SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Erbitux. For information on changes after approval please refer to module 8.

1. Introduction

Erbitux contains the active substance cetuximab, a chimeric monoclonal antibody of the immunoglobulin G_1 (IgG_1) class that is directed against the human epidermal growth factor receptor (EGFR). With the present application, the applicant sought a marketing authorisation for Erbitux, either in combination with irinotecan or as a single agent, for the treatment of patients with EGFR-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy. Following the assessment of the documentation submitted, the CPMP expressed doubts on whether there was sufficient evidence to establish a positive benefit risk profile for Erbitux as a single agent treatment in the applied indication. Subsequently, the applicant restricted the indication for Erbitux to the combination treatment with irinotecan. The scientific discussion in this report focuses on this indication.

Metastatic colorectal cancer

Colorectal cancer is the third most commonly diagnosed cancer worldwide, with an estimated 950,000 new cases diagnosed per year, and is the second most common cause of cancer mortality in Europe and North America. About 280,000 new cases and 150,000 deaths are expected in the European Economic Area including an enlarged EU, based on projected estimates for the year 2005 [1].

Surgery forms the mainstay of treatment for stages I and II patients. Radical resection with curative intent is appropriate for the majority of patients, whilst 10% to 15% of patients with primary colorectal cancer present with synchronous metastatic cancer [2]. Despite curative surgery, patients still have a significant probability of disease relapse and cancer-related death. Comparative trials have consistently demonstrated a benefit for adjuvant chemotherapy over surgery alone in stage III disease, with disease-free, 5-year survival rates of approximately 60%. Radiotherapy is often considered as adjuvant treatment of rectal cancer [2-4].

About 40 to 50% of patients develop metastatic (stage IV) disease [5,6]. Metastatic colorectal cancer is a resistant disease, and the long-term prognosis is poor. 5-FU/leucovorin (LV) (including new variants), oxaliplatin and irinotecan remain in different combinations mainstays in the treatment of stage IV colorectal cancer. Randomized phase III trials have shown that the infusional 5-FU/FA-based triple-drug combinations produced response rates of 38 to 58%, a median progression-free survival of 7 to 9 months, and a median overall survival of 17 to 21 months [7-22]. In patients failing irinotecan-based regimens, oxaliplatin-based regimens are used in Europe. Despite the progress obtained to date, metastatic CRC remains incurable except for some rare cases in patients whose tumors can be completely resected after first-line chemotherapy.

Cetuximab

EGFR is a member of the ErbB family of receptor tyrosine kinases. EGFR signalling in tumor cells is responsible for regulating a diverse network of cellular functions that influence neoplastic growth. The expression of EGFR in human cancer has provided a scientific rationale for the development of EGFR antagonists as potentially useful therapeutic agents. Monoclonal antibodies that inhibit EGFR function offer a specific class of EGFR antagonists. The EGFR expression rate in CRC is reported to be between 25 and 77% [23]. EGFR-expressing CRC tumors are associated with a worse stage and a poor prognosis in terms of survival [24-26].

Cetuximab (also referred to as C225-03, IMC-C225, C225, ch225) is a chimeric monoclonal antibody that binds with high specificity to the extracellular domain of the human EGFR. The antibody is intended to function as a competitive antagonist that inhibits ligand binding to the EGFR, and may lead to degradation of EGFR. Preclinical studies provided the initial rationale for the clinical evaluation of the combination therapy of cetuximab with topoisomerase I inhibitors [27,28]. Strong synergistic effects were observed when cetuximab was combined with irinotecan compared to the tumor growth control exerted by the single agents [29].

Cetuximab has been developed jointly by Merck KGaA and ImClone Systems Incorporated/Bristol-Myers Squibb for the treatment of several types of human cancer that express the EGFR, including colorectal cancer, squamous cell carcinoma of the head and neck, nasopharyngeal cancer, pancreatic cancer, ovarian cancer, and non-small cell lung cancer.

This marketing authorization application has been submitted as a complete and independent application (so-called "stand-alone application"), based on article 8.3(i) of Directive 2001/83/EC.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

The drug product is a sterile liquid formulation (100 mg cetuximab per vial) intended for intravenous infusion. The composition of the formulated product and the respective functions and quality standards of the various ingredients are summarised in Table A.

Table A. Composition of cetuximab

Component	Amount per vial	Amount (mg/ml)	Function	Quality standards
Cetuximab, chimeric antibody	100 mg	2 mg/ml	Active ingredient	In-house specification
Sodium chloride	424 mg	8.48 mg/ml	Isotonicity agent	Ph. Eur.
Sodium dihydrogen phosphate dihydrate	20 mg	0.40 mg/ml	Buffer	Ph. Eur.
Disodium phosphate dihydrate	66 mg	1.32 mg/ml	Buffer	Ph. Eur.
Water for injection	ad 50 ml*	ad 1 ml	Diluent	Ph. Eur.

* Action levels of the filling procedure are 50.5 to 52.0 ml of cetuximab solution. This overfill, which assures the specified extractable volume of 50 ml, does not represent a risk for the patient because the dose to be administered is calculated and controlled for each individual patient.

The drug product is presented at a concentration of 2 mg/ml in 50 ml type 1 glass vials closed with a Teflon-coated, bromobutyl rubber stopper. Both the primary packaging materials are of Ph. Eur. Quality.

Active substance

Production and control of starting materials

Cetuximab is a chimeric mouse/human monoclonal antibody. Cetuximab has two N-linked carbohydrate sites on both heavy chains. The molecular weight of cetuximab is approximately 152 kDa including carbohydrates. The recombinant protein is produced in a stably transfected murine myeloma cell line.

A holding step, concentrated bulk, is introduced during manufacture of drug substance. Drug substance is produced by a simple dilution of concentrated bulk in formulation buffer. The manufacture is performed at two sites using similar processes: The ImClone process (IC or CS-US) produces concentrated bulk for shipping and the Boehringer Ingelheim process (BI or CS-EU) produces concentrated bulk and drug substance.

Detailed description of the two commercial processes CS-US and CS-EU, (representing IC and BI, respectively) are provided. At each production site one vial of Working Cell Bank (WCB) yields one batch of concentrated bulk material. This bulk can then be divided or pooled to constitute the drug substance at 2 mg/ml.

Cell culture and harvesting

Cetuximab is produced by cell culture in 10,000 L or 12,000 L scale (IC and BI, respectively) stirred tank bioreactors, using batch mode. All cell culture steps upon thawing of WCB is performed in serum-free media. *Purification*

The cell-free media is concentrated and classified by diafiltration at 0.2µm.

One batch of fermentation corresponds to one batch of concentrated bulk as obtained from purification.

The final purification step is diafiltration into formulation buffer. This solution is sterile filtered and can be stored 1 year at 2-8^{o} C. Final preparation of drug substance is performed by dilution of the concentrated bulk to 2 mg/ml in formulation buffer.

Gene construct

The chimeric antibody is encoded from the variable region cDNAs of the murine monoclonal antibody M225 and the cDNAs for human kappa and gamma 1 constant regions. The cDNAs are inserted into an expression vector containing separate expression cassettes for light chain and heavy chain, respectively.

Cell banking system

The preparation of established cell banks have been described in sufficient detail and tests performed for stability and safety are in agreement with EU guidance.

A thorough genetic characterisation has been performed on the cell banks of concerns for production and includes separate tests of the transcription units for the heavy chain as well as the light chain.

In general, the extent of the control for manufacture of this recombinant product is considered adequate.

The documentation of the cell banks used is acceptable,

Control of steps

In-process testing encompass 3 categories of test:

In-process monitoring, In-process control parameters and In-process specifications.

The control of cell culture, starting from inoculum to production fermentor, is basically related to viability and purity from microorganisms.

Biochemical characterisation

The biochemical characterisation was performed using state-of-the-art methods, including mass spectroscopy. The substance exerts a significant degree of charge heterogeneity. Comparability

During the development of the manufacturing process different process development stages in different manufacturing sites have been documented. To demonstrate comparability of products, pivotal and supporting comparability studies have been presented. An extended characterisation has been performed to demonstrate comparability of commercial and clinical trial batches. The provided data are conclusive and demonstrate for instance that a similar extent of charge heterogeneity seen in commercial and clinical trials batches of cetuximab.

Control of drug substance

The methods and specifications chosen for routine control are adequate.

In addition, during the centralised procedure for marketing authorisation of cetuximab three commercial scale batches together with different standard materials have been analysed at the Paul-Ehrlich-Institut. Tests included visual inspection, determination of pH, osmolality, protein content, IEF, HP-SEC, SDS-PAGE (reduced and non-reduced), endotoxin and both potency assays (ELISA and DiFi).

The same list of specifications is also applied for drug product. The extent of specifications is acceptable.

Impurities

Impurities derived from fermentation and purification process are described. Their reduction has been evaluated in the process validation section and their profile has been evaluated in relation to comparability studies performed on commercial scales and intermediate scale.

Potential product-related impurities in drug substance have been characterised as being either degradation products, impurities induced by physical stress or aggregation products.

Drug product

Erbitux is a sterile solution for infusion, containing cetuximab at a concentration of 2 mg/ml. Each glass vial contains 50 ml solution (i.e. 100 mg cetuximab). Erbitux is formulated as a phosphate buffered saline (PBS) solution consisting of 10 mM sodium phosphate and 145 mM sodium chloride (ph 7.2). No other excipients are used (composition table introduced above). This formulation has been used in all clinical trials.

Container closure

The packaging components used by CH and BI were obtained from different suppliers. The choice of materials for the container closure system is adequate for the stability and use of the product. There are no significant differences between the container closure system used in the clinical trials and the one proposed for commercial material.

Microbiological attributes

Cetuximab drug product is manufactured aseptically and is presented as a sterile solution for injection containing no preservatives. All batches are tested for sterility and bacterial endotoxins during release of the drug product. The aseptic filling procedure has been validated using media fills. The integrity of the container closure system to prevent microbial contamination has been shown using a dye bath method.

Product development and finished product

Erbitux is manufactured simply by sterile filtration of the drug substance and then filling it into the final container. The sterilising filter is validated specifically. After filling and capping, all vials are visually inspected. Defective vials are rejected.

Clinical trial material has been produced at two sites: Cardinal Health (CH), formerly SP Pharmaceuticals in Albuquerque, New Mexico, USA, and Boehringer Ingelheim (BI) in Biberach, Germany. Only the German site will be used for production of commercial material. Minor differences in the formulation components between the US site and the proposed commercial formulation) are clearly described and should have no significance for the final formulation.

The product does not contain an overage but all vials are overfilled (target volume 51.0 ml) to assure the specified extractable volume.

A detailed comparison of manufacturing of cetuximab drug product at Cardinal Health and BI Pharma is presented. Pharmaceutical quality of cetuximab drug product manufactured at the two sites can be regarded as similar.

Packaging and labelling are performed by Merck KGaA in Germany.

Precipitation of cetuximab is observed during storage, yielding visible particles. Also sub-visible particles are present at levels exceeding the PhEur limits for parenteralia. As pointed out by the

Applicant, the product is exempted from the PhEur test for sub-visible particles, since it is to be used with a final filter.

The Applicant has shown that the particles consist of cetuximab, do not cause a measurable decrease in protein concentration after filtration, and can be eliminated by filtration. These experiments were made using a batch of Erbitux that had been stored for over 3 years and contained a relative high amount of sub-visible particles. It can thus be viewed as a "worst case" considering particle amount. The kinetics of particle formation in Erbitux has been studied by the applicant in three batches for one month (data from an ongoing study). The particles are formed already after one day, and after this time point no significant increases are seen. Regarding the influence of product age on particle amount, the applicant has provided data from analyses of subvisible particles on 16 batches of various ages. The influence of age on the particle amount differs between batches, but a possible trend is that older batches have more particles.

Control of the steps

In-process controls include filter integrity testing and filling weight control.

Process validation

A prospective validation of the manufacturing process has been performed.

All tests result complied with the pre-defined specifications. The aseptic filling has been validated. No vials with bacterial growth were detected.

Validation of primary packaging material was also done and all results were within pre-set acceptance criteria.

Control of exicipients

All excipients fulfil the criteria of Ph. Eur.

Control of the drug product

The proposed specifications for Erbitux are the same as those for drug substance, with the addition of tests for sterility and extractable volume. The comments made above regarding the specifications for the drug substance are valid also for the drug product specifications.

Analytical procedures

The same analytical package employed for release of drug substance is also used for release of drug product (with the exception of bioburden,). Release testing of cetuximab drug product bulk is performed at BI and the product is shipped to Merck KGaA for packaging and labelling. At Merck, an identity test by IEF is performed prior to final packaging.

Validation

Analytical procedures have been validated according to ICH guidelines. Testing included material from bulk drug substance as well as drug product.

Stability of the product

In support of the claimed shelf-life of 24 months, stability data up to 15 months are available for batches including cetuximab produced at the commercial scale at the US site and up to 9 months for batches including cetuximab produced at the EU site. In addition, data up to 30 months are available from supportive stability studies, with batches including cetuximab produced at pilot scale. No stability problems at 5ºC are seen so far in the studies. Particle amount was originally not monitored in the stability studies, but the Applicant has provided particle data on from a number of batches near and above the proposed shelf life of 24 months. The data shows that the particle amount in Erbitux batches during shelf life is not likely to significantly exceed the amount in the batch used in the filtration validation. The Applicant has committed to include the test for sub-visible particles (PhEur) in the ongoing stability studies of drug product, and to continue these studies for the duration of the proposed shelf life. Data from the finalised studies will be submitted to the authorities.

Adventitious agents

TSE risk assessment

Compliance with the TSE Guideline has been widely demonstrated. The active drug substance is produced in a serum-free culture medium. The only animal derived material added during fermentation of Cetuximab is Bovine Serum Albumin and Bovine Lipoprotein for which Certificates of Suitability have been provided. The MCB´s and WCB´s, which have been established, are free from TSE-risk substances.

Virus safety

The fermentation process of the monoclonal antibody Cetuximab is in a serum-free medium. The only animal derived material added during fermentation of Cetuximab is Bovine Serum Albumin and Bovine Lipoprotein both tested for bovine viruses. This minimises a possible contamination for adventitious viruses. The cells used for production of Cetuximab have been extensively screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the MCB of Cetuximab, with the exception of intracellular type-A and type-C retroviral particles which are well known to be present in murine hybridoma cells (Sp2/O-). However, this is acceptable since there is sufficient capacity within the manufacturing procedure of Cetuximab for reduction of this type of viral particles. Therefore, there are no concerns for the use in the production process of Cetuximab.

There are two important steps during purification of Cetuximab. The robustness and effectiveness of these steps for the inactivation/removal of enveloped viruses has been demonstrated. In addition, a chromatography purification step of the Cetuximab also contributes to the virus safety. However, the effectiveness of this step is virus specific and is very low for removal of small non-enveloped viruses (MVM). The other chromatographic steps might further contribute to additional virus removal capacity but this has not been validated. A filtration step also contributes only very limited to removal of small non-enveloped viruses. This can be accepted since routine virus screening for viruses including MVM is routinely performed at the end of the fermentation runs. In summary, the virus safety of Cetuximab is deemed acceptable.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

Introduction

The toxicology program included GLP studies of repeat-dose toxicity, genotoxocity and local tolerance. However, validation of the analytical method used for pharmacokinetics, and serum analysis of cetuximab were not in compliance with GLP.

Pharmacology

Primary pharmacodynamics (in vitro/in vivo)

The primary pharmacodynamic studies conducted by the applicant with Cetuximab included mainly tissue binding studies with normal and malignant human tissues, in vitro anti-tumor activity studies using EGFR-positive cancer cell lines and in vivo anti-tumor activity in EGFR-positive and EGFR-negative human tumor xenograft models, and in vivo and in vitro studies on combination therapy with Cetuximab and cytotoxic drugs.

Tissue binding

The binding affinity of cetuximab and the corresponding mouse monoclonal antibody M225 to human EGFR several-fold higher for the chimerised antibody cetuximab than for (Table 1)

In a non-GLP study, the binding affinity of cetuximab to immobilised soluble EGFR was compared to that of M225. The avidity (EC50) of cetuximab binding was about two-fold higher than that of M225. Both antibodies bound to the same epitope. Competition experiments showed that cetuximab displaced FITC-labelled EGF bound to human epidermal vulva cancer derived cell line A431 cells with an avidity 6-fold higher than that of unlabelled EGF. The EC50 for M225 was only slightly higher than for cetuximab.

