation therapy of the head and neck area, additional undesirable effects were those typical of radiation therapy (such as mucositis, radiation dermatitis, dysphagia or leukopenia, mainly presenting as lymphocytopenia). In a randomised controlled clinical study with 424 patients, reporting rates of severe acute radiation dermatitis and mucositis as well as of late radiation-therapy-related events were slightly higher in patients receiving radiation therapy in combination with cetuximab than in those receiving radiation therapy alone.

DOSAGE AND ADMINISTRATION

Erbitux must be administered under the supervision of a physician experienced in the use of antineoplastic agents. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured.

Prior to the first infusion, patients must receive a premedication with an antihistamine and a corticosteroid. Similar premedication is recommended prior to all subsequent infusions.

Erbitux is administered once a week for all indications. The initial dose is 400 mg cetuximab per m^2 body surface area. The subsequent weekly doses are 250 mg/m^2 each.

Colorectal cancer

It is recommended that the detection of *K-RAS* mutational status be performed by an experienced laboratory using a validated test method.

In patients with metastatic colorectal cancer, cetuximab is used as monotherapy or in combination with chemotherapy. It is recommended that cetuximab treatment be continued until progression of the underlying disease.

Squamous cell cancer of the head and neck

In patients with locally advanced squamous cell cancer of the head and neck, cetuximab is used concomitantly with radiation therapy. It is recommended to start cetuximab therapy one week before radiation therapy and to continue cetuximab therapy until the end of the radiation therapy period (see CLINICAL TRIALS section for further details).

In patients with recurrent and/or metastatic squamous cell cancer of the head and neck, cetuximab is used in combination with platinum-based chemotherapy followed by cetuximab as maintenance therapy until disease progression. Chemotherapy must not be administered earlier than 1 hour after the end of the cetuximab infusion.

Administration

Erbitux 5 mg/mL is administered intravenously with an infusion pump, gravity drip or a syringe pump (see Instructions for use and handling).

For the initial dose, the recommended infusion period is 120 minutes. For the subsequent weekly doses the recommended infusion period is 60 minutes. The maximum infusion rate must not exceed 10 mg/min.

Special recommendations

The following measures are to be taken if a patient experiences infusion- related or skin reactions:

Infusion-related reactions

Mild or moderate (symptoms include fever, chills, dizziness or dyspnoea): infusion rate should be decreased. It is recommended that the infusion rate remain at the lower value for all subsequent infusions.

Severe (symptoms include rapid onset of airway obstruction, urticaria, increase or decrease of blood pressure, loss of consciousness or shock; in rare cases, angina pectoris, myocardial infarction or cardiac arrest have also been observed): immediate and permanent discontinuation of cetuximab therapy. Emergency treatment may be necessary.

Skin reactions

First occurrence of severe skin reaction (grade 3; covering 50% or more of body surface area): cetuximab should be ceased for up to 2 consecutive weeks. If the reaction has resolved to grade 2 (characterised by rash up to 50% of body surface area) when the next infusion is due, treatment may be resumed without any change in dose level.

If a second grade 3 skin reaction occurs, cease cetuximab for up to 2 consecutive weeks. If the skin reaction has resolved to grade 2 when the next infusion is due, treatment may be resumed at a lower dose of 200 mg/m^2 body surface area.

If a third grade 3 skin reaction occurs at the lower dose, cease cetuximab for up to 2 consecutive weeks. If the skin reaction has resolved to grade 2 when the next infusion is due, treatment may be resumed at a lower dose of 150 mg/m^2 body surface area.

If a fourth grade 3 skin reaction occurs at 150 mg/m^2 body surface area or the skin reaction fails to resolve to grade 2 during interruption of treatment, permanent discontinuation of cetuximab is required.

Combination treatment

For the dosage or recommended dose modifications of concomitantly used chemotherapeutic agents, refer to the product information for these products. They may not be administered earlier than 1 hour after the end of the cetuximab infusion.

OVERDOSAGE

There is limited experience with single doses higher than 400 mg/m^2 body surface area to date or weekly administration of doses higher than 250 mg/m^2 body surface area. In clinical studies with doses up to 700 mg/m^2 given every two weeks the safety profile was consistent with that described in the ADVERSE EFFECTS Section.

Contact the Poisons Information Centre in Australia on 131 126 or in New Zealand on 0800 764 766 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Erbitux 5 mg/mL is a sterile, preservative-free solution for intravenous infusion containing 5 mg/mL of cetuximab. It is supplied in clear, colourless glass vials with a flurotec-coated bromobutyl rubber stopper and aluminium/polypropylene seal containing 10 mL, 20 mL, 50 mL or 100 mL. Each pack contains 1 single use vial.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Chemical and physical in-use stability of Erbitux 5 mg/mL has been demonstrated for 48 hours at 25°C if the solution is prepared as described in the Instructions for Use and Handling section below. To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours. In-use storage times and conditions are the responsibility of the user.

Instructions for use and handling

Erbitux 5 mg/mL may be administered via a gravity drip, an infusion pump or a syringe pump method. A separate infusion line must be used for the infusion, and the line must be flushed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection at the end of infusion.

Product is for single use in one patient only. Discard any residue.

Erbitux 5 mg/mL is compatible with:

- Polyethylene (PE), ethyl vinyl acetate (EVA) or polyvinyl chloride (PVC) bags,
- PE, polyurethane (PUR), EVA, polyolefine thermoplastic (TP) or PVC infusion sets,
- polypropylene (PP) syringes for syringe pump.

Since Erbitux does not contain any antimicrobial preservative or bacteriostatic agent, care must be taken to ensure aseptic handling when preparing the infusion.

Erbitux 5 mg/mL must be prepared as follows:

For administration with infusion pump or gravity drip (diluted with sterile sodium chloride 9 mg/mL (0.9% solution): Take an infusion bag of adequate size of sterile sodium chloride 9 mg/mL (0.9%) solution. Calculate the required volume of Erbitux. Remove an adequate volume of the sodium chloride solution from the infusion bag, using an appropriate sterile syringe with a suitable needle. Take an appropriate sterile syringe and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Transfer the Erbitux into the prepared infusion bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with the diluted Erbitux before starting the infusion. Use a gravity drip or an infusion pump for administration. Set and control the rate as explained in DOSAGE AND ADMINISTRATION section.

For administration with infusion pump (undiluted): Calculate the required volume of Erbitux. Take an appropriate sterile syringe (minimum 50 mL) and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Transfer the Erbitux into a sterile evacuated container or bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with Erbitux before starting the infusion. Use an infusion pump for administration. Set and control the rate as explained in the DOSAGE AND ADMINISTRATION section.

For administration with a syringe pump: Calculate the required volume of Erbitux. Take an appropriate sterile syringe and attach a suitable needle. Draw up the required volume of Erbitux from a vial. Remove the needle and put the syringe into the syringe pump. Connect the infusion line to the syringe, set and control the rate as explained in DOSAGE AND ADMINISTRATION section and start the infusion after priming the line with Erbitux or sterile sodium chloride 9 mg/mL (0.9%) solution. If necessary, repeat this procedure until the calculated volume has been infused.

Incompatibilities

Erbitux 5 mg/mL must not be mixed with other intravenously administered medicines, except sterile sodium chloride 9 mg/mL (0.9%) solution. A separate infusion line must be used.

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

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