SCIENTIFIC DISCUSSION

1. Introduction

Colorectal cancer (CRC), one of the most frequent cancers in the world, affects one person in 20 in the developed countries, being the second most common malignant disease with 700,000 new cases and 500,000 deaths world wide each year. Primary therapy is surgery with 75% of the patients being operable at the time of diagnosis. However, even when resection is considered curative, the overall five-year survival is only 50%. Approximately, 30% of all patients with CRC have metastatic disease at diagnosis. Five-year survival is 78% in stage II, 54% in stage III and only 5% in stage IV. Survival in stage III patients has been shown to be increased by application of adjuvant chemotherapy with 5-fluorouracil, folic acid. Current state-of-the-art therapies for metastatic disease approved in Europe include irinotecan and/or oxaliplatin, each in combination with bolus or infusional 5-fluorouracil, leucovorin.

More recently, 2 monoclonal antibodies have been approved in EU for colorectal cancer treatment. On one hand, bevacizumab which acts as a signal transduction inhibitor of Vascular Endothelial Growth Factor (VEGF) is approved as first-line treatment for metastatic colorectal cancer in combination with 5- fluorouracil-based chemotherapy. On the other hand, cetuximab which act as a signal transduction inhibitor of EGFR is approved for use in combination with irinotecan in patients with EGFR expressing metastatic colorectal cancer who has failed prior irinotecan therapy.

Patients treated with chemotherapy and monoclonal antibodies tend to progress after a certain time and their only treatment option is best supportive care.

Panitumumab is a fully human IgG2 monoclonal antibody that is directed against the human EGFR. The EGFR is a transmembrane glycoprotein that promotes cell growth in a variety of normal and transformed tissues. The receptor has several natural ligands including EGF and transforming growth factor-alpha. Binding of the ligand to the receptor stimulates cell proliferation. Blocking this interaction by means of a monoclonal antibody directed against the receptor inhibits tumour growth *in vivo*. Panitumumab is produced in a proprietary strain of mouse (XenoMouse) in which the murine heavy and light chain immunoglobulin genes were inactivated and most of the human heavy and light chain (both kappa and lambda) immunoglobulin genes were inserted.

Amgen Europe B.V. has applied for a marketing authorisation through the centralised procedure for Vectibix 20 mg/ml concentrate for solution for infusion in the treatment of metastatic carcinoma of the colon or rectum after failure of oxaliplatin- and/or irinotecan-containing chemotherapy regimens. The recommended dose of panitumumab is 6 mg/kg of body weight given once every 14 days as an intravenous infusion.

2. Quality aspects

Introduction

Panitumumab is produced from Chinese Hamster Ovary (CHO) cells and purified by a series of chromatography steps, viral inactivation step, viral filtration step and ultrafiltration/diafiltration steps.

The active substance is formulated with sodium acetate trihydrate as buffering agent, sodium chloride as tonicity modifier, acetic acid for pH adjustment and water for injection.

Vectibix is presented as concentrate for solution for infusion (20 mg/ml) in a single-use vial of 5, 10 or 20 ml and is diluted in 0.9 % sodium chloride prior to administration.

Active Substance

Nomenclature

INN Name:	panitumumab
Compendial Name:	not applicable
Chemical Name:	anti-human epidermal growth factor receptor
USAN/BAN/JAN Name:	panitumumab
CAS Registry Number:	339177-26-3

Description of the active substance

Panitumumab is a recombinant, human monoclonal antibody of IgG2 subclass. Panitumumab has two gamma heavy chains and two kappa light chains. Glycosylated panitumumab has a total molecular weight of approximately 147 kDa. Panitumumab is expressed as a glycoprotein with a single consensus N-linked glycosylation site located on the heavy chain. Panitumumab is produced in genetically engineered mammalian (Chinese Hamster Ovary) cells.

- Manufacture

The active substance is manufactured at Amgen, Fremont, California, USA. This facility was inspected by the Dutch inspectorate (IGZ) and it is considered that this site is operated in accordance to current EU Good Manufacturing Practices (GMP), with standard operating procedures in place to describe all procedures and controls.

Development genetics

The expression plasmid containing the genes for the heavy and light chains was transfected into CHO cells. Following cloning and subcloning steps, one clone producing panitumumab at high levels was selected as lead cell line.

Cell bank system

A two-tiered cell banking system of Master Cell bank (MCB) and Working Cell Bank (WCB) has been developed and maintained in accordance to cGMP and ICH guidelines.

Procedures followed in the preparation of MCB and WCB have been appropriately described. An extensive range of tests has been performed for their characterisation, in accordance with ICH guidelines, including identity, viability, stability, presence of adventitious agents (bacteria, fungi, mycoplasma, viral contaminants including endogenous retrovirus-like particles known to be present in CHO cell lines).

Fermentation process

One vial of WCB is thawed and cells are expanded in a selective serum-free growth medium to generate the cell inoculum. A series of bioreactors with increasing volumes is then used to expand the cell mass to generate sufficient cells for the inoculation of the production bioreactor. Following the production phase, the bioreactor contents are harvested and clarified to generate a cell-free intermediate designated as harvested cell culture fluid.

Panitumumab cell culture conditions and in-process controls (IPC) have been sufficiently described and are considered appropriate.

Purification process

Panitumumab is purified using a series of chromatography, concentration and diafiltration and viral inactivation and filtration steps.

Each step of the purification process has been adequately described, and suitable IPC controls are in place, with acceptable limits.

Manufacturing process development and process validation
Several manufacturing changes were introduced during development, including change of cell line, scale-up of the fermentation process, various changes to the purification process and change of manufacturing site.

The comparability exercise and the overall data provided to support the different changes were considered acceptable.

The commercial manufacturing process was validated in order to demonstrate that the process consistently maintained process parameters within specified ranges and met pre-established acceptance criteria for performance indicators. Overall, process validation was considered satisfactory.

Characterisation
A) Elucidation of structure and other characteristics:

A1) Physicochemical characterisation:
The primary, secondary and tertiary structures of panitumumab were analysed by various techniques.

Several structural complexes resulting from different organisations of the disulfide bridges in the hinge region on the antibody were identified. These complexes were adequately analysed.

Several charge variants were identified, which all exhibit comparable potency to the reference standard.