The reactivity of cetuximab was tested against cryosections of liver tissue from mouse, rat, dog, Cynomolgus monkey, Rhesus monkey and baboon. Human placenta was used as a positive control. Cetuximab reacted only with the positive control. Subsequent studies using more sensitive methods (labelled cetuximab instead of a biotinylated secondary antibody) showed that FITC-labelled cetuximab had affinity to *epithelial* cells of Cynomolgus monkey and to *mesenchymal* cells of the colon, esophagus, fallopian tube, ovary, pancreas, parathyroid, peripheral nerve, spinal cord, stomach, testis, thymus, ureter, urinary bladder, and uterus.

Table 1 Binding affinities of cetuximab and M225 to human EGFR[30]

		Kd (nM)	
Method	**Receptor form**	**cetuximab**	**M225**
ELISA	Fixed A431 cells	0.15	1.2
SPR (Biacore)	soluble receptor	0.20	0.87

Mechanism of Action

EGFR

The EGFR family (Her family) consists of four closely related protein tyrosine kinase receptors, each with a number of synonyms: (1) EGFR, erb B-1, c-erb-B; (2) erb B-2/neu, Her-2/neu; (3) erb B-3, Her-3; (4) erb B-4, Her-4. EGFR signalling in tumor cells is responsible for regulating a diverse network of cellular functions that influence neoplastic growth including proliferation, survival, damage repair, adhesion, migration, and neovascularisation. EGFR is expressed at various levels in a number of human cancers of epithelial origin. Epithelial tumors that commonly express EGFR include bladder, breast, cervix, colon, head and neck, kidney, lung, pancreatic, and prostate.

Specific ligands of EGFR are EGF and EGF-related peptides including transforming growth factor-α (TGF-α), amphiregulin, and heparin-binding EGF-like growth factor. EGF and TGF-α, stimulate molecular events necessary for the transition through the restriction point, R, near the end of the G1-phase of the cell cycle. Once past the R-point, cells are committed to continue through the other stages of the cell cycle, even in the absence of growth factors. Erb B-2, erb B-3 and erb B-4 are receptors for the cell-signalling neuregulin proteins. The erb B-2 receptor is overexpressed in a significant number of adenocarcinomas, and is the target of antibody (trastuzumab) therapy of breast cancer. Overexpression of the erbB-3 receptor is associated with tumorigenesis.

To activate EGFR, the ligand EGF (a monomer) binds simultaneously and cross-links two adjacent receptor chains. The cross-linking enables intracellular kinase domains of the receptor chains to phosphorylate each other on multiple tyrosines. The tyrosine kinase activity of the receptor chains is thus increased and will in turn activate several signaling pathways such as the Ras-induced MAP-kinase pathway, the PI3-kinase pathway and the JAK/STAT pathway.

Excessive EGFR function, through receptor overexpression and constitutive activation (not requiring a ligand) of EGFR mutants and autocrine stimulation, have been implicated in a wide variety of cancers. Human carcinomas of colon, head and neck, pancreas, lung, breast, kidney, ovary, brain, and bladder frequently overexpress EGFR. The oncogenic effects of EGFR include initiation of DNA synthesis, enhanced cell growth, invasion, and metastasis. Specific abrogation of EGFR results in cell cycle arrest, apoptosis, and dedifferentiation of cancer cells.

Mechanism of action of cetuximab

The direct mechanism of action of cetuximab is the blockade of ligand-receptor binding and thereby inhibition of ligand-mediated activation of the EGFR tyrosine kinase. As a result of this EGFR blockade a variety of processes regulated by the EGFR-signaling pathways in tumor cells or stromal cells in the tumor microenvironment were shown to be disrupted. Several such processes relevant for the tumor phenotype have been identified in nonclinical models, including EGFR downregulation[31,32], inhibition of intracellular signalling[33], inhibition of cell cycle progression[34-39], induction of apoptosis[39-42], inhibition of DNA repair[39,43], inhibition of angiogenesis[44-55], and inhibition of tumor cell motility, invasion and metastasis[46,50,56]. Stimulation of antibody-dependent cellular cytotoxicity (ADCC) has also been described[57].

Preclinical studies on the effects of the combination of cetuximab and the camptothecin analogue topotecan on the growth behavior of GEO cells (colon adenocarcinoma) *in vitro* and as xenografts provided the initial rationale for the clinical evaluation of the combination therapy of cetuximab with topoisomerase I inhibitors [27,28]. The studies with GEO cells were extended in 2 additional colorectal xenograft models with the DLD-1 and HT-29 cell lines and the combination of cetuximab with irinotecan. In those models, strong synergistic effects were observed when cetuximab was combined with irinotecan compared to the tumor growth control exerted by the single agents [29].

Synergies between receptor signaling and genotoxic agents can be hypothesised based on theoretical grounds. Tumor cells can react to genotoxic treatment with an upregulation of the activity of their growth factor signal pathways. Growth factor dependent enhancement of DNA damage repair might be an important mechanism by which cells try to compensate genotoxic treatment effects [58-61].

Anticancer activity

In vivo tumour models

In immuno-deficient mice, GEO (human colon cancer) cell tumour growth was markedly reduced by cetuximab 1 mg twice weekly for 3-5 weeks and even more by a combination of cetuximab and VEGF antisense. Tumour growth resumed after discontinued treatment [48]. Tumour growth was also inhibited by 0.25 mg/dose of cetuximab twice weekly [47].

According to the results of a non-GLP study submitted by the applicant, mice with renal carcinoma Caki-1 cell i.p. xenografts had an increased survival rate after cetuximab treatment for 4 weeks. The number of mice in each group is not given in the report, but probably 6/7 in the control group were dead after 8 weeks as compared to 1/7 in the treated group. Another study showed similar results, and included tumour volume data from mice xenografted with renal carcinoma SK-RC-29 cells in the right flank [29]. The 200 mm^3 tumour volume reached before treatment started was almost unchanged in the treatment group for 5 weeks of treatment plus a further three weeks, therafter tumour growth resumed in these previously treated animals. In control animals, an at least 5-fold increase in the tumour volume was seen after 5+3 weeks.

Renal cancer ACHN cell subcutaneous xenografts did not grow after initiation of twice weekly 0.25 mg cetuximab treatment, and combination of cetuximab and a protein kinase A antisense oligonucleotide resulted in reduction of the tumour volume, while control tumours tripled in volume during the 3 weeks treatment period [62].

According to the results of a non-GLP study submitted by the applicant, colon adenocarcinoma IMC480rz cell and gastric carcinoma KKVR cell subcutaneous xenograft growth was not significantly inhibited by cetuximab treatment. These cells do not express EGFR and the result supports the hypothesis that the antitumour effect of cetuximab is linked to blockade of EGFR.

Epidermoid vulva cancer A431 cell subcutaneous xenografts regressed in a dose-dependent fashion after initiation of twice weekly 0.2 to 1 mg cetuximab treatment, while control tumours increased in size at least 3-fold during the 5 weeks treatment period[30]. Treatment with the mouse antibody M225 had only minor effects and the difference might be due to the lower a higher affinity of the chimeric antibody for human EGFR compared to the M225 mouse antibody. By starting the M225 treatment at time of inoculation of A431, or shortly after, (rather than at the time of established tumours) tumour formation was completely inhibited [63-65].

Secondary pharmacodynamics

Specific secondary pharmacodynamic studies have not been submitted. According to the applicant, the major adverse effects observed in toxicology studies with cetuximab can be clearly related to its primary pharmacological effects (i.e. skin reactions due to interaction with EGFR) and as the safety pharmacological evaluation yielded no concerns. Secondary pharmacodynamic investigations have not been performed.

Safety pharmacology

Safety pharmacology was studied in Cynomolgus monkeys in a dedicated study after single administration, and as part of the 39-week toxicology study.

A single-dose safety pharmacology GLP study was conducted to assess cardiovascular and respiratory effects after administration of 0, 9.84, 31 and 98.4 mg/kg of cetuximab in male anaesthetised Cynomolgus monkeys (4 animals per group). The high dose was chosen to be more than 10-fold the human therapeutic loading dose level of 400 mg/m^2 body surface, and the low dose to be similar to the therapeutic dose. The high dose of cetuximab did not elicit any noticeable changes in cardiovascular parameters examined. A transient hypotension following administration of the intermediate dose was observed in 2 of 4 animals. An increase in heart rate was observed in the low dose group. The effects were not statistically significant and not dose-related and thus considered to be of no pharmacological relevance. Small gradual increases in the rate and depth of respiration were common to all groups and were not considered to have biological significance. Serum concentrations of cetuximab were measured during 3 hours after infusion. No cetuximab was detected in the serum of control monkeys, mean peak serum levels were 246, 765 and 1990 µg/ml for the respective groups. A validated ELISA method was used for analysis.

Safety pharmacology endpoints have been incorportated in the design of a 39-week repeat-dose toxicology study in Cynomolgus monkeys. Electrocardiography, determination of heart rate and blood pressure (pre-dose, week 4, 13, 26 and 39, 1 h after infusion) revealed no findings related to treatment with cetuximab. There were no apparent changes in respiratory rate. In conclusion, there were no indications of an effect of cetuximab on the cardiovascular and respiratory system.

Effects on the central nervous system (CNS) were not specifically investigated. However, no findings indicative of CNS effects were observed within the 39-week repeat-dose toxicity study in Cynomolgus monkeys.

Pharmacodynamic drug interactions

The applicant submitted the results of a non-GLP study using xenografts of the human colon carcinoma cell lines DLD-1 and HT-29, which are poorly responsive to irinotecan, to study the combined effect of cetuximab and the topoisomerase inhibitor irinotecan. Cetuximab (twice weekly during the 8 week study) or irinotecan (100 mg/kg weekly for 3 weeks) alone had little effect on DLD-1 tumours; combination treatment significantly reduced tumour growth. Cetuximab alone had some activity against HT-29 cells and the combination with irinotecan resulted in significant enhancement of the antitumour activity. Histological examination of the tumours showed large areas of necrosis and fibrosis. A marked decrease in tumour cell proliferation was observed after combined treatment, in comparison to control or single agent-treated tumours. A marked decrease in tumor cell proliferation was also observed in cetuximab/irinotecan treated tumors, as measured by anti-Ki-67 IHC, in comparison to control or single agent-treated tumors. In addition, a decrease in microvessel density was observed using anti-CD31 IHC.

Combination therapy of 0.25 mg/dose of cetuximab and 2 mg/kg of the topoisomerase inhibitor topotecan twice weekly resulted in a significantly prolonged delay of tumour growth in mice with established tumours, as compared to either drug alone [28]. Furthermore, cetuximab in combination with radiotherapy, 10 Gy/day for 4 days, also resulted in a significantly prolonged delay of tumour growth, as compared to either treatment alone 66.

Pharmacokinetics

Pharmacokinetic and toxicokinetic data were collected in studies with the *Cynomolgus* monkey and in rats.

Methods of analysis

Serum concentrations of cetuximab were determined via surface plasmon resonance (SPR) using a Biacore instrument. In this assay soluble human recombinant EGFR is immobilised to the sensor surface. Test solutions containing cetuximab flow continously over the sensor surface. As cetuximab binds to the immobilised EGFR a response is registered. The SPR assay was accepted if the two quality control samples (0.2 and 5 nM, in serum-free buffer) were within 15% of the expected value.

Absorption- Bioavailability

Cetuximab is administered intravenously and the bioavailability is therefore 100%. No studies have been performed to address absorption of cetuximab.

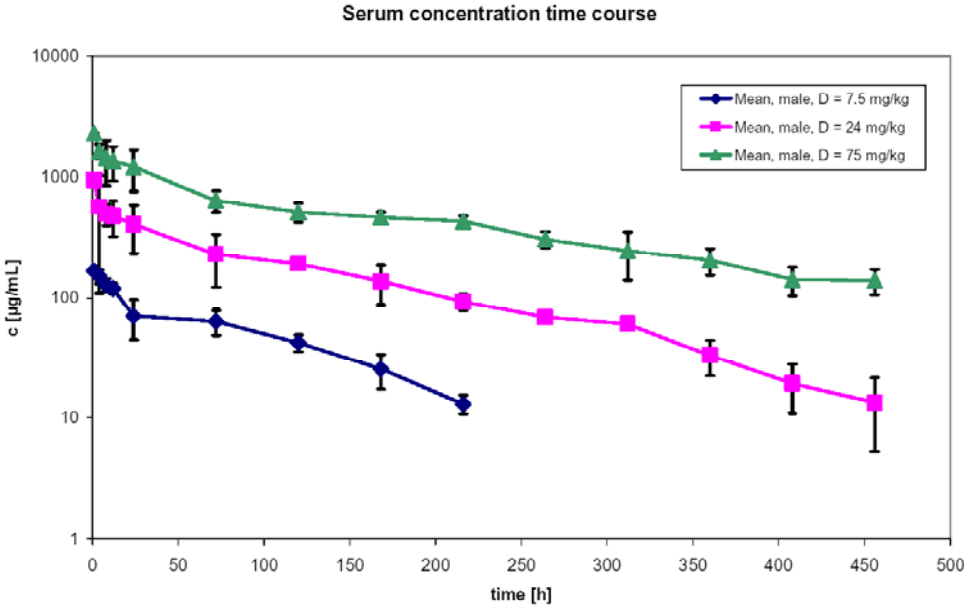
The results of a pharmacokinetics of cetuximab after a single intravenous infusion to Cynomolgus monkeys were submitted. Groups of 3 male and 3 female animals received 7.5, 24 and 75 mg/kg for 60 minutes. Samples were taken before infusion, at end of infusion (1h), at 4, 8, 12, 24 hours, and days 3, 5, 7, 9, 11, 13, 15, 17 and 19 (Table 2and Figure 1. Clearance decreased and terminal half-life increased with increasing dose, indicating a saturated clearance at higher doses. Distribution volume indicated that cetuximab is mainly located in the plasma volume.

Table 2 Summary of mean pharmacokinetic parameters after a single infusion

Dose (mg/kg)	**7.5**		**24**		**75**	
Gender	**M**	**F**	**M**	**F**	**M**	**F**
Cmax** (µg/ml)	166	175	949	936	2300	2460
Cmax (nM)	1100	1150	6200	6100	15000	16000
Cmax/Dose ([µg/ml]/[mg/kg])	22	23	40	39	31	33
t½ (days)	2.7	3.1	4.0	4.7	6.8	6.7
AUClast* (µg/ml × h)	10933	8854	61113	65523	200753	213637
AUCinf/Dose ([µg/ml × h] / [mg/kg])	1619	1354	2623	2877	3149	3187
CL (ml/h/kg)	0.6	0.8	0.4	0.3	0.3	0.3
Vss (ml/kg)	61	76	50	48	67	64

*AUC at the last measurement taken, see figure below.
**Tmax was at the end of the infusion period.

Figure 1 Serum concentrations of cetuximab after a single infusion, n=3.



Toxicokinetics after repeated infusions of cetuximab to Cynomolgus monkeys, (0, 12, 38 and 120 mg/kg at week 1, subsequent weekly doses 0, 7.5, 24 and 75 mg/kg). No accumulation after daily dosing beyond week 4 was observed.

Distribution

No studies in a relevant species have been performed to address the distribution of cetuximab. ^{111}Indium-labelled mouse monoclonal M225 was studied in mose xenograft models of human tumours, showing specific uptake into the tumours [67].

Metabolism and Excretion

No studies addressing the metabolism and excretion of cetuximab were performed.

Pharmacokinetic drug interactions

No pharmacokinetic studies in non-clinical models of disease were performed.

Toxicology

Single dose toxicity

No single dose toxicity studies were performed in relevant species. Doses of 300 mg/kg in mice and 200 mg/kg in rats revealed no significant signs of toxicity in the parameters body weight, food consumption, clinical hematology, serum biochemistry and gross necropsy.

Repeat dose toxicity (with toxicokinetics)
The pivotal repeat-dose toxicity study is a 39 week study in Cynomolgus monkeys (study 070-087). A 4-week study in Sprague-Dawley rats was also conducted (study 54167).

Study 070-087

The dosage was based on the human therapeutic starting dose of 400 mg/m^2 and subsequent weekly doses of 250 mg/m^2, which translates to 12 and 7.5 mg/kg for a human ofbody surface area of 1.8 m^2 and 60 kg body weight. The initial doses and subsequent weekly doses were 12 and 7.5 mg/kg for the low dose group, 38 and 24 mg/kg for the intermediate dose group, and 120 and 75 5 mg/kg for the high dose group. Two additional animals were included in the control and high dose groups for recovery assessment during 6 additional weeks. Due to 5 deaths the high dose group was terminated with one surviving male at 36 weeks, and at 36 weeks plus a 9-week recovery period (2 males and 2 females).