Characterisation of glycosylation indicated that panitumumab has a single consensus N-linked glycosylation site located on the heavy chain. The predominant glycan structures observed correspond to complex bi-antennary structures terminating with or without galactose residues. Fucosylated forms have also been observed. No O-linked glycosylation was detected.

The size distribution of panitumumab was appropriately evaluated by different techniques.

Free sulfhydryl content was consistently detected, indicating low levels of unpaired cysteine residues that are not assigned.

The active substance has been comprehensively characterised, using state-of-the-art methods for physicochemical characteristics. Sources of heterogeneity have been analysed in detail using a wide variety of state-of-the-art techniques.

A2) Biological characterisation:
The methods used for the evaluation of the biological activity were based on the ability of panitumumab to bind directly to the extracellular domain of EGFR and inhibit ligand binding and subsequent cellular responses.

The biological properties of panitumumab have been properly characterised and the assays that were chosen and the data provided are considered adequate.

B) Impurities:
The potential product-related impurities identified are aggregates, fragments and other product variants. Potential process-related impurities include cell substrate derived impurities (host cell proteins, DNA), cell culture derived and downstream derived impurities.

Overall, impurities have been properly identified and characterised.

Specifications
The active substance release specifications have been suitably justified and are supported by consistent data from multiple lots.

Stability
The design of the stability programme, including the testing intervals and temperature storage conditions, are in accordance with current ICH guidelines. The tests chosen are a subset of tests from the release specifications selected for stability-indicating properties.

The stability data provided were within the specifications and support a shelf life of 24 months at 2-8°C.

Finished Product

Pharmaceutical Development
Sodium chloride is used in the formulation to provide an isotonic solution for intravenous infusion and is used as a stabiliser against thermally induced aggregation. Acetic acid is used to adjust pH to target of 5.8. Water for injection is also used as solvent in the formulation. There are no overages in the formulation.

Panitumumab finished product is diluted in 0.9% sodium chloride and administered via an infusion pump, using an 0.2 µm in-line filter to reduce sub-visible particles, through a peripheral line or indwelling catheter. Data provided demonstrated that this in-line filter is effective at removing panitumumab particulates to levels below Ph. Eur. limits without any impact on protein concentration.

The proposed container for panitumumab finished product is a single-use vial (type I glass) with an elastomeric stopper, aluminium seal and a plastic flip-off cap. One vial contains 100 mg of panitumumab in 5 ml, 200 mg panitumumab in 10 ml, or 400 mg panitumumab in 20 ml of concentrate for solution for infusion.

Adventitious agents
An assessment performed on all materials used for the panitumumab commercial manufacturing process concluded that the risk for TSE associated with any material of animal origin is negligible. The active substance is produced in a serum-free culture medium.

The applicant has demonstrated that the cell banks are free of detectable viruses except for the presence of retroviral particles known to be present in CHO cell lines. Routine testing of the unprocessed bulk is performed as part of the viral safety programme.

The viral clearance studies presented by the applicant demonstrate that the panitumumab purification process provides sufficient clearance of the model viruses.

Manufacture of the product
The finished product is manufactured by a facility that was inspected by the Dutch inspectorate (IGZ) and it is considered that this site is operated in accordance to current EU Good Manufacturing Practices (GMP).

The finished product manufacturing process consists of a formulation step followed by aseptic filtration, using two 0.2 µm filters, aseptic filling into vials, stoppering and capping steps.

Criteria for re-filtration of formulated bulk have been established and justified.

The media fill and process validation results, lot-to-lot consistency data and critical process controls have shown that the sterile filtration and aseptic filling process are robust and well controlled and that the finished product can be consistently manufactured.

Specifications
The control of finished product relies to a large extent on the same analytical methods as those used for the control of the active substance. The tests and rationale for the acceptance criteria for the finished product were considered acceptable.

Stability of the Product
Real-time and accelerated stability studies were initiated in accordance with ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of finished product. Based on the data provided, the approvable shelf life for the finished product is 24 months at 2-8°C.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

Information on the source and generation of the cell substrate and analysis of the expression construct are considered satisfactory.

Master and working cell banks have been established and adequately described and characterised.

The active substance manufacturing process is well defined and adequately controlled, with appropriate in-process controls and acceptance criteria in place.

The comparability exercise to support the different manufacturing changes during development was considered acceptable.
The active substance has been well characterised. Sources of heterogeneity have been assessed in detail using a wide variety of state-of-the-art techniques.

The active substance release specifications have been suitably justified and are supported by consistent data from multiple lots.

The stability data provided support the proposed active substance and finished product shelf life of 24 months at 2-8°C.

The pharmaceutical development of the finished product and the manufacturing process of the finished product have been adequately described. Suitable IPC are in place. Process validation for the finished product is satisfactory.

The control of finished product relies to a large extent on the same analytical methods as those used for the control of the active substance. The tests and rationale for the acceptance criteria for the finished product were considered acceptable.

Viral safety and safety concerning other adventitious agents including TSE are sufficiently assured.

The last inspection of the active substance and finished product manufacturing facilities showed compliance to the current EU-GMP.

3. Non-clinical aspects

Introduction

Safety studies complied with GLP. However, the dose formulation analyses and some of the analytical tests to quantify panitumumab and antibodies to panitumumab were not in compliance with GLP but were in compliance with Standard Operating Procedures at the laboratories.

Pharmacology

The ability of panitumumab to inhibit growth of EGFR-expressing tumour cells was tested using *in vitro* methods and *in vivo* in tumour-xenotransplanted mice. Effects of panitumumab in combination with other therapeutic agents were assessed. Cross reactivity supported the choice of the cynomolgus monkey for safety testing.

- Primary pharmacodynamics

Panitumumab acts as a competitive antagonist at the ligand binding site of EGFR to inhibit binding and signalling mediated by EGF and transforming growth factor α, the natural ligands for this receptor. The affinity of binding of hybridoma-derived and CHO-derived panitumumab to the EGFR was determined in recombinant EGFR using BIAcore methods. Binding affinity of hybridoma-derived panitumumab was determined to be 5×10^{-11}M; binding affinity of CHO-derived panitumumab was determined, in two experiments, to be 3.5 and 5.7×10^{-12}M; in comparison the binding affinity of EGF reported in the literature is 3×10^{-9}M.

Inhibition of binding of EGF was shown in A431 cells, a human epidermal carcinoma cell line that expresses EGFR. Intracellular acidification, phosphorylation and internalisation of the EGFR, that occur upon binding of EGF to EGFR, were blocked in a dose-dependent manner by panitumumab in A431 cells. Panitumumab was also shown to inhibit cell growth in vitro and in vivo (xenotransplants in mice) in the same cell line. Additionally, panitumumab could be detected in tumour tissue.

The ability of panitumumab to inhibit growth of a range of tumour types when these were transplanted into athymic mice was shown. Comparisons of cell surface levels of EGFR versus Her2 and response to panitumumab treatment indicate a correlation between a higher EGFR:Her2 ratio and responsiveness to panitumumab. Tumour types that express 17,000 EGFR per cell or more may respond to panitumumab.

In combination with 5-fluorouracil or with oxaliplatin, no additional efficacy of panitumumab was shown in comparison to monotherapy. However, with irinotecan, additional tumour inhibitory effect was shown when the effect of the combination was compared to each agent alone.

- Secondary pharmacodynamics

The characterisation of secondary pharmacodynamics included assessment of the effects of panitumumab, either as a single agent, or in combination, in a large number of studies in mice xenotransplanted with different tumour types. These studies are supportive of the potential use of panitumumab in other tumours whose growth is EGFR-dependent.

- Safety pharmacology programme

One study was conducted to assess potential toxicity to the cardiovascular, respiratory and central nervous systems in conscious cynomolgus monkeys, by telemetry methods. Groups of 4 males were given a single intravenous dose of panitumumab at 0, 7.5, 30 or 60 mg/kg. These dosages resulted in exposure that is similar to, or 4 or 8 times the exposure in patients given a therapeutic dose. The animals were observed for at least 6 days post-dose to assess the reversibility, persistence, or delayed occurrence of effects related to panitumumab administration.

In this study, no clinical signs related to panitumumab were observed. Neuro-behavioural tests did not reveal any effect on the central nervous system. Neither effects of panitumumab on respiratory rate, minute and tidal volume nor on body temperature were identified. There was also no electrocardiographic evidence of test article action. There were neither test-article –related effects on PR interval, QRS interval, RR interval or QTc interval nor on systolic, diastolic or mean blood pressure. However, QT was significantly prolonged across all doses at sporadic time points. Examination of individual data for QT over this time period indicates that the maximal individual QT interval is 317 ms and is in the low dose (7.5 mg/kg) group, at 12 hours post dose. Heart rate shows a significant decrease over this time period. QTc shows no such effect and QTc values are 346, 347, 345 and 346 over the period 0–2 hours in the control, low, mid- and high dose groups respectively.

- Pharmacodynamic drug interactions

Pharmacodynamic interaction studies were performed with a range of chemotherapeutic and targeted agents as described above.

Pharmacokinetics

Quantification of panitumumab and of antibodies to panitumumab used either an ELISA or an electrochemiluminescence (ECL) method validated for use in monkey serum. Validation of the quantification in mouse serum was not provided and therefore these data are not considered further. Tissue distribution studies were performed in cynomolgus monkeys after administration of ^{125}I-iodinated panitumumab.

Pharmacokinetics of panitumumab is presented from a one-month repeated dose study using once weekly intravenous injection in cynomolgus monkeys. Panitumumab showed dose-dependent kinetics and a ten-fold increase in dose was associated with an approximately proportionate increase in C_{max}, C_{avg} and AUC (Table 4).

Table 4. Study BQAW-102: Pharmacokinetic parameters by group and day

Group	Dose mg/kg	N	Study Day	C_{max} mcg/ml	AUC (0-7 d) mcg*d/ml	C_{avg} mcg/ml	$t_{1/2}$ days
2	6	6	1	145 (21.6)	402 (116)	57.5 (16.5)	2.64 (0.41)
	3	6	22	61.5 (39.8)	61.0 (64.9)	8.76 (9.29)	0.90 (0.75)
3	60	6	1	1600 (247)	5050 (590)	721 (84.1)	5.06 (0.85)
	30	4	22	1090 (290)	3680 (1530)	525 (218)	3.53 (2.46)
4	60	6	1	1710 (276)	5350 (799)	765 (114)	5.35 (1.40)
	30	6	22	1320 (311)	3680 (790)	526 (113)	4.16 (1.72)
5	60	6	1	1690 (368)	4210 (1170)	602 (166)	5.60 (2.02)
	30	4	22	921 (442)	1360 (1180)	194 (169)	1.17 (0.80)

Mean (SD)

Panitumumab pharmacokinetic is dose-dependent and consistent with saturation of clearance of the antibody. No accumulation on repeated, weekly, administration was noted. Nine of ten monkeys in the low dose group were MAHA positive (Monkey anti-human antibody defined as anti-panitumumab antibody); frequency for MAHA positive was 2/10 and 1/10 in the mid and high dose groups. Monkeys that developed MAHA were noted to have more rapid elimination of panitumumab.

- Absorption

The drug is administered IV.

- Distribution

Three reports on the distribution of panitumumab are provided. The most representative study consisted in a single intravenous dose of 7.5 mg/kg ^{125}I-panitumumab administered to male and female monkeys. One animal of each sex per time point was killed at 2, 48, 120 and 216 hours after dosing to examine tissue distribution with whole body auto-radiography. Blood was also drawn from available monkeys for quantification of ^{125}I-panitumumab. Urine and faeces were collected to quantify elimination. Pharmacokinetic data from the study are presented in the Table 5.

Table 5. Pharmacokinetic parameters for radioactivity in serum after administration of a single intravenous dose of ^{125}I-ABX-EGF (7.5 mg/kg) to male and female Cynomolgus monkeys

Animal Number	Sacrifice Time (hours)	T_{max} (hours)	C_{max} (µg Equiv ^{125}I-ABX-EGF/g)	AUC_{0-t} (µg Equiv ^{125}I-ABX-EGF*hour/g)	t at last timepoint (hours)	$AUC_{0-\infty}$ (µg Equiv ^{125}I-ABX-EGF*hour/g)	$T_{1/2}$ (hours)
Males							
I00288	48	2	188	5450	48	7880	28.0
I00317	120	2	155	7000	120	8650	54.9
I00500	216	2	173	8900	216	9590	64.5
Females							
I00509	48	2	185	5140	48	7000	25.0
I00513	120	2	164	7990	120	9320	45.0
I00516	216	2	162	7980	216	8290	48.7

Equiv Equivalents

Tissue:serum concentration ratios of panitumumab in male monkeys were the following: thyroid (> 1), blood (0.709), lung (0.562), gall bladder (0.512), liver (0.502), renal medulla (0.489), adrenal gland (0.434), spleen (0.416) [both red and white pulp], oesophagus (0.339), uveal tract (0.327), kidney (0.317), renal cortex (0.297), stomach (0.260), seminal vesicles (0.253), nasal turbinates (0.235), small intestine (0.223), thymus (0.211) myocardium (0.209), salivary gland (0.176), urinary bladder (0.165), prostate (0.161), pancreas (0.155), pituitary gland (0.159), large intestine (0.148), skin (0.132), bone marrow (0.131), parotid gland (0.127), diaphragm (0.123), trachea (0.110).