Clinical and necropsy findings indicated that the skin was the primary target organ, with dose-dependent effects observed at all dose levels. Severe skin reactions and 5 intercurrent deaths were observed in the high dose group. Due to moderate to severe skin reactions in all high dose females, treatment of these females was discontinued from weeks 25 to 28. Following improvement in the general health status of these animals, treatment was resumed from week 29. One high dose male was found dead in week 30 and 1 additional male and 3 females were sacrificed in moribund condition between weeks 14 and 35.The 5 high dose decedents displayed reduced food consumption, body weight loss or reduced body weight gain, apathy, prostration and general morbidity preceding death. Weight loss of dead or moribund animals was up to 40%.

The intercurrent deaths were considered to be drug-related due to sequelae of skin lesions as well as tongue, nasal cavity and esophageal lesions leading to infection, and impairment of food consumption and body weight development. Further sequelae of skin lesions included scale formation at legs, arms, extremities, inguinal region and whole body, erythema/redness, swelling, exanthema, dermatitis, hair thinning/loss, wounds/fissures, and paleness, which in most cases manifested as the study progressed. The development of the skin alterations, their severity and the incidence of the lesions were dose-related. The onset of the skin toxicity (scaling) was 15, 22, and 64 days in high; mid and low dose groups, respectively. There was no evidence of moderation of skin effects during treatment. Conjunctivitis, reddened, swollen and/or incrusted eyes observed in individual monkeys of the cetuximab-treated groups can also be interpreted as alterations related to the epithelial effects of cetuximab. At the end of a 9-week treatment-free recovery period, skin lesions in 4 high dose animals were less pronounced but proved to be not fully reversible within this time period.

Diarrhea or soft feces were noted in the majority of high dose monkeys. Soft feces and/or diarrhea were also noted in several monkeys treated with a single dose of cetuximab within the single dose pharmacokinetic study. A relation of cetuximab to the intestinal disturbances observed cannot be excluded.

Further alterations noted in high dose animals essentially comprised occasional changes in red and white blood cell counts as well as increases in serum enzymes (gamma glutamyl transferase [GGT], glutamate dehydrogenase, alanine aminotransferase) and globulin levels and decreases in albumin and

albumin/globulin ratio (A/G ratio). The changes observed for GGT, albumin, A/G ratio and globulin were observed in the intermediate and low dose groups as well and generally showed dose-dependency.

Tremor during infusion was observed occasionally in few monkeys, predominantly of the high dose group, on days 57 and occured repeatedly until days 225. The cause of this observation has not been established; a relation to an immunogenic reaction cannot be totally excluded. Other treatment related findings were seen in some animals during infusion on day 22 (hypoactivity & sluggishness).

Organ weight determination revealed increases in popliteal lymph node and kidney weights in all cetuximab-treated groups. In high dose decedents, elevated weights for adrenals, spleen and liver were found additionally.

Major gross necropsy findings included skin lesions in all cetuximab treated groups that were clearly dose-related. Enlarged popliteal lymph nodes were also noted in several cetuximab-treated animals. Further gross necropsy findings in high dose decedents included enlargement of liver, spleen and kidneys or liquefaction of sternal bone marrow, which were considered to be the result of secondary infections. At the end of the treatment-free recovery period, the occurrence of squamous skin in the high dose group was partly associated with hair loss/alopecia.

Histopathology revealed epidermal lesions (circumscribed to multifocal) of the skin in all monkeys treated with cetuximab. The severity was dose-dependent. The squamous epithelium of tongue, nasal cavity and esophagus showed alterations comparable to those observed in the skin in some high dose animals. Pathogenetically the skin lesions were considered to be related to a pharmacologically-mediated maturation defect of the epidermis. This defect accounts for hyper-, parakeratosis, acanthosis, and acantholysis with clefts, pustules, and vesicle formation. All of these findings can be summarized as dermatosis.

Secondary bacterial superinfections, especially in high dose animals caused an erosive to ulcerative dermatitis with subsequent involvement of inner organs due to septicemia, especially in liver, spleen, bone marrow, and kidney. The degree of severity and organs affected varied among animals. Skin lesions were still observed in high dose animals at the end of the treatmentfree recovery period. A microscopic correlate to these changes was found in the presence of purulent superficial skin inflammation at the injection sites.

Microscopy of lymphoid tissues (spleen, thymus, lymph nodes) and bone marrow yielded no indications for an immunotoxicological concern. Thus, no separate immunotoxicity studies have been performed.

Electrocardiography, determination of heart rate and blood pressure revealed no findings related to treatment with cetuximab. There were no apparent changes in respiratory rate. In conclusion, there were no indications of an effect of cetuximab on the cardiovascular and respiratory system.

Study 54167

In a standard repeated dose toxicity study 0; 2,5; 10 and 40 mg/kg cetuximab were administered to groups of 30 rats (15F+15M) for 4 weeks. Parameters studied were food consumption/body weight; hematology, clinical chemistry and urinalysis. These parameters were not significantly affected by the administration of Cetuximab.

Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were performed. In the 39-week repeat-dose toxicity study in Cynomolgus monkeys, examination of individual sexual cycle length from week 25 onwards, including the treatment-free period, revealed an impairment of menstrual cyclicity in Cetuximab treated females such as increased incidences of irregular cyclicity or absence of cyclicity when compared to controls. However, since pre-treatment cycles were not evaluated in any of the females in any group, this result cannot be confirmed. Evaluation of testosterone data and sperm analysis did not show any toxicologically significant differences among the treated groups when compared to controls. Histological examinations of organs of the reproductive system in the males and females treated with Cetuximab revealed no abnormalities attributable to Cetuximab.

Genotoxicity

In vitro genotoxicity investigations using *Salmonella typhimurium* and *Escherichia coli* as test systems with and without addition of liver S9 mix as external metabolising system yielded no indications of a mutagenic potential of Cetuximab. Furthermore, in an in vivo cytogenetic assay performed as a micronucleus test in male Wistar rats, cetuximab was not genotoxic. The results of the micronucleus test are considered of limited value due to the lack of immunoreactivity of Cetuximab with tissues from rats

Carcinogenicity

No carcinogenicity studies were performed.

Local tolerance

Local tolerance testing has been performed in New Zealand White rabbits with material originating from three different production processes. Cetuximab drug product and the vehicle were administered to 12 female rabbits - 6 females received IV, IM, and SC injections and 6 females received IA and PV injections - as a single injection of each type of administration on day 1. Afterwards animals were observed for 48 hours (3 females that received IV, IM, and SC; 3 females that received IA and PV) or 96 hours (the remaining 3 females of each group) before their scheduled necropsy.

No signs of systemic toxicity were observed. Gross pathological and histological examinations revealed no toxicologically relevant alterations.

Other toxicity studies

Immunogenicity

Antigenicity was demonstrated in rats as expected for chimeric proteinaceous product. Antibody responses were observed in 3/22 (13.6%) Cynomolgus monkeys. An effect on cetuximab serum concentrations was observed for one of these animals only. The assay for anti-cetuximab response was a non-species specific double antigen radiometric assay.

Immunotoxicity

No separate studies were performed.

Dependence

No studies were performed

Metabolites

No studies were performed

Studies on impurities

No studies were performed.

Ecotoxicity/environmental risk assessment

No environmental risk assessment was submitted.

Discussion on the non-clinical aspects

Comparability of the various batches used in the submitted studies and clinical batches has been discussed (data not shown). The drug batches used in the published pharmacodynamic studies have not been described.

Pharmacodynamics

Although batch characteristics for the cetuximab substance used are not described, overall, there is sufficient knowledge from *in vitro* studies published in the literature that cetuximab binds to the EGFR and to some degree inhibits the signals required for cell growth and expression of angiogenetic factors. Cetuximab binds to the EGFR with an affinity that is approximately 5- to 10fold higher than that of endogenous ligands. Cetuximab blocks binding of endogenous EGFR ligands resulting in inhibition of the function of the receptor. It further induces the internalisation of EGFR, which could lead to down-regulation of EGFR (see SPC section 5.1).

A number of effects have been observed on cultured cancer cell lines with respect to cell cycle progression, which was arrested in the G1 phase, induction of apoptosis, inhibition of angiogenesis and expression of angiogenetic growth factors, of ras-MAPK-signalling, of tumour cell motility and metastasis, of cell proliferation, of DNA repair after exposure to radiation, and of stimulation of antibody-dependent cellular cytotoxicity. Cetuximab also targets cytotoxic immune effector cells towards EGFR-expressing tumour cells (antibody dependent cell-mediated cytotoxicity, ADCC). These effects are adequately summarised in the SPC (see section 5.1).

Data on cross-reactivity or binding to the other receptors of the EGFR family, for example erb B-2 have not been submitted, and at present, there is no evidence to suggest that cetuximab binds receptors outside the EGFR family. However, because of their structural relationship, the other members of the EGFR family are candidates for a cross-reactivity of cetuximab. Since heteromerization of the members of EGFR family occurs in cell signalling, it is of special interest to know whether cetuximab binds to any member of the family beside EGFR and whether it interferes with receptor heteromerization and signal transduction of receptor heteromers. The applicant has committed to submit the results of an ongoing study to address this issue.

The applicant has submitted a justification for the lack of specific secondary pharmacodynamic studies. Taking into consideration the findings from the safety pharmacology studies, it is not expected that additional secondary pharmacodynamic studies would contribute significantly to the safety evaluation for potential adverse effects in humans [68].

The applicant has submitted a justification for not conducting specific studies on the effects of cetuximab on the CNS. Taking into consideration the nature of the product, the specific receptor targeting, and the findings from the toxicology studies, the justification provided by the applicant is acceptable. Additional investigations such as using a functional observation battery to investigate effects on the CNS would not contribute significantly to the safety evaluation for potential adverse effects in humans [68].

Pharmacokinetics

The lack of distribution data is acceptable considering the nature of the product.

Cetuximab is expected to be metabolised following the pathway of antibodies in general, and classical biotranformation studies are not needed [69].

It is not known whether cetuximab is excreted in breast milk. Low levels of maternal IgG are also found in breast milk of normal humans[70,71], including xenogenic IgG[72]. Therefore, besides a placental passage, a transfer of cetuximab into breast milk cannot be excluded. It is recommended that women do not breast-feed during treatment with Erbitux and for 1 month after the last dose (see SPC, section 4.6).

No pharmacokinetic studies in non-clinical models of disease were performed. Given the extensive clinical data available (see Part IV, Clinical aspects), which allow the provision of adequate information in the SPC (see section 5.2), additional non-clinical studies are not required.

Toxicology

A comprehensive 39-week repeat-dose toxicology study in the Cynomolgus monkey was conducted. The study was of adequate duration in line with applicable requirements [73,74].

In this study, severe toxicity was observed with cetuximab. Dose-related skin lesions were observed in all animals. Occasionally other epithelial effects e.g. conjunctivitis, reddened and swollen eyes were noted, as were signs of intestinal disturbances. Half of the animals in the high dose group died as a result of the treatment, which caused lesions of the skin, tongue, nasal cavity and oesophagus.

Pathogenetically the skin lesions were considered to be related to a Cetuximab induced maturation defect of the epidermis. This defect accounts for hyper-, parakeratosis, acanthosis, and acantholysis with clefts, pustules, and vesicle formation, summarised as dermatosis. Secondary bacterial superinfections, especially in high dose animals caused an erosive to ulcerative dermatitis with subsequent involvement of inner organs due to septicemia, especially in liver, spleen, bone marrow, and kidney.

The results of the 39-week toxicology study were in general agreement with those obtained from human clinical trials, where skin reactions were observed in >80 % of patients receiving cetuximab in the target indication studies and approximately 14 % experienced a grade 3 or 4 toxicity (see Part IV, Clinical aspects). However, obvious hypersensitivity reactions were not noted in the chronic primate toxicology study whereas this adverse event was of most clinical concern in humans.

The Cynomolgus monkey was considered an appropriate species for safety testing of cetuximab. The similarity of adverse reactions seen in monkeys and humans supports this notion. However, information about the binding affinity of cetuximab to monkey EGFR relative to human EGFR is lacking, and this makes the evaluation of the toxicology findings difficult.

Based on pharmacodynamic data, a potentiation of the toxicity of cetuximab in combination could be expected (although this has not been observed in the clinical studies). No toxicological studies have investigated the the co-administration of cetuximab and irinotecan. The applicant has committed to submit further clinical data on the combination of cetuximab and irinotecan generated in the ongoing/planned phase III studies. These studies will allow assessment of potential interactions of cetuximab and irinotecan in more than 1,000 patients over prolonged periods of time. Thus, the lack of non-clinical invistigations on the toxicity of co-administration with irinotecan has been adequately justified by the applicant.

Toxicology studies revealed no cardiovascular and respiratory effects. However, it is possible that non-clinical studies are not suitable for evaluation of cardiovascular effects mediated by receptors of the EGFR family, and that the risk assessment must be based on clinical data. The clinical experience with trastuzumab (a humanised monoclonal antibody to the erb B-2 receptor, which is closely related to EGFR), has revealed cardiotoxicity (particularly when combined with anthracyclines) as a main safety concern[75-78]. The applicant has committed to include the potential risk of cardiotoxicity in its safety surveillance programme.

Genotoxicity studies would normally not be required for pure proteins other than growth factors [79]. However, since cetuximab was shown to induce redistribution from the nucleus to the cytosol of the enzyme DNA-dependent protein kinase[43], which repairs breaks in DNA, the applicant decided to perform a partial genotoxicity study using in vitro and in vivo assays in terms of an AMES test and a rat micronucleus test. No genotoxic potential of Cetuximab was observed.

No standard carcinogenicity studies were performed with cetuximab as these are generally considered inappropriate for biotechnology-derived products[79]. The patient population targeted within the current indication comprises male and female adults suffering from metastatic colorectal cancer with palliative treatment options only (and the disease being at a life-threatening stage) and an anticipated life-expectancy of generally less than 1 year. Based on the life-expectancy in the intended therapeutic indication, no long-term carcinogenisity studies are required[80]. Rodents were considered unsuitable for toxicity testing of cetuximab in consideration of the potential immunogenic responses to a humanised protein. In addition, there were no concerns regarding carcinogenicity from the results of the genotoxicity studies and the chronic toxicity study in Cynomolgus monkeys, so that the lack of carcinogenicity studies seems justified[80].

Based on the repeated dose toxicity study, there are no serious concerns regarding reproductive toxicity as the only alteration possibly related to treatment with cetuximab was an impairment of menstrual cyclicity. Studies of toxicity to reproduction are not required for anticancer agents, since it is assumed that reproductive occurrences are generally expected [81].

EGFR has been described as being implicated in the control of prenatal development such that EGFR may be essential for fertility and implantation as well as normal organogenesis and may play a role in proliferation and differentiation. Since antibodies of the IgG class are actively transported across the placenta, cetuximab might be transported across the placental barrier. Additionally, considerable immunoreactivity of cetuximab was observed with placental probes of human or Cynomolgus monkey origin. Cetuximab should not be given to pregnant patients unless the potential benefit for the mother outweighs the potential risk to the fetus. It is also recommended that females should not breast-feed during cetuximab treatment or for 1 month after the last dose (see SPC section 4.6).

The local tolerance studies submitted by the applicant are not informative because the species (rabbit) is not considered relevant. In the pivotal repeated dose toxicity study in Cynomolgus monkeys

purulent superficial skin inflammation at the injection sites were detected. Given the extensive clinical experience available, further local tolerance testing are not required [81].

For EGFR inhibitors no immunotoxicological profiles have been reported. This seems to be in line with the lack of EGFR expression on immune cells. Nevertheless immunomodulatory effects of EGFR inhibitors cannot be excluded entirely. From limited published data it can be speculated that EGFR inhibitors might interfere with the epitheliotrophic functions of EGFR in primary and/or secondary immune organs [82-84]. No significant hematological aberrations were observed so far in patients under cetuximab monotherapy. No formal studies on immunotoxicological effects of cetuximab are planned in nonclinical primate models. The applicant has committed to conduct specific monitoring of the effects of Erbitux treatment on haematological-immunotoxicological parameters in ongoing and planned clinical trials.