In females, tissue:serum concentration ratios were found for abdominal (0.155) and brown fat (0.192), and the ovary (0.541) and uterus (0.441).

Radioactivity was also noted in brain and spinal cord tissue.

- Metabolism

Metabolism studies were not conducted with panitumumab.

- Excretion

Excretion of radioactivity after administration of ^{125}I-panitumumab was predominantly in urine. After 216 hours, 65.6% (in males) and 76.5% (in females) of the administered dose was excreted in urine with only 1.6% excreted in faeces. Overall recovery of radioactivity was over 80% at 216 hours. In urine, radioactivity was present in the form of free iodide or as small peptides.

- Pharmacokinetic Drug Interaction Studies

No studies were performed with panitumumab.

Toxicology

- Single dose toxicity

No single dose general toxicology studies were conducted.

- Repeat dose toxicity (with toxicokinetics)

Repeated dose general toxicity studies were conducted using intravenous administration of panitumumab to male and female cynomolgus monkeys. These studies had a dosing duration from 4 weeks to 6 months, and all used once-a-week dosing. Table 6 summarises the general toxicity studies.

Table 6. Overview of the major findings from toxicology studies

Study	Dosage Groups mg/kg IV	N M	N F	Mean AUC mcg* day/ml	Narrative of major findings
1 month	0	5	5	-	Diarrhoea and skin lesions (erythema). Electrolyte
Feb 1999	0.6 / 0.3	3	3	14.0 ± 2.6	imbalances, dehydration. Atrophy of lymphoid
	6 / 3	3	3	399.8 ± 90.9	tissues of thymus, spleen. Myocardial
	60 / 30	5	5	8129.6 ± 3835.9	degeneration.
					No effects on: ECG, ophthalmology, coagulation, urinalysis
1 month	0	5	1	-	Diarrhoea and skin lesions (scab formation, dry
Mar 2000	6 / 3	6	0	61.0 ± 64.9	flaky skin, erythema, swelling). Electrolyte
	60 / 30	6	0	3880 ± 1530	imbalances, dehydration, mucosal hyperplasia of
	60 / 30	6	0	3680 ± 790	the large intestines and adrenocortical
	60 / 30	6	0	1360 ± 1180	hyperplasia. Increased fibrinogen.
					No effects on: ECG, ophthalmology and urinalysis.
1 month**	0	6	0	-	Hypercontraction with myofibril stretching,
Feb 2001	60 / 30	2 8	0	ND	glycogen accumulation possibly, but not conclusively, linked with mild cardiotoxicity.
3 months	0	5	5	-	Diarrhoea and skin lesions (dry flaky skin,
Oct 2000	3	5	5	11.0 ± 24.1	thinning fur, rough coat, erythema). Dehydration.
	7.5	5	5	326 ± 183	No effects on: ECG, cardiac enzymes,
	15	5	5	1030 ± 426	coagulation and urinalysis. No notable findings on macroscopic pathology, except in skin. No notable findings on electron microscopy of heart tissues.
6 months	0	6	6	-	Skin rash (erythema with irritation, flaky/dandruff
Oct 2003	7.5	6	6	774 ± 259*	appearance, papules, ulceration / necrosis) and
	15	6	6	1660 ± 266*	diarrhoea. Blepharitis in association with skin
	30	6	6	3260 ± 1300*	changes in eyelid. Fatal suspected anaphylactic shock on Day 134 at 15 mg/kg. 5 monkeys with infusion-related reactions.
					No effects on: ECG, cardiac enzymes. No notable findings on macroscopic pathology, except in skin.

All studies used dosing at weekly intervals. Where two dosages are given, the first dose was at the first dosage amount indicated with subsequent doses at the lower dosage. Dosage groups in **bold** indicate unscheduled deaths in this group.

ND no data (AUC was not calculable).

* from monkeys that were MAHA -ve only (no AUC was determinable in MAHA +ve monkeys)

** study designed to explore myocardial degeneration seen in the first study.

Toxicity to skin and diarrhoea was the primary toxicity of panitumumab in monkeys. These effects were severe enough to cause a significant number of unscheduled deaths. There were 4 unexpected deaths that were caused by either electrolyte imbalance or allergic-type reactions.

The onset of skin toxicity was typically within 7–14 days (i.e. after two or three doses). Severity correlated with dose and there is evidence that severity also correlated with duration of dosing. There was improvement in condition of monkeys after stopping dosing. The severity of toxicity to skin at times resulted in some monkeys skipping doses and various veterinary treatments were applied to alleviate discomfort (e.g. ketoprofen anti-inflammatory, cephazolin antibiotic etc). Skin toxicity is described as: erythema, irritation, crusting (with secondary infection), flaky skin (dandruff-like), loss of fur, abrasions, pustular dermatitis, hyperkeratosis, acanthosis, scabs, chronic dermal inflammation, chronic folliculitis, dermal oedema, papules and ulceration/necrosis, which could affect most areas of the body.

Diarrhoea, or soft or liquid faeces, was also a common finding and also occurred in the lowest dose groups. Intestinal mucosal hyperplasia of the large intestines was observed in the initial toxicology studies. The GI tract was histologically unremarkable in subsequent studies, including the 6-month

toxicity study. Severe electrolyte disturbances occurred (hyponatraemia, hyperkalaemia, hypochloraemia) with greater severity in higher dose groups. This effect was observed only in the early studies (secondary to the severe diarrhoea) where supportive fluids were not administered. It was not observed in subsequent studies, including the 6-month toxicity study, when supportive fluids were administered. Diarrhoea was a contributory factor to dehydration, and, it was suggested, to reductions in albumin in serum. Changes in food intake and body weight (described as cachexia in some cases) were considered to be related to general malaise arising from both these primary toxic effects.