EGFR signalling blockade before antigen challenge can enhance the immune response with increased chemokine expression and heavier inflammatory cell infiltrate[85]. EGFR targeting will thus have an impact on inflammatory and immune responses. Depending on the disease and the role of EGFR signalling in that disease, the outcome could be adverse, no effect or beneficial. Patients with medical histories of inflammatory diseases, should be assessed for any possible aggravation of these conditions following Erbitux treatment in ongoing and planned clinical studies. The applicant has committed to conduct specific monitoring of the effects of Erbitux treatment on underlying inflammatory disorders in ongoing and planned clinical trials.

No environmental risk assessment was submitted. Considering the intended use, the metabolic pathways of antibodies in general and the ubiquitous presence of decomposing organisms, no environmental concerns are expected with use of cetuximab.

4. Part IV: Clinical aspects

A total of 19 Phase I/II studies have been submitted evaluating the pharmacokinetic (PK) of intravenously administered cetuximab in 906 cancer patients. The documentation on clinical efficacy is based on three phase II clinical trials: EMR 62 202-007 (pivotal), IMCL CP02-9923, and IMCL CP02-0141. Clinical trials were conducted according to the principles of Good Clinical Practice (GCP).

Pharmacokinetics

The PK profiles of cetuximab have been investigated after administration of single or multiple intravenous (iv) doses in cancer patients. Results from individual studies were analysed by non-compartmental PK analysis. Results of all studies were analysed by a population PK approach with a total of 8388 concentration values.

All pharmacokinetic studies were performed in cancer patients with different solid tumours of epithelial origin. In most studies, only patients with EGFR positive tumours were included. A diagnostic assay (EGFR pharmDx^{TM}) was used for immunohistochemical detection of EGFR expression in tumour material. Approximately 80% of the patients with metastatic colorectal cancer screened for clinical studies had an EGFR-expressing tumour and were therefore considered eligible for cetuximab treatment. Four of the target-dose studies were performed in patients with colorectal cancer. In the studies where full pharmacokinetic profiling was performed, the mean age ranged between 50 and 64 years (range 22 – 86 years). No formal studies in healthy volunteers were conducted due to the risk of hypersensitisation.

Summaries of single- and multiple dose pharmacokinetic parameters of cetuximab as monotherapy at the target dose are presented in Table 3 and Table 4. The exposure to cetuximab was similar when cetuximab was administered in combination with irinotecan.

Intrasubject variability was not determined. The inter-individual variability was wide spread and ranged from approximately 30-100% in study CP02-9502 to 4-50% in study CP02-9607. The interpatient variability of the PK parameter estimates from the population PK analyses ranged between 6% and 40%.

Table 3. Pharmacokinetic parameters of cetuximab after single doses of 400 or 500 mg/m2 as monotherapy (target-dose study IMCL CP02-9710 and dose-escalation studies CA225004 and CA225005) (modified from clinical summary)

	Dose (mg/m²)	400	400
Parameter	**Study**	IMCL CP02-9710	CA225 004, 005
C_{max} (µg/ml)	Mean (S.D.)	167.83 (45.47)	226.14 (61.62)
	N	*35*	*10*
$AUC_{0-\infty}$ (µg /ml*h)	Mean (S.D.)	19263 (6878)	22051 (8413)
	N	*33*	*10*
$t_{1/2}$ (h)	Mean (S.D.)	93.53 (35.14)	87.03 (19.13)
	N	*33*	*10*
CL (L/hr/m²)	Mean (S.D.)	0.024 (0.009)	0.021 (0.008)
	N	*33*	*10*
V_{ss} (L/m²)	Mean (S.D.)	3.04 (0.95)	2.51 (1.03)
	N	*33*	*10*

Table 4. Combined pharmacokinetic parameters of cetuximab from different studies at the target dose 400/250 mg/m^2, once weekly dosing (modified from clinical summary).

Weeks	**Studies**	**Statistic**	**CL (L/h)**	**AUC (µg/ml*h)**	**$t_{1/2}$ (h)**	**V_{ss} (L)**
1	IMCL CP02-9503, 9504, 9607, 9608, 9709, 9710; CA225004, 005	*N*	*53*	*53*	*53*	*53*
		Mean	**0.022**	**21142**	**97.24**	**2.88**
		S.D.	0.009	8657	37.38	0.93
3	IMCL CP02-9709 and EMR 62 202-012	*N*	*8*	*8*	*8*	*8*
		Mean	**0.020**	**22723**	**123.25**	**2.30**
		S.D.	0.006	10313	41.39	0.83
4	IMCL CP02-9607, 9608 and EMR 62 202-012	*N*	*13*	*11*	*11*	*11*
		Mean	**0.017**	**24329**	**108.09**	**2.00**
		S.D.	0.006	11202	29.32	0.59

- Distribution

The mean volume of distribution at steady state, V_{ss}, was about 2-3 L/m^2 at the target dose (absolute values about 4-6.5 L), suggesting distribution only within the vascular space. The volume of distribution was independent of dose.

In the population pharmacokinetic analysis, the estimated volumes of the central and peripheral compartments were 4.49 and 4.54 L, respectively, with a 27% reduction in the typical value of the central volume in females. Total V_{ss} from the population analysis was, thus, about 9 L.

Plasma protein binding studies were not performed.

- Elimination

The elimination pathways of cetuximab have not been specifically studied.

- Dose proportionality

Single-dose pharmacokinetics of cetuximab as monotherapy at different doses was evaluated in three studies. Doses from 5 to 500 mg/m^2 were administered as single infusion, and plasma sampling was performed during 3 or 4 weeks after dosing. In all three studies, C_{max} increased in a dose-related manner, while AUC increased more than dose proportionally. Mean CL values decreased from 0.079 L/h/m^2 after a single dose of 20 mg/m^2 to 0.018-0.022 L/h/m^2 after a single dose of 200-500 mg/m^2. These observations were supported by the population PK, indicating that following single infusions in the range of 250 to 500 mg/m^2 the clearance tends to become constant. A dose-dependant relationship

was also observed for the elimination half-life ($t_{1/2}$). The mean $t_{1/2}$ values increased with dose from 33.9 h to 119.4 h after single doses of 20 mg/m^2 to 500 mg/m^2. At the target dose, 400/250 mg/m^2, $t_{1/2}$ values were about 80-120 hr.

- **Time dependency**

Peak and trough concentrations of cetuximab were determined after up to eight weekly doses. No apparent changes in pharmacokinetics of cetuximab over time at repeated dosing were observed. In general, the peak and trough concentration appeared to be stable from dose three or four and onwards, which is consistent with a half-life of about 100 hours.

- **Antibody formation**

Anti-cetuximab antibodies (HACA) data were available from a total of 534 patients. Most of these patients were treated at target dose. The incidence of positive antibody response in individual studies was variable and did not follow a clear trend. In total, only 20 patients (3.7%) displayed positive HACA responses. Data from two patients indicated that anti-cetuximab antibody response leads to lower cetuximab exposure. There was no clear relationship between response incidence and cetuximab dose.

- Special populations

There are no formal studies in special patient sub-populations, but a population pharmacokinetic analysis was performed. The database included data from all cetuximab studies with pharmacokinetic sampling. The final dataset contained 8388 observations from 906 patients, and from 19 studies. Approximately 45% of the observations came from three studies (CP02-9504, CP02-9710 and EMR 202-007). A two-compartment model with a single saturable elimination pathway was finally selected. Adding a linear elimination pathway to the model only marginally improved the model, and the linear pathway was estimated to be more than 30 times slower than the saturable pathway.

Impaired renal function

Only 49 and 4 patients (of total 906) had moderate and severe impairment, respectvely. Renal function (based on CLcr) was not identified as an important factor for cetuximab pharmacokinetics. The median CLcr in the population was 93.3 ml/min with the range 6.7 to 150 ml/min.

Impaired hepatic function

More than 90 % of the patients had normal hepatic function, as assessed by AST and total bilirubin levels. Thus, influence of hepatic function on cetuximab pharmacokinetics could not be adequately estimated.

Gender

Of the patients included in the final dataset, 578 were male (63.8%) and 328 were female (36.2%). Gender was identified as a significant co-variate for volume of the central compartment (absolute volume) and for CL (V_{max} and Km). However, the effect did not necessitate dose adjustments based on gender.

Race

The majority of patients included in the integrated pharmacokinetic database were Caucasian (815 patients, representing 90%). An evaluation of impact on race could not be made.

Weight

The median weight was 73.5 kg, range 36.8 to 167 kg. Weight and BSA were identified as significant co-variates for volume of the central compartment.

Elderly

The median age was 60 and 57 years for males and females, respectively. The age range was 22 to 88 years. Age did not seem to have an impact on volume of distribution (absolute volume) or CL of cetuximab.

Children

There are no pharmacokinetic data for children.

Interaction studies

In an interaction study with irinotecan (Study EMR 62 202-012), cetuximab and irinotecan were administered at the therapeutic dosages. Effects of cetuximab on pharmacokinetics of irinotecan and its active metabolite SN-38 were assessed in patients who received irinotecan day 1 and 22, and cetuximab day 8, 15 and 22. Effects of irinotecan on cetuximab were evaluated in another group, receiving cetuximab on day 1, 8, 15 and 22 and irinotecan on day 22. Statistical analysis of the data was not performed, but there were no apparent changes in pharmacokinetics of either irinotecan or cetuximab, when administered together with the other drug. For SN-38 the variability was large and since only samples around T_{max} had SN-38 levels above LLQ, a meaningful analysis of data could not be made for the metabolite. A possible impact of co-administered chemotherapies and radiation therapy on the PK of cetuximab was evaluated in the population pharmacokinetic analysis (data not shown).

Discussion on pharmacokinetics

The pharmacokinetics of cetuximab were investigated in patients with solid, epithelial tumours using adequately validated assays. A population pharmacokinetic analysis was conducted using appropriate modelling techniques. Comparability of all investigated materials was demonstrated with regard to their structure and function. The manufacturing processes were also comparable. An integrated pharmacokinetic database analysis across all studies confirmed these findings showing that the use of different materials results in comparable PK profiles of cetuximab (data not shown).

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 three weeks of cetuximab monotherapy. Mean peak cetuximab concentrations were 155.8 microgram per ml in week 3 and 151.6 microgram per ml in week 8, whereas the corresponding mean trough concentrations were 41.3 and 55.4 microgram per ml, respectively. In a study of cetuximab administered in combination with irinotecan, the mean cetuximab trough levels were 50.0 microgram per ml in week 12 and 49.4 microgram per ml in week 36 (see SPC section 5.2). The interpatient variability was generally large.

Throughout the clinical development, cetuximab was dosed based on body surface area (BSA). The accuracy of this regimen has not been convincingly demonstrated. The population pharmacokinetic analysis did indicate a relationship between weight as well as BSA and cetuximab volume of distribution, but not with clearance. Simulations of plasma concentrations in patients with different BSA indicated that higher steady state concentrations are reached in patients with a large BSA, while observed trough concentrations did not seem to correlate with BSA. The estimated clearance was slightly higher in men than in women, which to some extent may be explained by gender differences in body weight. The effect was minor, and small compared to the overall variability. Consequently, dosing based on BSA is not supported by the population pharmacokinetic analysis and a risk for underexposure in patients with a small BSA cannot be completely excluded. Indeed, a tendency to higher incidence of skin reactions in patients with larger BSA has been observed. The Applicant therefore intends to further evaluate a potential difference in exposure depending on BSA, when more data become available from ongoing and planned clinical studies.

No metabolism or mass-balance studies have been performed, and this is acceptable since biotechnology-derived pharmaceuticals are expected to degrade into small peptides and individual amino acids [79]. Several pathways have been described that may contribute to the metabolism of antibodies. Targeted antibodies such as cetuximab disappear from the central compartment via a specific, saturable target (antigen) specific elimination process based on receptor/ligand internalization[86-88]. At a certain serum concentration, the EGF receptors will become saturated. At this point, second, non-saturable, unspecific elimination becomes apparent, as indicated by the observation that CL and $t_{1/2}$ values remain constant. This elimination pathway is common for all antibodies. Antibodies are usually recognized by several receptors that have binding affinities to either the protein and carbohydrate moieties on the Fc region. Binding of antibodies to these receptors is usually followed by internalization and further catabolism [89,90]. This process of antibody catabolism is

believed to take place primarily in the intestine, the liver and the reticuloendothelial system. Due to the very large number of receptors in the body it is believed that these receptors are not saturable at cetuximab doses that were applied in clinical studies. All of these pathways involve the biodegradation of the antibody to smaller molecules, i.e. small peptides or amino acids (see SPC section 5.2).

Plasma protein binding studies were not performed. Such studies are not considered necessary as significant binding to plasma proteins in not expected for a humanised monoclonal IgG1 antibody.

The population pharmacokinetic analysis showed that the overall pharmacokinetic characteristics of cetuximab did not appear to be importantly influenced by race, age, gender, renal or hepatic status (see SPC setion 5.2). However, due to the low number of patients with significantly impaired renal or hepatic function included in the analysis, conclusions regarding these populations cannot be drawn. Moreover, the relevance of the two chosen markers for hepatic function for all types of hepatic impairment might be questioned. The lack of data is adequately refelected in the SPC (see section 4.4 and 5.2).

Only one formal interaction study has been performed, with cetuximab and irinotecan. No effects were seen on either cetuximab or irinotecan pharmacokinetic parameters when the two were given in combination (see SPC, section 4.5). According to the population pharmacokinetic analysis there were no effects of other concomitant cytotoxics or irradiation on cetuximab pharmacokinetics, but for most of the concomitantly used treatments, there were too few patients to draw definite conclusions (data not shown). However, the potential for pharmacokinetic interactions with cetuximab is expected to be small. Thus, the lack of other formal interaction studies than that with irinotecan is accepted.

Like other monoclonal antibodies Cetuximab has the potential to induce an immune response and to form antibodies when administered to patients. Most study protocols included sampling for determination of anti-cetuximab antibodies (HACA). The analysis methods for HACA are considered at best qualitative, and large amounts of cetuximab still present in the samples may have interfered with the analysis, masking a positive antibody response. Thus, data regarding antibody formation are difficult to interpret. The data indicate that only few patients (3.7%) had a positive antibody response to cetuximab treatment. Data from two patients indicate that anti-cetuximab antibody response leads to lower cetuximab exposure. Thus, the observations that cetuximab pharmacokinetics do not change over time may support a low frequency of antibody response. The appearance of HACA did not correlate with the occurrence of hypersensitivity reactions or any other undesirable effect to cetuximab (see SPC, section 5.1). However, there remain potential effects of antibodies on the results of the cetuximab assays. Serum from patients with high titres of antibodies did not inhibit cetuximab-induced effects on cell growth *in vitro*. The lack of conclusive data has been adequately reflected in the SPC (see section 5.1).

Pharmacodynamics

Two studies were performed to evaluate the pharmacodynamics of cetuximab: IMCL CP02-9608 and CA225005.

In study IMCL CP02-9608 tumour tissues from 12 patients were obtained at baseline, 24 hours after the initial infusion and 24 hours before the third infusion in order to assess tumour EGFR binding and function. Results of immunohistochemistry indicated saturation by cetuximab of tumour EGFR of between 10 and 95 % depending on dose.

In study CA225005, with PK data collected for 26 patients, the PK/pharmacodynamic relationships were investigated in skin and tumor biopsies after single cetuximab doses of 50 to 500 mg/m². Single doses of cetuximab at 250, 400, and 500 mg/m² resulted in decreases of EGFR protein levels in skin. The administration of cetuximab doses lower than 250 mg/m² resulted in a slight increase in EGFR protein levels. EGFR receptor saturation could not be reliably determined. Attempts were made to investigate expression of related down-stream proteins. Results were, however, inconclusive.

In addition, the relationship between cetuximab serum concentrations after the target dose and efficacy were investigated in the integrated PK database analysis. No association between clearance and efficacy was observed.

<u>Dose finding</u>

The maximum tolerated dose was not reached in the clinical dose-escalation studies. The chosen dose and dosing regimen are based on the results of the PK analysis in combination with the efficacy and safety data generated in the clinical studies. Based on the PK data (half life of about 4 days, no relevant accumulation), a weekly regimen is expected to give a predictable PK for cetuximab using the target dose. Cmax and AUC values increased linearly with dose, while the CL values at the target dose are approximately 0.02 L/h/m2. The pharmacokinetic behavior of cetuximab appeared to remain similar after multiple dosing. A concentration dependent decrease in clearance, interpreted as saturation of receptor mediated clearance and finally a "plateau" in the incidence of skin reactions contributed to the choice of dose and dosing regimen.

Irinotecan was used at the approved dose in the 3 target-indication studies, and this is recommended for combination therapy. The 2 drugs did not show overlapping toxicities, and there was no evidence for a PK interaction.

Discussion on pharmacodynamics

The limited data presented indicate that cetuximab at doses within the target dose-range led to down-regulation of EGFR in normal tissue and there was some correspondence between higher $AUC_{0\text{-}inf}$ values and decrease in EGFR expression. The variability was large and at low dosages, an apparent upregulation of EGFR and activated (phosphorylated) EGFR was noted. The number of samples was much too low, however, to allow a meaningful interpretation and the applicant has committed to conduct further studies in order better to characterise the prerequisites for cetuximab activity.

Partial reversal of resistance to cytotoxic compounds has been convincingly demonstrated and is of major clinical interest, but the hypothesis that this is due to inhibition of EGF signalling requires further confirmation (ADCC is an alternative explanation). Further studies have been initiated in order better to characterise cetuximab activity.

No studies evaluating pharmacodynamic interactions especially with irinotecan have been performed. There were no studies designed in order to try to disentangle the mechanisms behind reversal of irinotecan resistance. It is acknowledged that the poor predictive value in general of *in vitro* studies makes them less than ideal to address this issue. It is also acknowledged that biopsy data under clinical conditions in general are likely to be much more informative than data derived from fresh tumour samples under *ex vivo* conditions. However, clinical biopsies seem less suitable to disentangle the mechanisms behind reversal of irinotecan resistance. From this perspective, it would be of some interest to know, *e.g.* whether add-on of cetixumab to irinotecan (and other compounds) *in vitro* is similarly active in samples resistant or not to irinotecan. Further pharmacokinetic, pharmacodynamic and pharmacogenomic studies have been designed to explore different cetuximab dosing strategies.

With respect to cetuximab resistance, the applicant has committed to further investigate the issue of primary resistance in studies programme, including biopsy data at time of progression of disease.

For conventional cytotoxic compounds, toxicity is an accepted surrogate for efficacy in dose-finding trials. In principle, the same approach has been used here although not aiming at defining the maximum tolerated dose. Thus, dose selection essentially relies on three elements, all seemingly related to effects on normal tissues: EGFR down-regulation, saturation of elimination capacity and skin toxicity.

Sparse data on receptor down-regulation in healthy tissue (skin), saturation of likely receptor mediated clearance of the compound (see pharmacokinetics) and "maximum" skin toxicity altogether indicates receptor saturation. It could be said, however, that for a large molecule such as a monoclonal antibody, apparent saturation of normal tissue EGFR might not reflect saturation of deep tumour tissue receptors.

At this stage, however, the proposed posology is considered reasonably justified, but further dose finding studies are in the planning phase. The posology and method of administration are adequately described in the SPC (section 4.2). Erbitux is administered once a week, until progression. The initial dose is 400 mg cetuximab per m^2 body surface area. The subsequent weekly doses are 250 mg/m^2 each. Normally, the same dose of irinotecan is used as administered in the last cycles of the prior irinotecan-containing regimen.

Clinical efficacy

Main study(ies)

Study EMR 62202-007 (BOND) was an open, randomised, multi-center, phase II study of cetuximab alone or in combination with irinotecan in patients with metastatic colorectal adenocarcinoma expressing the epidermal growth factor receptor (EGFR) and progressing on a defined irinotecan based regimen [91].

Methods

- Study Participants

The main eligbility criteria were stage IV histologically confirmed adenocarcinoma of the colon or rectum with measurable disease (at least 1 unidimensionally measurable lesionoutside previously irradiated area), immunohistochemical evidence of positive EGFR expression prior to study entry in primary tumor or at least 1 metastasis, documented progression by comparison of CT or MRI scans (new lung lesions could be documented by chest X-ray) on irinotecan-based therapy (irinotecan 125 mg/m² weekly for 4 consecutive weeks, followed by 2 weeks rest, as a single agent or in combination with 5-FU/FA, or irinotecan 180 mg/m² every 2 weeks in combination with 5-FU/FA, or irinotecan 350 mg/m² every 3 weeks as a single agent; with a maximum of 2 licensed dose reductions) for at least 6 weeks within 3 months of randomization. Other criteria included age ≥18 years, Kanofsky performance status ≥60, life expectancy of ≥3 months, effective contraception, neutrophils $\geq 1.5\times10^9$/L, platelets $\geq 100\times10^9$/L, and hemoglobin ≥9 g/dL; bilirubin level <1.5×ULN (upper limit of normal range), aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) ≤5×ULN, serum creatinine <1.5×ULN, recovery from relevant toxicities. Patients who met one or more of the following criteria were to be excluded from the study: brain metastasis (known or suspected), surgery (excluding diagnostic biopsy) or irradiation in the 4 weeks prior to study entry, concurrent chronic systemic immune therapy, or hormone therapy not allowed by the protocol, any investigational agent(s) within 4 weeks prior to study entry, previous exposure to EGF, monoclonal antibodies, signal transduction inhibitors, or EGFR-targeting therapy, clinically relevant coronary artery disease or history of myocardial infarction within the last 12 months, acute or subacute intestinal occlusion or history of inflammatory bowel disease, known grade 3 or 4 allergic reactions to any of the components of the study treatment, pregnancy or breast feeding, previous malignancy with the exception of a history of a previous basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix, known drug or alcohol abuse.

- Treatments

All patients were to be treated with study medication until PD or occurrence of unacceptable toxicity. The treatment period consisted of 2 parts:

Part 1:

– Arm A: Patients received cetuximab in combination with the same irinotecan regimen to which they became refractory. Patients who benefited from the combination therapy but developed unacceptable toxicity to irinotecan were allowed to continue cetuximab as a single agent.

– Arm B: Patients received cetuximab monotherapy. Patients with treatment failure were eligible for part 2 of the study.

Part 2:

Patients who failed cetuximab monotherapy in arm B of part 1 could continue cetuximab treatment in combination with the same irinotecan regimen to which they had become refractory. Irinotecan was to be reintroduced within 2 weeks after documentation of PD on cetuximab monotherapy. Cetuximab was to be continued as weekly therapy without an initial dose whereby therapy could be interrupted for up to 2 weeks after documentation of PD on cetuximab as a single agent.

Cetuximab was to be administered as an initial dose of 400 mg/m² (infusion duration 120 min), including a test dose of 20 mg, followed by weekly doses of 250 mg/m² (infusion duration 60 min). Infusions were given via an infusion pump or gravity drip, whereby the infusion rate was not to exceed 10 mg/min (5 ml/min). A physician had to be present during the first administration of

cetuximab (i.e. initial dose). The cetuximab infusion was to end at least 1 hour before the start of the irinotecan infusion.

Irinotecan was to be administered over 30 to 90 minutes at the same dosage regimen on which the patient had become refractory (including up to 2 dose reductions for prior irinotecan-associated toxicity), i.e. 125 mg/m² weekly for 4 consecutive weeks, followed by 2 weeks rest, 180 mg/m² every 2 weeks, or 350 mg/m² every 3 weeks

- Objectives and endpoints

The primary objective was to determine the confirmed objective response rate of the combination of cetuximab plus irinotecan and of cetuximab as a single agent. Secondary objectives included the assessment of progression-free survival, duration of response, overall survival, toxicity, population pharmacokinetic parameters, response rate and time to second progression in part 2 of the study. Objective tumour response rate was defined as the proportion of patients in the study population with best overall confirmed complete response (CR) or partial response (PR). An Independent Review Committee (IRC) assessed the primary efficacy endpoints according to modified WHO criteria for part 1 of the study[92]. Response was also assessed by the investigators according to the Response Evaluation Criteria in Solid Tumours (RECIST)[93]. Assessments of tumour response were based on computed tomography (CT) or magnetic resonance imaging (MRI) scans that were to be performed every 6 weeks. The size of index lesions was measured, non-index lesions were assessed, and new lesions recorded. The IRC comprised 3 qualified radiologists (readers) and 1 oncologist who did not participate in this study. Each IRC was blinded with regard to institution, patient and treatment group but was not blinded with regard to pre- versus on study scans. The IRCs reviewed all images and appropriate clinical data, but were not presented with information on efficacy from the clinical investigator, such as lesion measurements or response assessments based on CT or MRI scans. The IRCs were convened separately to review the pre-study irinotecan data and the on study efficacy data. Data from each patient were evaluated independently by 2 of the radiologists who were asked to determine: date of PD (if any) on prior irinotecan therapy, the primary efficacy endpoint of best overall response, date of response, date of response confirmation, date of progression. If the 2 readers disagreed on any of the assessments, the third reader had to adjudicate the differences. Finally, the third reader and the oncologist re-assessed the patient response based on integration of the clinical data with the existing radiological findings.

- Sample size

Initially the study was designed to enrol 225 patients: 150 to be treated with cetuximab in combination with irinotecan and 75 with cetuximab monotherapy. The sample size for the combination group was calculated in order to allow for an observed lower 95%-confidence limit of about 12% when anticipating an observed response rate of 19%. No formal rationale was given for the number of patients receiving monotherapy.

Discussions with authorities during the study revealed that a patient population that fulfilled more restrictive inclusion criterion of being progressive at most 1 month after end of irinotecan treatment course would be considered truly refractory to irinotecan. Thus, the sample size of this study was increased to a total of 300 patients (200 combination and 100 monotherapy) in order to ensure that the study objectives could be met for the subset of patients who fulfil the stricter definition of 'failure of irinotecan treatment'. While this increase of sample size was primarily made to achieve sufficient power for a subgroup of patients, it increased the chance of distinguishing the effect of the combination therapy from that of monotherapy in the primary ITT population (secondary objective of the study).

This was considered desirable because evidence from another study indicated that the response rate under cetuximab monotherapy was higher than expected at the time when the study was planned. With the final sample size a statistical comparison between the 2 treatments would have a power of about 80% to detect an association (Fisher's exact test) if the response rates in the 2 treatments groups were 19% (combination therapy) and 7% (monotherapy), respectively.

- Randomisation

Eligible patients who had given their written informed consent were centrally randomised by means of telephone randomisation. Patients were randomised in a ratio of 2:1 to cetuximab in combination with

irinotecan or cetuximab monotherapy. The time between randomisation and first infusion of cetuximab was not to exceed 3 days. Randomisation was performed by minimisation with the following stratification factors: KPS: 60 to 70 vs. 80 to 100, previous treatment (first-line treatment, subsequent treatment line with or without prior oxaliplatin), as well as centre.

- Blinding (masking)

This was an open-label study. Radiological scans and clinical data for evaluation of tumour response were assessed by an independent review committee blinded to patient's treatment. No information on efficacy as reported by the clinical investigator was passed to this committee (see also objectives and endpoints).

- Statistical methods

Analyses of objective response (as the primary parameter), disease control rate, best overall response, duration of response, time to response, and time to progression (TTP) were based on the IRC assessed data. Point estimates and (exact) 95% confidence interval were used to describe objective response, disease control rate and best overall response for both treatment groups. Objective confirmed response rates as well as disease control rates were compared using 2-sided Fisher's exact test and Cochran-Mantel-Haenszel test to adjust for stratification factors used in the randomisation process (KPS and line of treatment). In addition, the difference in response rates between groups and its 95% confidence interval (CI) were computed.

For those mono-therapy patients who entered part 2 of the study, descriptive statistics for best overall response as well as for disease control rate (according investigator) were presented. No formal testing was done in part 2.

Results

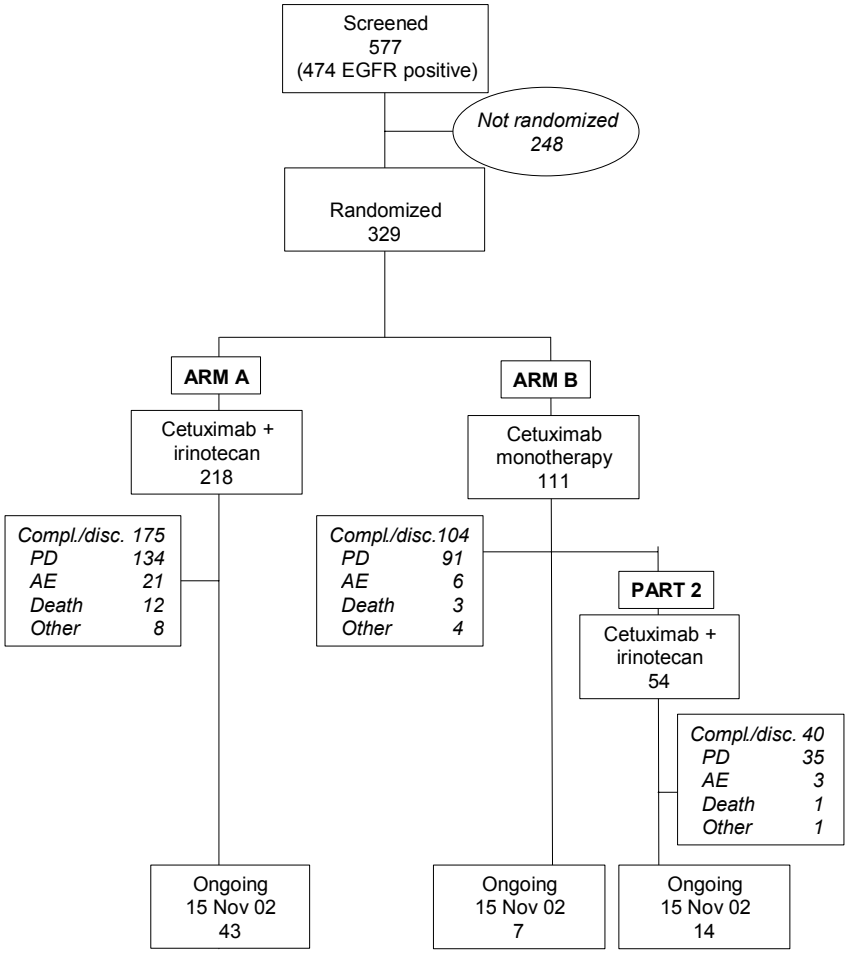
Patients were enrolled at 56 centres in 11 European countries (Austria, Belgium, France, Germany, Italy, The Netherlands, Norway, Spain, Switzerland, Sweden, United Kingdom).

- Participant flow

At 56 centres in 11 European countries the EGFR status of 577 patients was pre-screened, 474 (82.1%) were positive and screened for eligibility. Finally 329 patients were randomised to study medication in a 2:1 ratio: 218 to cetuximab in combination with the same irinotecan regimen to which they had become refractory (arm A) and 111 to cetuximab monotherapy (arm B). The most common reasons for not randomizing patients into the study were: no PD on previous irinotecan before stop of recruitment (n=58), patient not eligible (n=38), rapid PD or death (n=18), worsening of physical condition (n=16), and refusal (n=8)
In both groups 1 patient was randomised, although they were not EGFR positive. Two patients randomised in arm A did not receive any study medication. Four patients were randomised to the combination group, but received only 1 dose of cetuximab as a single agent due to a severe hypersensitivity reaction. In the efficacy evaluation these patients were analysed as randomised, in the safety population they were analysed together with the other patients of the monotherapy group.

After randomisation 279 (84.8%) patients discontinued from or completed part 1 of the study, mostly because of PD: 82.0% of monotherapy patients discontinued due to PD compared with 61.5% of combination therapy patients until the cut-off date. The percentage of withdrawals due to AEs and deaths was higher in the combination therapy group than in the monotherapy group, which can be explained by the longer observation period. In part 1 of the study 54 patients with PD under monotherapy elected to start combination therapy in part2, but finally 40 of these patients discontinued from the study. Three patients with major protocol deviations were excluded from the per-protocol population and analysed in the ITT population: one patient in each treatment group without positive EGFR status and one patient without metastatic CRC at baseline in the monotherapy group (Figure 2).

Figure 2. Partcipant flow of study EMR 62202-007



- Baseline data

Both randomised groups were well balanced with regard to demographic, baseline and disease characteristics (Table 5). The median age of the overall population was 59 years. There were only 12 patients (4%) aged 75 years or above. All but 6 of the 329 patients were Caucasian. There were no differences with regard to the number of metastases or their location. In both treatment arms, over half of the patients had <20% EGFR-positively stained cells. The maximal EGFR staining intensity of tumour material was similar in both groups. In about one-third of the patients (33.1%) staining intensity was classified as strong.