Myocardial degeneration was evident in the first 1-month study. Changes were focal to focally extensive with affected myocytes adjacent to normal myocytes and involved the myocardium of both the septum and ventricular free walls. Degenerative changes were described as sarcoplasmic vacuolisation/fatty change, hypereosinophilia, ring fibre formation and fibre shrinkage. No significant inflammatory cell infiltrates were present. Immunohistochemical examination showed that panitumumab bound to endomysial cells of the myocardium plus nerve supporting cells and epicardial mesothelium. Human heart binding was examined for comparison and, in contrast, there was only binding to human endomysial cells, not to nerve or epicardial cells. Specific testing of cardiac enzymes did not indicate presence of myocardial toxicity. Examination of hearts from monkeys in the 3-month general toxicity study by electron microscopy could not identify any abnormality in relation to treatment. No abnormal effects on the ECG were evident and of unexpected deaths, none were suspected to be due to an arrhythmia. Follow-up studies in which supportive fluids were administered determined that the cardiotoxicity observed in the initial 1-month study was related to prolonged and untreated dehydration and electrolyte imbalance secondary to severe diarrhoea. As a result, supportive fluids were administered to prevent dehydration in all subsequent studies. No evidence of treatment-related cardiac toxicity was observed in animals administered supportive fluids, including the 6-month toxicity study. Additionally, no effects on cardiovascular function were observed in a formal safety pharmacology study conducted in cynomolgus monkeys.

Other effects included anaemia, diffuse hyperplasia in the adrenal glands and enlargement of inguinal, axillary and lumbar lymph nodes. This later one correlated with lymphoid cell hyperplasia and plasma cell hyperplasia after histopathological examination. Toxicity to male fertility was not identified on histopathological examination of relevant tissues. No consistent changes were observed in serum magnesium concentrations.

- Genotoxicity

Panitumumab has not been evaluated in genotoxicity studies.

- Carcinogenicity

No carcinogenicity studies have been conducted.

- Reproduction Toxicity

One study was conducted to assess reproductive performance and early embryonic development. A total of 44 female cynomolgus monkeys were given doses of 0, 7.5, 15 or 30 mg/kg IV once weekly for two menstrual cycles throughout the mating period to Day 20 of gestation. Males were not dosed. Overall rates of pregnancy in control, low-, mid- and high-dose groups were 6/12 (50%), 2/5 (40.0%), 1/6 (16.7%) and 2/6 (33.3%). In total, 5 out of 17 (29.4%) monkeys that were mated, having been treated with panitumumab, became pregnant. There were notable findings of amenorrhea and of prolonged menstrual cycles. Because of the different length of cycle in each animal, the number of administered doses was variable across the study and ranged from 7 to 23 doses. The day at which maximal concentrations of serum 17β-oestradiol and progesterone were reached was significantly delayed by panitumumab treatment, and the maximal concentration of progesterone (but not serum 17β-oestradiol) was also reduced.

Panitumumab was administered intravenously to pregnant female cynomolgus monkeys to assess potential embryotoxic and teratogenic effects. Dosage groups were 0, 7.5, 15 and 30 mg/kg and group sizes were 12, 15, 18 and 5 respectively -at 30 mg/kg, three of the first five monkeys aborted. Each monkey was dosed once weekly from Day 20 of gestation for a total of 5 doses. The last dosing day was Day 48. Pregnancies were terminated at Day 100 to 103 and foetuses were examined. The high

dose group showed a statistically significantly higher frequency of abortion/foetal death than the control group. Data for total abortion/foetal death are:

Dose (iv, mg/kg)	Frequency of abortion/foetal death
0	8.3 % (1/12)
7.5	33.3% (5/15)
15	16.7% (3/15)
30	60.0% (2/5)

However, there was no effect on foetal weight, organ weights, placental weights, foetal and placental external measurements, and foetal and placental histopathology. There was no NOAEL in this study, as even the lowest dose was associated with foetal abortions or death and with significant maternal toxicity. No teratogenic effect was observed in surviving foetuses.

- Local tolerance

Local tolerance was studied as part of the general toxicology studies using the intravenous route.

- Other toxicity studies

Comparability of hybridoma-derived and CHO-derived panitumumab

A repeated-dose general toxicity study was conducted in cynomolgus monkeys to compare the kinetics and toxicity of hybridoma-derived and CHO-derived panitumumab, using once-a-week injections for 4 weeks followed by a 4-week recovery period. Dosage groups were 0, 7.5 and 30 mg/kg IV. There was no evidence of difference between hybridoma-derived and CHO-derived panitumumab.

Comparability of 2-kl and 12-kl litre scale CHO-derived panitumumab

A study of similar design was performed in cynomolgus monkeys to compare toxicity and toxicokinetics of panitumumab manufactured at two different scales: 2,000 litres or 12,000 litres (commercial scale). Monkeys were dosed with 0, 7.5 or 30 mg/kg IV, once-a-week, for 3 months, with a recovery period of 6 weeks. During dosing, a 0.22 μm filter was in place. There was an additional group of monkeys who were dose with 7.5 mg/kg every two weeks and an additional further group of monkeys who were dosed with 30 mg/kg every week, but without a filter. It was concluded that there was no apparent difference in the toxicology or kinetics of panitumumab, dependent on the scale of its manufacture.

Ecotoxicity/environmental risk assessment

Not required as per ERA guideline.

Discussion on the non-clinical aspects

Pharmacology

The rationale for EGFR inhibition in metastatic colorectal cancer is well established. The applicant has shown that panitumumab specifically binds to epidermal growth factor receptors and inhibits signalling through this receptor. As an IgG_2, panitumumab is not expected to act via Fc-dependent mechanisms (e.g., antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity).

The induction of hypomagnesaemia by panitumumab occurs in clinical use (6%) but was not detected in monkeys. It could be that there is a genuine species difference between monkeys and humans or that the studies in monkeys simply failed to detect this effect, due to the low frequency of its occurrence. Hypomagnesaemia has been adequately addressed in clinical studies.

It was concluded that the statistically significant prolongation of QT seen is not biologically relevant. Nevertheless, apparent greater frequency of QT prolongation at the highest dose group over the period closest to drug administration could represent a potential signal. The lack of change in QTc is reassuring. There was no evidence of treatment-related effect on cardiovascular parameters (heart rate,

PR intervals, QRS intervals, RR intervals, QT intervals, QTc intervals, systolic and diastolic pressure, mean arterial pressure) in the formal safety pharmacology study.

Pharmacokinetics
Two methods to quantify panitumumab in monkey serum were used. However, data suggested that these are not equivalent and that the validated ECL method may have quantified panitumumab concentrations at significantly higher than the ELISA method. The presence of anti-idiotypic MAHA directed against the antigen-binding site of panitumumab was raised as a possible interference factor. In view that significant immunogenicity response has not been reported in humans and that levels of panitumumab in serum will not be determined in the clinical setting the issue has not been considered of clinical relevance.

Quantification of panitumumab in mouse serum has not been validated. Therefore, the data on mice are judged merely indicative. The studies in cynomolgus monkeys provide sufficient information on the distribution and elimination of panitumumab. Although no study was specifically conducted to assess foetal exposure, this is considered likely, as IgG_2 immunoglobulins are known to cross the placenta and to be secreted in milk.

Toxicology
In the initial repeat-dose toxicity study where no supportive fluids were administered myocardial degeneration was seen in all treatment groups, both at Day 29 and following 14 days recovery. No evidence of myocardial degeneration was observed in any other studies where supportive fluids were administered to prevent dehydration secondary to diarrhoea, including the 6-month toxicity study. Immunohistochemical staining of cardiac tissues revealed variable tissue binding of panitumumab to cells of the myocardium and of the epicardial mesothelium in the monkey heart tissue samples. However, specificity of the staining could not be determined and it is possible that the positive staining observed in study was an artefact. In support for this argument, there were no clear correlation between myocardial degeneration and cardiac staining. Further, no binding of panitumumab was noted in human or monkey cardiac tissue in a formal tissue cross-reactivity studies which utilised optimised immunohistochemical techniques to assess specific panitumumab binding.

Toxicity to skin and diarrhoea was the primary toxicity of panitumumab in monkeys. These effects are also seen with cetuximab, a chimeric anti-EGFR antibody and with small molecule inhibitors of EGFR such as gefitinib. It is considered directly related to the pharmacological action of drugs that inhibit EGFR signalling.

Animal studies are insufficient with respect to embryo-foetal development since foetal panitumumab exposure levels were not examined. EGF and EGF receptors are involved in embryo-foetal growth and development, and effects on growth and development would therefore be expected. Indeed, panitumumab has been shown to be an abortifacient in cynomolgus monkeys when administered during the period of organogenesis at doses up to 5-fold the exposure of recommended human dose of 6 mg/kg every 2 weeks.

No pre- and post-natal development animal studies have been conducted with panitumumab.

4. Clinical aspect

Introduction

Panitumumab is a fully human IgG2 monoclonal antibody that is directed against the EGFR. The EGFR is a transmembrane glycoprotein that promotes cell growth in a variety of normal and transformed tissues. The receptor has several natural ligands including EGF and transforming growth factor-alpha. Binding of the ligand to the receptor stimulates cell proliferation. Blocking this interaction by means of a monoclonal antibody directed against the receptor inhibits tumour growth in vivo.

The clinical development of panitumumab was designed to assess its efficacy and safety in patients with metastatic carcinoma of the colon or rectum after failure of oxaliplatin- and/or irinotecan-containing chemotherapy regimens. The clinical studies submitted included 15 clinical studies in patients with a variety of solid tumours (n = 1304). Among those studies, one Phase III, four Phase II and three pharmacokinetics studies were submitted in the target patient population. With regard to clinical efficacy, progression-free survival, overall survival, objective tumour response and disease-related symptoms as well as quality of life were assessed. During the development of panitumumab, clinical trials have been conducted under the sponsorship of 3 companies, Abgenix Inc., Immunex Corporation and Amgen Inc.

At the initiation of the clinical programme, panitumumab was produced by a human hybridoma cell line. Later, a decision was made to shift to CHO cells. The change took place in two steps. The first was from hybridoma to small scale CHO fermentation (2 kl), and subsequently to a commercial scale production (12 kl). Therefore, the clinical programme has involved patients receiving panitumumab of all three origins, with steps in between seeking to show equivalence between them.

GCP

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

Pharmacokinetics

Pharmacokinetic data were obtained as part of the clinical safety and efficacy studies. Healthy volunteers were not used. The pharmacokinetic programme (Table 7) involved use of panitumumab from different sources, in various cancer forms, at various dose regimens and in some cases also with concomitant administration of chemotherapy.

Table 7. Overview the PK-related programme

Study number	Objective	Cancer type(s)[1]	No. doses /duration	Dose (mg/kg)	No. enrolled (aim per protocol)	Concomitant therapy	Source[2]
20030138	Safety, PK, dose finding	CRC+var.	4 doses	0.1-9.0	97 (136)	None	CHO 2 kl Hybridoma cells
20030251	Safety, PK, efficacy, dose finding	CRC+var.	Unlimited	6, 9	57 (85)	None	CHO 12 kl
20040192	Safety, PK, efficacy, dose finding	CRC+var.	Unlimited	2.5-9.0	12 (18)	None	CHO 12 kl
20025409	Safety, efficacy, PK	CRC	≤ 48 weeks.	2.5	24 (84)	irinotecan, 5-fluorouracil, leucovorin	Hybridoma cells
20025408	Efficacy, safety, PK	Lung	≤ 48 weeks	2.5	9 (75)	None	Hybridoma cells
20030110	Safety, efficacy, PK	Prostate	≤ 48 weeks	2.5	33 (30-50)	None	Hybridoma cells
20040116	Safety, PK	CRC+var.	6 months	0.01-9.0	20 (136)	None	CHO 2 kl
20020374	Safety, efficacy, PK	Renal	10 months	1-2.5	202 (up to 180)	None	Hybridoma cells
20020408	Safety, efficacy	CRC	Unlimited	6	463 (430)	None	CHO 2 kl
20025405	Safety, efficacy	CRC	Unlimited	2.5	150 (150)	None	Hybridoma cells
20030167	Safety, efficacy	CRC	24 months	6	93 (300)	None	CHO 2 kl
20030250	Efficacy, safety	CRC	24 months	6	88 (150)	None	CHO 2 kl
20025404	Safety, PK, efficacy	Lung	36 weeks	1-2.5	194 (up to 255)	Paclitaxel, carboplatin	Hybridoma cells

1 CRC = colorectal cancer, var. = various other solid tumour cancer forms
2 CHO = Chinese hamster ovary cells, 2 kl= produced in 2000 litre tanks, 12 kl= produced in 12000 litre tanks

For human samples, an immunoassay with electrochemiluminescence detection was used to measure panitumumab. A biotinylated, anti-idiotypic antibody was immobilised on magnetic beads to bind to panitumumab in serum. A ruthenium-labelled panitumumab anti-idiotypic antibody was used to detect panitumumab by electrochemiluminescence. The lower limit of quantification was 78 ng/ml in serum.