A total of 141 (42.8%) patients had 3 or more prior treatment lines for metastatic CRC, 206 (62.6%) received a previous oxaliplatin-based regimen, and 59 (27.1%) patients had prior adjuvant chemotherapy. The majority of the patients, 178 (54.1%), received 180 mg/m^2 irinotecan every 2 weeks as their most recent pre-study regimen. The median duration of the most recent irinotecan treatment was 79 days and the best overall response to the most recent irinotecan-containing chemotherapy was PR in 23 (7.0%) patients and SD in 71 (21.6%) patients. The time between the end of the last course of pre-study irinotecan treatment and documented PD (IRC) was <30 days in 249 (75.7%) patients and >30 days in 40 (12.2%) patients; the pre-study IRC-PD dates were not available for the remaining 40 (12.2%) patients.

Table 5: Baseline characteristics

Characteristic		Combination therapy (N=218)	Monotherapy (N=111)	Total (N=329)
Age (years)				
	Median	59	58	59
	Range	26–82	39–84	26–84
Age categories, n (%)				
	<65 yrs	155 (71.1%)	78 (70.3%)	233 (70.8%)
	>65 yrs	63 (28.9%)	33 (29.7%)	96 (29.2%)
Gender, n (%)				
	Males	143 (65.6%)	63 (56.8%)	206 (62.6%)
	Females	75 (34.4%)	48 (43.2%)	123 (37.4%)
KPS <80		25 (11.5%)	15 (13.5%)	40 (12.2%)
KPS ≥80		193 (88.5%)	96 (86.5%)	289 (87.8%)
Metastatic CRC(months)				
	Median	16	17	16.1
	Range	1.4–97.1	0.1–64.6	0.1–97.1
Tumour localisation (n;%)				
	Colon	125 (57.3%)	65 (58.6%)	190 (57.8%)
	Rectum	90 (41.3%)	43 (38.7%)	133 (40.4%)
	Missing	3 (1.4%)	3 (2.7%)	6 (1.8%)
Metastatic sites (n;%)				
	1	102 (46.8%)	62 (55.9%)	164 (49.8%)
	2	78 (35.8%)	27 (24.3%)	105 (31.9%)
	>2	9 (4.1%)	6 (5.4%)	15 (4.6%)
Location (n;%)				
	Liver	153 (70.2%)	76 (68.5%)	229 (69.6%)
	Lung/ lymph node chest	71 (32.6%)	29 (26.1%)	100 (30.4%)
	Lymph node abdomen/ pelvis	21 (9.6%)	16 (14.4%)	37 (11.2%)
	Intestine/ bowel/ visceral	3 (1.4%)	0 (0%)	3 (0.9%)
	Other	38 (17.4%)	13 (11.7%)	51 (15.5%)
No. (%) patients with EGFR-positive cells				
	0%	1 (0.5%)	1 (0.9%)	2 (0.6%)
	>0-<10%	93 (42.7%)	40 (36.0%)	133 (40.4%)
	10-<20%	23 (10.6%)	22 (19.8%)	45 (13.7%)
	20-<30%	18 (8.3%)	10 (9.0%)	28 (8.5%)
	30-<40%	21 (9.6%)	6 (5.4%)	27 (8.2%)
	≥40%	62 (28.4%)	32 (28.8%)	94 (28.6%)
Degree of EGFR staining, no. (%) patients				
	Faint/barely	53 (24.3%)	21 (18.9%)	74 (22.5%)
	Weak/moderate	89 (40.8%)	55 (49.5%)	144 (43.8%)
	Strong	75 (34.4%)	34 (30.6%)	109 (33.1%)
	Missing	1 (0.5%)	1 (0.9%)	2 (0.6%)
treatment lines for CRC				
	3	61 (28.0%)	20 (18.0%)	81 (24.6%)
	>3	37 (17.0%)	23 (20.7%)	60 (18.2%)
Prior adjuvant therapy		59 (27.1%)	37 (33.3%)	96 (29.2%)

- Numbers analysed

The number of patients analysed for efficacy in the different patient populations are summarized in Table 6.

Table 6: Analysed patients populations

	Number of patients analysed		
Population	Combination	Monotherapy	Total
ITT	218	111	329
IRC-PD[1]	135	71	206
ITT oxali[2]	135	71	206
IRC-PD oxali[3]	84	46	130
Per protocol	122	66	188

1 – all ITT patients with objective confirmed irinotecan refractory status
2 – all ITT patients with prior oxaliplatin treatment
3 – all IRC-PD patients with prior oxaliplatin treatment

Outcomes and estimation

The primary and secondary efficacy results are summarised in Tables 7 and 8. The proportion of responders in the combination group was 22.9% (95%-CI: 17.5% - 29.1%), exceeding the minimum 12% limit prespecified as clinically important. No complete responses were observed. In the monotherapy group, the proportion of responders was 10.8% (95%-CI: 4.1% - 20.2%). An exploratory treatment comparison showed that the combination treatment results in a statistically significant difference of 12.1% favouring the combination arm (p=0.0074). The difference in the disease control rate (CR+PD+SD) was also statistically significant (23,1% and p=0.0001) favouring the combination therapy (55.5%) over the monotherapy (32.4%).

The investigators'and the IRC assessments of objective response rate and disease control rate were compared for the ITT and the IRC-PD population. In the majority of patients (236, 71.7%), the evaluation was conform with similar objective response rates in both treatment groups. However, in comparison to the IRC the disease control rate was higher assessed by the investigators.

In the IRC-PD population, a difference to the ITT population was found for the monotherapy group with a higher assessed response rate by the investigator (16.9% vs. 13.5%).

The combination therapy with cetuximab + irinotecan was superior to the monotherapeutic regimen with cetuximab alone. With regard to the median time to progression (TTP) this difference was statistically significant (combination 4.1 months vs. 1.5 months in the monotherapy group). The estimated hazard ratio was 0.54 (95%-CI: 0.42 – 0.71) indicating a 46% risk reduction for progression for a patient receiving the combination instead of cetuximab alone. The robustness of this statistically significant difference was confirmed by the hazard ratios in all four subpopulations (IRC-PD, ITT oxali, IRC-PD oxali, per protocol) assessed.

Subgroup analysis according to demographic and baseline characteristics revealed that in almost all subgroups there was a significant risk reduction for progression under combination compared to monotherapy. Patients with an objective response (CR+PR) after receiving the combination therapy had a TTP of 8.4 months in comparison to patients in the monotherapy with a TTP of 5.6 months.

Cut-off date for survival data was 31 January 2003. Up to this timepoint 215 (65.3%) of the 329 ITT patients had died (140 in the combination therapy group, 75 in the monotherapy group).

In the combination therapy group patients had a longer median survival time of 8.6 months (95% CI 7.6, 9.6) compared with 6.9 months (95% CI 5.6, 9.1) in the monotherapy group, resulting in a harzard ratio of 0.91 (95% CI: 0.68 – 1.21). This difference was not statistically significant (p=0.48). In the other populations the survival time was similar to the ITT population. Overall the 1-year survival rate was around 1 year.

Table 7. Summary objective response rates and disease control rates in the ITT population and in secondary analysis populations (IRC assessment)

Response parameter	**Combination therapy (N=218)**		**Monotherapy (N=111)**		**Difference in Proportions**	
	n	**% (95%-CI)**	**n**	**% (95%-CI)**	**% (95%-CI)**	**p-value***
Objective response (CR+PR)	50	22.9 (17.5, 29.1)	12	10. 8 (5.7, 18.1)	12.1 (4.1, 20.2)	0.0074
Disease control (CR+PR+SD)	121	55.5 (48.6, 62.2)	36	32.4 (23.9, 34.0)	23.1 (12.1, 34.0)	0.0001
	n/N	**%**	**n/N**	**%**	**%**	**p-value***
IRC-PD						
Objective response rate	34/135	25.2 (18.1, 33.4)	10/71	14.1 (7.0, 24.3)	11.1	0.0747
Disease control rate	76/135	56.3 (47.5, 64.8)	24/71	33.8 (23.0, 46.0)	22.5	0.0032
ITT oxali						
Objective response rate	30/135	22.2	6/71	8.5	13.8	0.0127
Disease control rate	68/135	50.4	22/71	31.0	19.4	0.0081
IRC-PD oxali						
Objective response rate	21/84	25.0	5/46	10.9	14.1	0.0673
Disease control rate	45/84	53.6	14/46	30.4	23.1	0.0163
Per-protocol						
Objective response rate	34/122	27.9	10/66	15.2	12.7	0.0702
Disease control rate	74/122	60.7	23/66	34.8	25.8	0.0008

*p-value for difference between treatment groups determined by Fisher's exact test (2-tailed).

Efficacy analysis in part 2 of the study:

Fifty-four patients with PD in the monotherapy group entered part 2 of the study until the cut-off date. Efficacy variables for this part were only assessed by the investigators. Only 1 patient (1.9%) reached the primary endpoint, the objective response rate (CR+PR) while being in PR. However, 21 patients (38.9%) had SD, resulting in an overall disease control rate of 40.7%.

Table 8: Secondary efficacy endpoints

Endpoint	**Combination therapy**		**Monotherapy**		
	ITT (N=218)	**IRC-PD (N=135)**	**ITT (N =111)**	**IRC-PD (N=71)**	
Duration of response	n=50	n=34	n=12	n=10	
Median months	5.7	4.2	4.2	4.1	
Time to response	n=50	n=34	n=12	n=10	
Median months	1.4	1.4	1.4	1.4	
Duration of disease control	n=121	n=76	n=36	n=24	
Median months	6.0	5.6	4.0	4.1	
Time to progression (TTP)	n=152	n=97	n=92	n=62	Hazard ratio 0.54
Median months	4.1	4.0	1.5	1.5	95% CI 0.42; 0.71 P<0.0001 (ITT) P<0.0001 (IRC-PD)
Time to treatment failure	n=218	n=135	n=111	n=71	
Median months	4.1	4.0	1.7	1.8	
Survival time (n died)	n=140	n=89	n=75	n=49	Hazard ratio 0.91
Median months	8.6	8.4	6.9	7.0	95% CI 0.68; 1.12 P=0.48 (ITT) P=0.59 (IRC-PD)
% survived	36%	34%	32%	31%	

n denotes the number of patients with PD or death, N denotes the total number of patients in the specified treatment group and population

- Ancillary analyses

Objective response, TTP and survival were additionally evaluated for subgroups. In general the analyses confirmed the advantage of the combination therapy in comparison to the monotherapy. In both treatment arms better results were seen in those subgroups of patients with a predictive factor for a favourable outcome of CRC (male patients, KPS≥80, 1 metastatic site, leukocytes at base line ≤ 10000/mm^3 or and AP at baseline <300U/l).

The combination regimen possibly slightly favoured patients with grade 3 to 4 skin reactions and patients with a prior 2 weekly irinotecan dose of 250 mg/m^2, whereas the monotherapy increased the survival time in patients with a prior weekly irinotecan dose of 125 mg/m^2 (Tables 9 and 10). In both regimens the beginning of a cetuximab therapy ≥30 days after the most recent pre-study irinotecan treatment was correlated with a more favourable outcome in both studies. With respect to grade 3 and 4 reactions, it should be noted that about 40 % of these reactions were reported after week 10 thus introducing a lead-time bias. As regards "any reactions", however, the vast majority was observed prior to week 4.

Patients with EGFR-expressing metastatic CRC were eligible for treatment in the 3 target-indication studies. An immunohistochemical assessment was selected as an appropriate method to measure EGFR expression. The used kit (EGFR pharmDx^{TM} Kit, DakoCytomation) allowed direct detection of the target. Older samples, in most cases from the primary surgery, were used. EGFR staining with respect to percentage of stained cells (from less than 10 to more than 35%) or intensity (from faint to strong) showed no relationship to ORR, PFS or OS.

In the pivotal study, 24.6% of patients had received 3 treatment lines and 18.2% of patients had received more than 3 treatment lines therapy for CRC. These subgroups of patients showed no significant differences compared to the whole population.

Table 9. Skin reactions vs. outcome

	Combination therapy				Monotherapy			
	N	RR %	PFS median	OS median	n	RR %	PFS median	OS median
None	32	6	1.4	3.0	18	0	1.3	2.5
Any	186	26	4.2	9.1	93	13	1.6	8.1
Grade 3 o 4	29	55	8.2	13.7	6	33	2.7	7.3

Table 10. Efficacy, in relation to last prior irinotecan regimen

Most recent irinotecan regimen	Combination		Monotherapy	
	ORR	95% CI	ORR	95% CI
125 mg/m^2 weekly	5/33	5.1; 31.9	4/20	5.7; 43.7
180 mg/m^2 every 2 wk	29/124	16.3; 31.8	5/54	3.1; 20.3
350 mg/ m^2 every 3 week	15/57	15.5; 39.7	2/31	0.8; 21.4

Supportive study(ies)

Two studies were considered as supportive studies, IMCL CP02-0141 for the monotherapy and IMCL CP02-9923 for the combination therapy with an approved irinotecan regimen. Both studies were open-label, phase II, multi-center, uncontrolled studies in patients with EGFR-expressing, metastatic CRC, who had shown progression of disease on an irinotecan-containing regimen. The primary objective of IMCL CP02-9923 was to evaluate the response rate to cetuximab administered in combination with irinotecan in patients with advanced colorectal carcinoma who were refractory to treatment with an irinotecan-containing regimen. Per protocol refractory was defined as either stable disease (SD) following 12 weeks of irinotecan therapy or progressive disease (PD) at any time following treatment with irinotecan. In the statistical analyses presented, the definition of refractory was PD based on an Independent Review Committee's (IRC) review of selected prestudy scans and clinical information. IMCL CP02-0141 was designed to evaluate the response rate to single-agent cetuximab administered to patients with stage IV advanced colorectal carcinoma who were refractory, i.e., had documented progressive disease, to treatment with an irinotecan-containing regimen. Demographic and baseline characteristics in the ITT population of both studies were similar to the pivotal study, except for disease characteristics and pre-study treatment. In the supportiv) studies the primary tumour was

localised in around 80% in the colon and in 20% in the rectum compared to 60% and 40% in the pivotal study. The majority of patients in study IMCL CP02-9923 had tumour material with at least 20% EGFR-positive cells, whereas in the pivotal study most patients had tumour material with ≤20% EGFR-positive cells. Approximately 60% of the patients in the European study had received prior oxaliplatin treatment compared to only 10% or 14% in the supportive studies IMCL CP02-9923 and 0141, respectively.

This difference can be explained by the fact that oxaliplatin was not approved in the US when studies IMCL CP02-9923 and 0141 were initiated. All patients were pre-treated with irinotecan, but in study IMCL CP02-9923 79% received irinotecan as monotherapy compared to 63.8% in the BOND and 75.4% in study IMCL CP02-141 who were pre-treated with a combination mostly including 5-FU/FA. The majority of patients in the pivotal study received irinotecan 180 mg/m² given every 2 weeks as their most recent pre-study treatment. However, this regimen was not used in the IMCL CP02-9923, where about 80% of patients in IMCL CP02-9923 received 125 mg/m².

The efficacy results for the supportive studies are summarised in table 11. For the monotherapy group the results did not show any difference between the pivotal and supportive studies, however, the objective response rate was higher for the pivotal trial (25.2%) receiving the combination therapy than in the supportive trial (13.3%).

Table 11. Efficacy results of the supportive studies

		IMCL CP02-9923 Combination therapy		**IMCL CP02-0141 Monotherapy**	
		All treated (N=138) (95% CI)	IRC-PD (N=83)	All treated (N=57) (95% CI)	IRC-PD (N=28)
Primary endpoint	**Objective response rate** (CR+PR)	15.2% (9.7, 22.3)	13.3% (6.8, 22.5)	8.8% (2.9, 19.3)	14.3% (4.0, 32.7)
Secondary endpoints	**Disease control rate** (CR+PR+SD)	60.9% (52.2, 69.1)	53.0% (41.7, 64.1)	45.6% (32.4, 59.3)	39.3% (21.5, 59.4)
	Duration of response Median months	6.5	5.7	4.2	4.2
	Time to response Median months	2.6	1.3	1.2	1.9
	Duration of disease control Median months	5.5	5.4	5.3	5.3
	Time to progression (TTP) Median months	2.9 (2.6, 4.1)	2.6 (1.7, 3.1)	1.4 (1.3, 2.8)	1.3 (1.3, 3.2)
	Survival time (n/N died) Median months	8.4 (7.2, 10.3)	7.7 (6.2, 9.8)	6.4 (4.1, 10.8)	8.8 (4.1, 12.9)
	1-year survival rate	32%	25%	33%	36%

CI = confidence interval, disease control rate (patients with complete response, partial response, or stable disease for at least 6 weeks)

Discussion on clinical efficacy

Two exploratory, proof of concept studies were conducted in patients failing irinotecan therapy for advanced CRC. In the first study, cetuximab was added to the failing regimen. The study results were compatible with improved anti-tumour activity if cetuximab was administered as add-on to the failing regimen. This hypothesis was further explored in an open-label, randomised, multicentre study ("BOND") comparing combination with monotherapy in 329 patients with metastatic CRC failing defined and recognised irinotecan regimens. Also in this study, patients randomised to the combination arm continued the failing irinotecan regime (without 5-FU/LV if part of the failing regimen). With respect to resistance to irinotecan, the best overall response to the most recent regimen was partial response (PR) in 7.0% of the patients and about 3 in 4 patients showed progressive disease on or within 30 days after the last treatment course. The clear majority of patients may, thus, be characterised as refractory to irinotecan therapy.

The BOND study convincingly demonstrated superior anti-tumour activity of cetuximab as add-on to a failing irinotecan regimen compared with cetuximab alone, but no effects on survival have been

established. In terms ORR and PFS, the activity of the combination regimen is clinically relevant. At the time of study initiation, there were no generally recognised treatment options available for patients failing irinotecan-based regimens. The results of cetuximab combination treatment compare favourably to what has been reported recently for the oxaliplatin plus infusional 5-FU/FA (FOLFOX4) regimen used in second line in patients failing irinotecan. One study compared FOLFOX4 with intermittent infusional 5FU/FA alone (De Gramont regimen) and with single-agent oxaliplatin [94]. The treatments were administered as second-line therapy to patients with metastatic CRC whose disease progressed during or within 6 months after cessation of first-line treatment with irinotecan combined with bolus 5-FU/FA (IFL regimen). Oxaliplatin combined with infusional 5-FU/FA showed statistically significant advantages over intermittent infusional 5-FU/FA alone in terms of response rate (10% versus 1%) and median TTP (5.6 versus 2.6 months), however the median survival time was not statistically significantly prolonged (9.8 versus 8.7 months). Single-agent oxaliplatin achieved a response rate of 1%, a median TTP of 2.6 months and a median survival time of 8.1 months. About 80% of the patients showed progression within 6 weeks after last prior regimen. In this subgroup (n=126) and for the FOLFOX4 regimen, the ORR was 9.5% (5.0; 16.1%) and median PFS 4.9 months (4,2; 6.3). The ORR in the cetuximab combination arm thus appears higher while PFS is similar or numerically shorter. In another study, the sequence FOLFOX6 (infusional 5FU/LV + oxaliplatin) at time of progression followed by FOLFIRI (infusional 5FU/LV + irinotecan) was compared with FOLFIRI followed by FOLFOX6. With respect to OS, the results were similar (p=0.99). The ORR for FOLFOX6, second line to FOLFIRI was 15% and PFS was 4.2 months[13].

Despite median two prior regimens, the patients had overall good performance status, were relatively young (median 60 years) and close to 50% had only one metastatic site. From that perspective, included patients are non-representative for patients with advanced CRC, but rather typical for confirmatory late-line studies. This has been reflected in the SPC.

The principal features of the study are in accordance with the Note for Guidance on Evaluation of Anticancer Medicinal Products in Man[95]. The randomisation procedure is judged to be appropriate. The assessment of the primary and secondary endpoints is based on modified international standards[92,93]. As required given the pivotal role of the trial, the evaluation of response was undertaken by an external Independent Review Committee (IRC). The measures of blinding taken seem appropriate to avoid a bias in the assessment of the primary endpoint. In general the statistical methods used are appropriate.

Only few patients were treated with the 125 mg/m^2 weekly regimen, a regimen currently not approved in the EU, but possibile as an alternative in risk patients. For the approved regimens activity was similar, but as expected the 180 mg/m^2 every 2 weeks dominated.

In the pivotal trial, an apparent relationship was demonstrated between skin toxicity and tumour response but this could have been due to lead time bias. Further studies are planned in order to test whether dose escalation in case of absence of skin toxicity will result in improved anti-tumour activity. The studies programme also includes pharmacogenomics.

All patients in the pivotal study had EGFR expressing tumours. Concernig assessment of EGFR expression, prerequisites for laboratories that perform the tests have been appropriately described in the SPC (section 4.2). Adequate guidelines on the perfomance of such tests are available in the respective product information.

No relationship was found between degree of expression (percentage of positive cells or intensity of staining) and tumour response. Similar findings have been reported from studies with EGFR-selective tyrosine-kinase inhibitors such as erlotinib [96]. This is in apparent contrast to, *e.g.* HER-2/neu expression and trastuzumab [97]. It should be noted that most samples derived from the time of diagnosis and that EGFR expression is likely to increase over time. The applicant has committed to further address this issue within the planned studies programme.

Clinical safety

Data from the 3 target-indication studies were pooled according to whether the patients received cetuximab in combination with irinotecan (N=350) or as a single agent (N=172).

Patient exposure

In the target-indication studies, cetuximab was to be administered at an initial dose of 400 mg/m² followed by weekly doses of 250 mg/m². According to the study protocols, the dose could only be modified in the case of allergic reactions and skin reactions. Irinotecan regimens were to be continued at the same dose under which the patient progressed. Dose modifications in accordance with the product label were allowed for both the pre- and on-study phases. 473 (90.6%) patients discontinued study treatment: 308 (88.0%) patients in the combination therapy group and 165 (95.9%) in the monotherapy group. The main reasons for discontinuations were progressive disease (68.6% vs 82.0%), AEs (9.4% vs 8.7%), and withdrawal of consent (2.6% vs 0.6%).

Patients on combination therapy received a median number of 12.5 cetuximab infusions (range 1 to 84). Patients on monotherapy received a median number of 7 cetuximab infusions (range 1 to 63). The median cumulative dose was 3256 mg/m² in the combination therapy group and 1839 mg/m² in the monotherapy group. The cetuximab dose was reduced (mainly 1 reduction) in 5.3% and 3.5% patients, respectively. In both treatment groups, more than 86% of the patients received at least 80% of the planned dose intensity of cetuximab. In the combination therapy group, almost half of the patients (163 [46%]) received the 125 mg/m² irinotecan regimen, 108 (31%) received the 180 mg/m² regimen, and 75 (21%) received the 350 mg/m² regimen. The 4 remaining patients received some other undefined regimen. 61% of the patients in the 180 mg/m² biweekly group and 60% of the patients in the 350 mg/m² 3-weekly group received at least 80% of the planned dose density of irinotecan. The corresponding percentage for the 125 mg/m² weekly regimen was only 34%.

Adverse events and serious adverse events/deaths

All patients in the pooled combination therapy group and the pooled monotherapy group of the target-indication studies experienced at least one AE, irrespective of relationship to cetuximab.

The very commonly occurring AEs in the target indication studies are presented in Table 12. The most frequent AEs occurring in more than one-third of patients under combination therapy were (in decreasing order of frequency) diarrhea, asthenia, nausea, rash, abdominal pain, vomiting, acne, and anorexia. The most common AEs under monotherapy were asthenia, acne, fever, and rash.

Grade 3 or 4 AEs were reported in 251 (71.7%) patients in the combination therapy group and 91 (52.9%) in the monotherapy group. The most common grade 3 and 4 AEs are listed in Table 13. Although a reliable causality assessment was difficult, cetuximab-related AEs were reported in 96.9% of the patients in the combination therapy group and 97.7% in the monotherapy group (Table 14). The most common cetuximab-related AEs observed in more than one-third of patients in both treatment groups were rash, asthenia, and acne. Further AEs observed in more than one-third of patients were diarrhea in the combination therapy group and fever in the monotherapy group.

Table 12. Frequency of very commonly occurring AEs (≥10% patients) in target indication studies

COSTART preferred term	% patients with AE	
	Pooled combination (N=350)	Pooled monotherapy (N=172)
Any	100.0	100.0
Abdominal pain	43.1	31.4
Acne	37.7	45.9
Alopecia	21.7	5.8
Anemia	16.3	6.4
Anorexia	35.7	25.6
Asthenia	70.9	55.2
Back pain	16.0	11.0
Chills	11.1	12.2
Conjunctivitis	14.6	6.4
Constipation	29.1	32.0
Cough increased	20.0	12.8
Dehydration	14.9	4.7
Diarrhea	72.0	27.9
Dry skin	29.7	24.4
Dyspepsia	12.9	9.3
Dyspnea	22.3	25.6
Fever	32.9	44.2
Headache	14.0	25.6
Infection	16.0	12.2
Insomnia	12.0	11.6
Leukopenia	24.6	0.6
Nail disorder	12.6	15.1
Nausea	54.9	26.7
Pain	22.0	18.0
Peripheral edema	15.1	8.1
Pruritus	10.3	11.0
Rash	53.4	39.0
Skin disorder	15.1	10.5
Stomatitis	25.7	11.0
Vomiting	40.6	26.2
Weight loss	21.1	9.9

Table 13. Most common grade 3 or 4 AEs occurring in ≥5% patients in target-indication studies.

COSTART preferred term	Irinotecan plus cetuximab (N=350) (%)	Cetuximab monotherapy (N=172) (%)
Diarrhea	21.7	1.7
Leukopenia	16.6	0.0
Asthenia	13.7	10.5
Vomiting	6.6	3.5
Abdominal pain	6.3	7.0
Dehydration	6.3	1.7
Rash	6.0	3.5
Acne	5.7	5.8
Nausea	5.7	1.7
Pain	5.4	4.1
Dyspnea	1.7	9.9

Table 14. Number (%) of patients with treatment-related grade 4 and corresponding grade 3 or 4 AEs in target indication studies

COSTART preferred term	Pooled combination therapy (N=350)		Pooled monotherapy (N=172)	
	Grade 3 + 4	Grade 4	Grade 3 + 4	Grade 4
Any	141 (40.3)	23 (6.6)	49 (28.5)	4 (2.3)
Anaphylactoid reaction	4 (1.1)	4 (1.1)	2 (1.2)	1 (0.6)
Anorexia	7 (2.0)	4 (1.1)	0 (0.0)	0 (0.0)
Asthenia	22 (6.3)	2 (0.6)	8 (4.7)	0 (0.0)
Dehydration	4 (1.1)	2 (0.6)	0 (0.0)	0 (0.0)
Diarrhea	28 (8.0)	3 (0.9)	2 (1.2)	0 (0.0)
Dyspnea	2 (0.6)	0 (0.0)	5 (2.9)	2 (1.2)
Exfoliative dermatitis	5 (1.4)	1 (0.3)	3 (1.7)	0 (0.0)
Fever	4 (1.1)	1 (0.3)	0 (0.0)	0 (0.0)
Headache	3 (0.9)	1 (0.3)	3 (1.7)	0 (0.0)
Herpes simplex	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Hypocalcemia	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Hypokalemia	3 (0.9)	1 (0.3)	1 (0.6)	0 (0.0)
Hypotension	2 (0.6)	1 (0.3)	1 (0.6)	0 (0.0)
Infection	3 (0.9)	1 (0.3)	0 (0.0)	0 (0.0)
Intestinal obstruction	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Kidney failure	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Leucopenia	19 (5.4)	3 (0.9)	0 (0.0)	0 (0.0)
Myocardial infarct	1 (0.3)	1 (0.3)	1 (0.6)	1 (0.6)
Nausea	11 (3.1)	2 (0.6)	1 (0.6)	0 (0.0)
Pulmonary embolus	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Thrombocytopenia	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)
Vesiculobullous rash	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Vomiting	9 (2.6)	2 (0.6)	2 (1.2)	0 (0.0)

- Serious adverse event/deaths/other significant events

In the integrated database, death within 30 days of last cetuximab administration was reported for 14.6% (180/1230) of patients. The primary reason for death was most frequently disease progression, followed by disease-related complications and intercurrent illnesses/events unrelated to treatment.

In one patient the death was considered related to cetuximab. Shortly after the first cetuximab infusion, this patient developed an anaphylactic reaction and failure to intubate due to larynx oedema and obstruction by the tumour of the tongue caused his death. AEs related to chemotherapy (irinotecan, cisplatin) were held responsible in two patients. The cause of death was unknown in 9 patients.

AEs causing discontinuation of cetuximab were reported for 51 (14.6%) patients under combination therapy and 21 (12.2%) patients under monotherapy.

Hypersensitivity Reactions (HSRs)

A total of 65 patients experienced 70 cetuximab-related HSRs, including 32 patients experiencing grade 3 or 4 HSRs. In the target indication studies 13/522 (2.5%) experienced a grade 3 or 4 HSR event.

The first occurrence of any cetuximab-related HSR was reported during or after the first infusion of cetuximab in 54/65 of the patients, and in 27/32 of the patients with a grade 3 or 4 event. One serious event, however, was reported as late as after the 33rd infusion. Five patients were re-exposed after a HSR and no change in severity was observed in 4 patients while one patient with a grade 1 event at infusion number 31 experienced a grade 3 event at infusion 33.

The vast majority (63/65) occurred within one day after administration, but the general database did not provide more detailed information on the temporal relationship. Further analyses based on patients administered a test dose (20 mg/m^2, 20 minutes prior to the remainder of the dose) showed that 11 out of 21 patients experiencing a grade 3 or 4 reaction, had this reaction before administration of the remainder of the initial dose. Two developed a HSR during administration of the remainder of the dose, 4 after (exact time unknown) and 4 during subsequent administrations.

The overall incidence of discontinuations of treatment due to cetuximab-related HSRs was 1.1% (4/350) in the combination therapy group and 4.1% (7/172) in the monotherapy group.

Skin Reactions

Skin reactions, including acne-like rash characterise EGFR targeting substances. Skin reactions in target indication studies are summarised in Table 15. There is no specific therapy, but dose-reduction/interruption is considered efficient in case the toxicity is considered unacceptable. Two percent of the patients discontinued due to skin toxicity. In about half of the patients the reaction resolved within 30 days of discontinuing therapy (all reasons).

Table 15. Skin reactions in target indication studies

Parameter	**% patients**	
	Pooled combination therapy	**Pooled monotherapy**
Severity of AE (grade)	(N=350)	(N=172)
Any grade	87.7	86.6
1+2	73.7	75.6
3	13.7	11.0
4	0.3	0.0
Duration of skin reaction (days)	(N=307)	(N=149)
1-7	1.4	1.2
8-21	7.1	2.3
22-60	15.1	15.7
61-90	6.3	6.4
>90	27.7	23.8
Ongoing	22.6	33.1
Time to first occurrence of skin reaction (weeks)	(N=307)	(N=149)
1	61.2	71.8
2-5	31.9	22.8
6-10	4.9	4.0
>10	2.0	1.3

Respiratory Disorders

Altogether 10 cases on “interstitial pneumonitis” were identified during a search of the database carried out 3 March 2003.

Laboratory findings

Frequencies of patients with any NCI-CTC toxicities (grade 1–4) or grade 3 or 4 toxicities are summarized for the most clinically relevant variables in Table 16.

Table 16: Summary of NCI-CTC grades of laboratory parameters in the target indication

Variable	No. (%) of cetuximab patients											
	Combination therapy (N=350)						Monotherapy (N=172)					
	Any grade		Grade 3 or 4		Grade 4		Any grade		Grade 3 or 4		Grade 4	
Hematology												
Anemia	133	(38.0)	6	(1.7)	0	(0.0)	42	(24.4)	2	(1.2)	0	(0.0)
Thrombo-cytopenia	48	(13.7)	1	(0.3)	0	(0.0)	10	(5.8)	0	(0.0)	0	(0.0)
Neutropenia	115	(32.9)	36	(10.3)	9	(2.6)	15	(8.7)	4	(2.3)	2	(1.2)
Leukopenia	184	(52.6)	31	(8.9)	5	(1.4)	35	(20.3)	4	(2.3)	1	(0.6)
Blood chemistry												
High creatinine	13	(3.7)	1	(0.3)	0	(0.0)	5	(2.9)	0	(0.0)	0	(0.0)
High gamma-GT	121	(34.6)	49	(14.0)	4	(1.1)	57	(33.1)	24	(14.0)	5	(2.9)
High AP	201	(57.4)	24	(6.9)	0	(0.0)	91	(52.9)	16	(9.3)	0	(0.0)
High ASAT	119	(34.0)	2	(0.6)	0	(0.0)	57	(33.1)	5	(2.9)	0	(0.0)
High ALAT	93	(26.6)	1	(0.3)	0	(0.0)	22	(12.8)	1	(0.6)	0	(0.0)
High total bilirubin	34	(9.7)	5	(1.4)	2	(0.6)	21	(12.2)	4	(2.3)	1	(0.6)
Low serum albumin	186	(53.1)	66	(18.9)	0	(0.0)	84	(48.8)	24	(14.0)	0	(0.0)

Two immune assays were used to detect anti-cetuximab antibodies. Both assays relied on capture of free antibodies by cetuximab itself and interference with excess amount of free cetuximab in the samples might thus decrease the sensitivity. In addition a bioassay was tested in two individuals with a high titre antibody response. Altogether 20 patients with anti-antibodies were also analysed with respect to possible effects on pharmacokinetics.