- Absorption

The drug is administered IV.

- Distribution

In Study 20030138 where modelling has been applied, the results indicate a central volume of distribution of 42 ml/kg which corresponds to the typical plasma volume in humans.

- Elimination

The applicant quotes ICHS6, that biotransformation studies are not required for monoclonal antibodies as it is expected that the antibody is degraded to small peptides and individual aminoacids. The modelled half-life was approximately 8 days at steady state for doses ranging from 2.5 mg/kg once a week to 9 mg/kg every 3 weeks.

- Dose proportionality and time dependencies

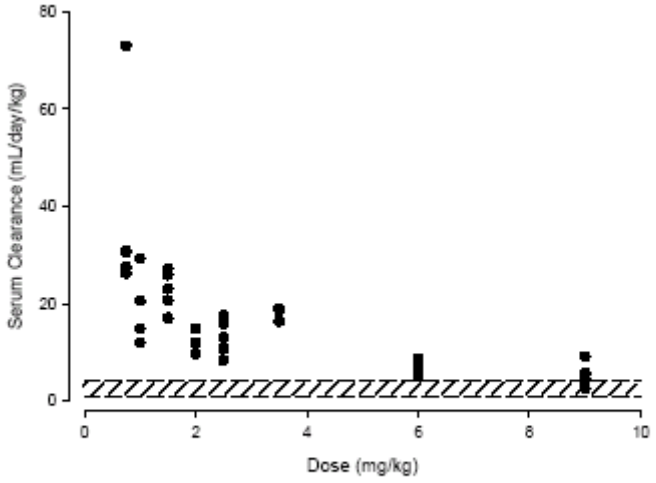
Dose-finding used skin toxicity as a marker of primary pharmacodynamic effect. A plateau in the incidence of integument (skin, nails and hair) and eye toxicity occurred at 2.5 mg/kg once weekly. At this dose the trough concentrations exceeded the panitumumab concentration at which the non-linear pathway is saturated by 90% in animal xenograft models.

Pharmacokinetic simulations suggested that mean ±SD C_{max} concentrations for 2.5 mg/kg once a week, 6 mg/kg every two weeks or 9 mg/kg every three weeks were 119±35, 219±54 and 257±41 µg/ml, respectively and trough concentrations were 56 ± 22, 47 ± 19 and 49 ± 29 µg/ml, respectively.

In Study 20030138, steady state was reached after six weeks of treatment and the half-life after the 2.5 mg/kg once/week, 6 mg/kg every two weeks or 9 mg/kg every three weeks were 8.5, 7.5 and 8.4 days, respectively.

The modelling suggests that plasma concentrations *vs*. time can be described by a two-compartmental model with two elimination pathways: elimination occurs in a first-order fashion via the reticuloendothelial system like other IgG and by internationalisation of the EGF receptor. Non-linear pharmacokinetics was observed in the dose-range 0.75-9.0 mg/kg. The time-averaged clearance value decreases with increasing dose. The panitumumab concentration that produces 90% saturation of the nonlinear clearance pathway was to be 9.77 ± 1.94 µg/ml (95% CI: 5.93-13.6). The relationship between doses and clearance is visualised in Figure 5.

Figure 5. Individual panitumumab average clearance after the first dose



Shaded area represents the typical human IgG_1 and IgG_2 clearance values expected when antigen-mediated clearance is absent (Humira®, 2002; ABX-IL8, Abgenix data on file)

- Special populations

The population pharmacokinetic analyses used data from five studies with intensive sampling; for the other eight studies only peak and trough samples were taken. There were 463 men and 243 women included in the analysis, of these 600 were classified as white and 106 as other race. The tumour type was classified as colon/rectum in 247, lung in 162, renal in 210 and other in 87. The product was manufactured by hybridoma in 613 patients and CHO cells in 93. Concurrent chemotherapy was given in 167 and not in 539. Weight mean and range were 81 kg (32-166); for age 60 years (21-88); for body surface area 2 m^2 (1-3); for height 1.72 m (1.31-1.98) and for EGFR maximum staining intensity 2, (0-3).

Panitumumab serum concentrations and body weight showed a correlation with higher concentrations in heavier patients when dosed by weight. Despite this, dosing according to body weight, as recommended in the proposed labelling, reduced inter-subject variability. Larger body weight was associated with larger volumes of distribution and higher clearance.

Population pharmacokinetic analyses were carried out using modelling. It is suggested that EGFR expression in tumour cells, primary tumour type, gender, race, age, impaired renal and impaired liver function did not affect the pharmacokinetics of panitumumab. Modelling showed inter-individual coefficients of variation for the volume of the central compartment and of clearance of 53% and 25% respectively.

The effect of gender was assessed in kinetic data from three studies where 83 patients, 37%, were women. These data indicate that peak concentrations were similar although the mean trough panitumumab concentration was 15% higher for women. In the same studies, 87 patients, 39%, were 65 or older and showed no differences in kinetics compared to those < 65 years. For those over 75, the mean panitumumab concentration was approximately 10% higher.

- Pharmacokinetic interaction studies

In vitro

No study is available.

In vivo

Interactions between panitumumab and chemotherapy agents were tested in two Phase II trials. Panitumumab had no effect on the pharmacokinetics of paclitaxel, paclitaxel + carboplatin, irinotecan or the active metabolite of irinotecan (SN-38). Irinotecan and its metabolite did not affect the pharmacokinetics of panitumumab. Interaction with carboplatin alone was not evaluated.

- Pharmacokinetics using human biomaterials

No *in vitro* permeability, metabolism or metabolic drug-drug interaction studies that used human biomaterials were performed for this programme.

- Bioequivalence

Bioequivalence between panitumumab of different origins and manufacturing process was explored in two studies: Studies 20030138 and 20030251.