Altogether 534 patients were considered evaluable for antibody response, thereof only 59 from the pivotal BOND study. In most cases, samples were drawn immediately prior to next infusion of cetuximab and in some (not further detailed cases) 6 weeks after end of therapy.

The overall incidence of anti-cetuximab responses was about 4% and responses were typically of low titre. The incidence appeared not to be affected by concomitant chemotherapy and if anything the incidence decreased with duration of therapy. Allergic reactions in patients receiving cetuximab did not appear to correlate with the presence of an anti-cetuximab antibodies. Increased clearance of cetuximab was shown in 2 of 20 tested anti-cetuximab positive patients (one at 100 mg/m^2 and one at 250 mg/m^2 weekly cetuximab dose). In the two individuals with a high titre response, no neutralising effect of serum was shown in the bioassay.

Safety in special populations

Safety data were detailed separately for the following groups of patients: age ≥65, male/female, white/non-white, KPS<80, creatinine ≥1.5xULN, cardiac disease, liver abnormalities (defined).

Due to the impact of irinotecan, this review is focused on monotherapy with cetuximab and only events where an apparent difference is noted and causality is not unlikely are presented. A higher incidence of grade 3 and 4 dyspnea was observed in the elderly (8/47 *vs.* 8/125). A higher incidence of acne was observed in male *vs.*female patients (52/102 *vs.* 27/70).

The number of individuals with KPS<80 was low, but seemingly fewer reported acne 5/21 *vs.* 74/151. The number of individuals with abnormal liver tests was low (n=21), but a seemingly higher incidence of skin reactions was observed in patients with normal tests (in-line with findings in the combination group). Dyspnea was more frequently reported in patients with a history of cardiac disease24/69 *vs.* 20/103 (for the combination arm, the corresponding figures were 38/168 *vs.*40/182). The overall incidence of heart failure was 10/1230.

Discussion on clinical safety

HSRs are expected for this kind of products, but the incidence of grade 3 and 4 events appears high, about 2.5% overall and even higher in the monotherapy setting. In the target indication studies, pre-medication with an antihistamine was required and a test dose was also administered. In the SPC, antihistamines are recommended. At present, the test dose is omitted since the incidence of serious events is unlikely to be reduced by this procedure. Erbitux must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. 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 (see SPC, section 4.2). Erbitux is contraindicated in patients with known severe (grade 3 or 4) hypersensitivity reactions to cetuximab (see SPC section 4.3). Symptoms usually occurred during the initial infusion and up to 1 hour after the end of infusion, but may occur after several hours. It is recommended to warn patients of the possibility of such a late onset and instruct them to contact their physician if symptoms of hypersensitivity occur. Occurrence of a severe hypersensitivity 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. If the patient experiences a mild or moderate (grade 1 or 2) hypersensitivity reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions (see SPC section 4.4).

Dyspnoea may occur in close temporal relationship to the cetuximab infusion as part of a hypersensitvity reaction, but has also been reported after several weeks of therapy, possibly related to the underlying disorder (see SPC section 4.8). Patients with high age, impaired performance status and underlying pulmonary disorders may be at increased risk for dyspnoea, which may be severe and/or long-standing. If patients develop dyspnoea during the course of cetuximab treatment, it is recommended to investigate them for signs of progressive pulmonary disorders as appropriate. Individual cases of interstitial lung disorders of unknown causal relationship to cetuximab have been reported (see SPC section 4.4).

Skin reactions, including acne-like rash characterise EGFR targeting substances. The experience as regards long-term exposure is limited and this constitutes a concern as severe skin reactions may occur relatively late (about 40% after ten weeks to be compared with a median duration of exposure of 12 and 7 weeks, in combination and monotherapy studies, respectively). Skin reactions as a putative entrance portal for infections were further investigated without conclusive findings. Several measures, including topical steroids or systemic tetracylines, have been tried on a single-patient basis. However, currently, there is no known specific therapy, but dose-reduction/interruption is considered efficient in case the toxicity is considered unacceptable. If a patient experiences a severe skin reaction (grade 3; NCI-CTC), cetuximab therapy must be interrupted. Treatment may only be resumed, if the reaction has resolved to grade 2 (see section SPC 4.4). This toxicity will be further studied in ongoing mechanistic studies, and will be part of the risk management programme.

EGFR targeting could have an impact on inflammatory and immune responses[85,98]. The applicant has committed to study that possible effects on underlying inflammatory conditions in the post-authorisation risk management programme.

EGFR is one of the major receptor tyrosine kinases involved in wound healing. Caution is indicated in the design of EGFR inhibitor studies with patients with surgical wounds or in patients with chronic wounds. The applicant has committed to conduct specific monitoring of the effects of Erbitux treatment on wound healing in ongoing and planned clinical trials.

The database as regards anti-cetuximab antibodies (HACA) is currently too limited to allow firm conclusions. In samples assessed for HACA at least 4 weeks after last dose of cetuximab the incidence of positive samples was 6/73 and after at least 6 weeks, corresponding figures were 5/37. There was no apparent relationship between HACA and allergic reactions. The applicant committed to present furher results from ongoing studies to confirm these aspects.

Only patients with adequate renal and hepatic function have been investigated to date (serum creatinine $\leq$ 1.5fold, transaminases $\leq$ 5fold and bilirubin $\leq$ 1.5fold the upper limit of normal). Cetuximab has not been studied in patients presenting with haemoglobin < 9 g/dl, leukocyte count < 3000/mm³, absolute neutrophil count < 1500/mm³, platelet count < 100000/mm³. The safety and effectiveness of cetuximab in paediatric patients have not been established. There is limited

experience in the use of cetuximab in combination with radiotherapy in colorectal cancer. The lack of available information is adequately refelected in the SPC (see section 4.4). No dose adjustment is required in the elderly, but the experience is limited in patients 75 years of age and above (see SPC, section 4.2).

Overall, the current knowledge on undesirable effects of cetuximab is adequately detailed in the SPC (see section 4.8). There is no evidence that the safety profile of cetuximab is influenced by irinotecan or vice versa. Infusion-related reactions, dyspnoea, fever and headache tended to be more frequently reported for monotherapy. This might be partly explained by differences as regards premedication, especially with respect to glucocorticosteroids. Excluding these reactions, no interaction in terms of toxicity was observed between irinotecan and cetuximab (see SPC section 4.5).

No studies on the effects on 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 (see SPC, section 4.7).

No case of overdose has been reported. There is no experience with single doses higher than 500 mg/m2 body surface area to date (see SPC, section 4.9).

5. Overall conclusions and benefit/risk assessment

Quality

The applicant has shown by extensive investigation that the particle formation does not lead to loss of potency and that particle-containing batches have been used in clinical trials using in-line filters. The company has provided further data suggesting to better characterise the occurrence of visible particles.

In addition, the applicant has also presented a plan for development of a new formulation (containing polysorbate) aimed at reducing the amount of particles. An extension application is planned to be submitted in 2005.

In summary the quality of the product is considered satisfactory on the basis of the submitted data, and the overall quality of Erbitux is considered acceptable. A number of follow-up measures will need to be resolved post-marketing.

Non-clinical pharmacology and toxicology

The *in vivo* inhibitory effect of cetuximab on xenograft tumours was impressive and thoroughly documented. Pharmacodynamic drug interactions of cetuximab with chemotherapeutic drugs have been extensively studied and are discussed in the literature. Combination therapy with a topoisomerase inhibitor or radiotherapy resulted in reduced tumour growth, and combination with various anti-cancer agents even induced reduction of the tumour volume (data not shown). It has been speculated that the discrepancy between the potency of the effects *in vitro* and *in vivo* illustrates the importance of angiogenesis inhibition, which would be of little importance in cell cultures and normal tissues (with few exceptions), but significant in tumours [49].

Resistance to cituximab therapy may be due to various intrinsic or acquired mechanisms, including redundancy in signalling by other EGFR receptors[99], autocrine or paracrine EGFR loops in the tumor[100], receptor transactivation[101,102]. Both inactivation of tumor suppressor genes (e.g. von Hippel-Lindau tumor suppressor gene[103]) or constitutive activation of protooncogenes like Ras downstream of the EGFR[104] could result in a reduced therapeutic efficacy of cetuximab. Although the relevance for CRC is unknown, different mutated EGFR variants have been identified in tumorigenic cell lines[105]. Lastly, cancer cells might be able to adapt to blockade of EGFR signaling by compensatory changes in angiogenic growth factor (VEGF) output[106].

Pharmacokinetic data both after single dose and at steady state were essentially as expected for a humanised antibody. Cetuximab is administered IV. The distribution volume corresponded to the plasma volume, Cmax was proportional to the dose, and the terminal half-life, $T_{½}$, was slightly less than one week. The values agree with those found in clinical studies. Clearance tended to decrease with increasing doses, and consequently $T_{½}$ tended to increase with increasing doses. The reason for this is not clear, but could be a consequence of the analytical method used rather than a true

physiological result. Steady state was apparently reached after 4 consecutive weekly doses, and no accumulation of cetuximab was noted over 26 weeks.

Skin toxicity was the major finding observed in a chronic repeat-dose toxicity study in Cynomolgus monkeys at clinically relevant levels. Cetuximab induced severe skin toxicity and lethal complications in monkeys, which exhibited blood levels of approximately 17-fold of those achieved under the standard human treatment regimen.

Preclinical data on genotoxicity and local tolerability after accidental administration by routes other than the intended infusion revealed no special hazard for humans.

No formal animal studies have been performed to establish the carcinogenic potential of cetuximab or to determine its effects on male and female fertility or its teratogenic potential.

Toxicity studies with co-administration of cetuximab and irinotecan have not been performed.

No preclinical data on the effect of anti-EGFR antibodies on wound healing are available to date. However, in preclinical wound healing models EGFR selective tyrosine kinase inhibitors were shown to retard wound healing.

Efficacy

A total of 356 patients with EGFR-expressing metastatic colorectal cancer who had recently failed irinotecan-including cytotoxic therapy and who had a minimum Karnofsky performance status of 60, but the majority of whom had a Karnofsky performance status of ≥ 80, received the combination treatment of cetuximab with irinotecan. In the main study, the proportion of responders in the combination group was 22.9% (95%-CI: 17.5% - 29.1%). The efficacy of the combination of cetuximab with irinotecan was superior to that of cetuximab monotherapy, in terms of objective response rate and progression-free survival, but no effects on overall survival were demonstrated (hazard ratio 0.91, p = 0.48).

Safety

Adverse reactions related to cetuximab may be separated in two categories, those non-specifically related to the antibody character of the compound and those related to EGF-R targeting. Infusion-related reactions including grade 3 and 4 hypersensitivity reactions were reported in a rather high frequency (about 6 and 3%, respectively). As regards EGFR targeting, skin and gastrointestinal reactions were most prominent. Cases of late occurring and durable dyspnoea have been reported, although the majority was reported in association with infusion of cetuximab. The possibility that EGFR blockade might enhance an underlying inflammatory condition should be considered. Cases of interstitial lung disorder have been reported, but the incidence appears similar to the reported background incidence, about 0.3%. Special warnings and special precautions for use are adequately addresse din the SPC (see section 4.4).

The toxicity profile of the combination regimen was dominated by irinotecan-related adverse reactions. The main toxicities of irinotecan are diarrhea, nausea and vomiting, early cholinergic syndrome, alopecia, and neutropenia [107]. Patients with metastatic CRC are known to suffer from asthenia and gastrointestinal symptoms [108].

Diarrhea, asthenia, nausea, rash, abdominal pain, vomiting, anorexia, stomatitis, leukopenia, alopecia, weight loss, and dehydration were more common in the combination therapy group than in the monotherapy group. In the monotherapy group, there was a tendency for more fever and headache than in the combination therapy group. Fever and headache are common findings in patients treated intravenously with monoclonal antibodies[109,110].

Undesirable effects related to cetuximab, include hypersensitivity reactions in approximately 5% of patients during treatment with cetuximab. Approximately half of these reactions are severe. Mild or moderate reactions (grade 1 or 2) include symptoms such as fever, chills, nausea, rash, or dyspnoea. Severe hypersensitivity reactions (grade 3 or 4) usually occur during or within 1 hour of the initial cetuximab infusion. Symptoms include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness, difficulty in speaking), urticaria, and/or hypotension. Conjunctivitis may be expected in approximately 5% of patients.

Dyspnoea has been reported in 25% of patients with end stage colorectal cancer. In elderly patients

and in patients with reduced performance status or pre-existing pulmonary disorders, an increased incidence of dyspnoea, sometimes severe, was observed.

Skin reactions may develop in more than 80% of patients; approximately 15% of these are severe. They mainly present as acne-like rash and/or, less frequently, as nail disorders (e.g. paronychia). The majority of skin reactions develop within the first week of therapy. They generally resolve, without sequelae, over time following cessation of treatment if the recommended adjustments in dose regimen are followed. 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.

In combination with irinotecan, additional reported undesirable effects were those expected with irinotecan (such as diarrhoea 72%, nausea 55%, vomiting 41%, mucositis, e.g. stomatitis 26%, fever 33%, leukopenia 25%, alopecia 22%).

Benefit/risk assessment

According to CPMP guidance[95], randomised clinical trials, which show superiority when compared with treatment regimens/strategies that have been used previously for the tumour type being treated, are required to prove efficacy and safety in previously treated patients with no existing established regimen. Concerning Erbitux, the data presented were of high quality, and robust methods have been used to minimise bias in the evaluation of efficacy, ensuring overall credibility of the results. In terms ORR and PFS the activity observed for the combination regimen met the prespecified criteria in an ITT population. Tumour response has been found to be a valid surrogate endpoint for overall survival for patients with advanced colorectal cancer, albeit for first-line chemotherapy with fluoropyrimidines[111]. Compared to the combination group, the monotherapy group included in the pivotal trial had similar baseline characteristics, and provided a reliable concurrent control. Although no differences in survival have been observed (this may in part be due to a cross-over from the monotherapy to the combination arm), in terms ORR and PFS from a clinical perspective it has been convincingly demonstrated that add-on of cetuximab to a failing irinotecan regimen results in a high level of tumour control and this is of clinical relevance. Further investigations are ongoing to clarify the value of different regimens that have been described recently in similar populations[13,94]. Second-line randomised studies studies are ongoing to study cetuximab + IRI vs. IRI (CA225006) and cetuximab+FOLFOX4 vs. FOLFOX4 (CA225014). The applicant committed to submit the results from these studies as follow-up measures. In conclusion, based on the randomised trial presented, a clear benefit has been established for Erbitux in combination with irinotecan for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

Concerning clinical safety, irinotecan dominates the toxicity profile of the combination regimen, and the incidence of fatigue, anorexia, diarrhoea is rather high for a therapy administered with palliative intent. Irinotecan, however, is an established therapy in this setting and skin toxicity, dyspnoea and infusion-related reactions due to cetuximab do not materially alter the risk profile. Altogether the benefit risk profile of the combination therapy is considered favourable. The proposed post-authorisation risk management programme is adequate and encompasses, as examples of potential risks, interstitial lung disorders and septicaemia.

Cetuximab in monotherapy has a clearly favourable toxicity profile, but activity in terms of ORR and especially PFS is rather modest and cannot be regarded as “outstanding” compared with available alternatives used in clinical practice. Furthermore, its use would most likely be focused on patients not expected to tolerate combination therapy. As reduced performance status (KPS >60 and <80) correlates with reduced antitumour activity, this indicates that in practice monotherapy will be even less active. Thus, given the data submitted the benefit/risk profile of cituximab monotherapy was not considered favourable, and the applicant restricted the indication to the combination therapy.

The applicant has committed to undertake certain follow-up measures addressing outstanding issues especially related to safety and pharmacodynamics. The accuracy of a dosage regimen based on BSA has not been convincingly demonstrated, and some further exploration will be made during future development of cetuximab. The proposed post-authorisation risk management programme is adequate and encompasses, as examples of potential risks, interstitial lung disorders and septicaemia.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk ratio of Erbitux in combination with irinotecan in the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy was favourable and therefore recommended the granting of the marketing authorisation.

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