Study 20030138 was an open-label, Phase I study enrolling 97 patients in 4 investigational centres. Diagnostic inclusion criteria were solid tumours that had proven refractory to chemotherapy. The primary objective was safety of multidose panitumumab (at various doses) and pharmacokinetics, as secondary objective. Patients received 4 doses of panitumumab ranging from 0.1 to 9.0 mg/kg where the panitumumab was sourced from hybridoma and 6.0 and 9.0 mg/kg from CHO 2 kl origin.

The drug was administered once a week (qw) for doses up to 5 mg/kg, every two weeks (q2w) for 6 mg/kg and every three weeks (q3w) for 9 mg/kg. Serum sampling times were, for qw-dosing at Dose 1: pre-infusion, 0.5, 1, 4, 8, 24, and 96 hours. At Doses 2, 3 and 4 only pre- and post-infusion samples were collected. Serum sampling times were, for q2w-doing at Doses 1 and 3: pre-infusion, 0.5, 8, 24, 96, 168, 240 and 288 hours. At Doses 2 and 4 only pre- and post-infusion samples were collected. Serum sampling times were, for q3w-doing at Doses 1 and 3: pre-infusion, 0.5, 8, 24, 96, 168, 336 and 408 hours. At Doses 2, and 4 only pre- and post-infusion samples were collected.

The population studied was 75% male, mean age 64 years (SD 11 years). Table 8 provides AUC and C_{max} for hybridoma-derived and CHO-derived panitumumab after the first dose of 6 and 9 mg/kg.

Table 8. Study 20030138: Comparison of CHO-derived vs. hybridoma-derived panitumumab

Parameter	2 kl CHO (test) Mean	%CV	n	2 kl Hybridoma (reference) Mean	%CV	n	Ratio (test/reference)	90% CI
6 mg/kg								
$AUC_{0\text{-}tau}$ (µg·day/ml)	862	21	10	816	21	7	105	87 to 127
C_{max} (µg/ml)	150	16	10	144	20	7	105	90 to 123
9 mg/kg								
$AUC_{0\text{-}tau}$ (µg·day/ml)	1597	17	16	1801	40	5	93	75 to 116
C_{max} (µg/ml)	226	22	16	253	32	5	91	73 to 112

$AUC_{0\text{-}tau}$	area under the serum concentration-time curve during the dosing interval
C_{max}	maximum observed concentration
Mean	arithmetic mean
Ratio	ratio of antilogs of treatment least squares mean values expressed as a percentage
90% CI	90% confidence interval estimate for ratio (test/reference) of treatment least-squares mean values expressed as a percentage

Study 20030251 was an open-label, Phase I study, enrolling 57 patients in 7 investigational centres. Diagnostic inclusion criteria were solid tumours that had proven refractory to standard chemotherapy. The primary objective was safety and pharmacokinetics of panitumumab derived from 12 kl CHO fermentation. The drug was administered at a concentration of 6 mg/kg every two weeks (as either a 30- or 60-minute infusion) and at 9 mg/kg every three weeks (60-min infusion). The treatment was administered until disease progression.

At Weeks 1 and 5, 20 patients who had received 6 mg/kg had samples drawn at pre-, post-dose and at 24, 96, 168 and 240 hours. Generally, pre- and post-dose samples were also drawn at Weeks 1, 3, 5, 7 and 8.

Table 9 displays comparative AUC and C_{max} for 2 and 12 kl fermentation process after the first and third dose of 6 mg/kg of panitumumab generated from Studies 20030138 and 20030251, respectively.

Table 9. Studies 20030138 and 20030251: Comparison of 2 kl and 12 kl CHO-derived panitumumab

Parameter	12 kl CHO (test) Mean	%CV	n	2 kl CHO (reference) Mean	%CV	n	Ratio (test/reference)	90% CI
After the first dose								
$AUC_{0\text{-}tau}$ (µg·day/ml)	744	26	29	862	21	10	85	71 to 101
C_{max} (µg/ml)	152	19	29	150	16	10	101	89 to 113
After the third dose								
$AUC_{0\text{-}tau}$ (µg·day/ml)	1311	28	22	1306	29	10	99	83 to 120
C_{max} (µg/ml)	232	31	22	213	28	10	108	89 to 130

$AUC_{0\text{-}tau}$	area under the serum concentration-time curve during the dosing interval
C_{max}	maximum observed concentration
Mean	arithmetic mean
Ratio	ratio of antilogs of treatment least squares mean values expressed as a percentage
90% CI	90% confidence interval estimate for ratio (test/reference) of treatment least-squares mean values expressed as a percentage

Pharmacodynamics

- Mechanism of action

The anti-tumour effects of panitumumab are thought to be primarily mediated by directly targeting the EGFR, as shown in the preclinical. Panitumumab binds to the EGFR ligand-binding domain and

blocks the tyrosine phosphorylation of EGFR by endogenous ligands, since it has no agonistic activity. In addition, panitumumab induces internalisation of the receptor in EGFR-expressing cells.

- Primary and Secondary pharmacology

No study was conducted in healthy volunteers because of concerns of toxicity. The primary pharmacology of an anti-cancer agent will come from the clinical efficacy data. Several other functions of EGFR can be used to detect pharmacodynamic effect such as the role of EGFR on epidermal cells, dose-finding studies were based on the incidence of rash used as a marker of pharmacodynamic activity.

Unwanted effects related to the primary mode of action occurred through the blockade of the EGFR. These included the skin and eye toxicity which occurred in 91% of the monotherapy patients. Hypomagnesaemia occurred in 39%. EGFR is expressed in the kidney, particularly in the ascending loop of Henle, where 70% of filtered magnesium is reabsorbed. It is thought that EGFR inhibitors block renal tubular reabsorption of filtered magnesium, or possibly by interfering with magnesium absorption in the gut.

Clinical efficacy

The clinical study programme for the assessment of efficacy comprises a total of five studies, one pivotal (Study 20020408) with an extension (Study 20030194) and three supportive studies (Studies 20025405, 20030167, 20030250) (Table 10) conducted in patients with metastatic colorectal cancer (mCRC) after failure of prior chemotherapy regimens including 5-fluorouracil, irinotecan, and/or oxaliplatin.

Panitumumab is also being investigated in the following indications:

- Advanced non–small cell lung cancer in combination with carboplatin and paclitaxel
- Renal carcinoma as monotherapy
- Hormone refractory prostate cancer with or without metastases as monotherapy

Table 10. Summary of studies providing clinical efficacy data

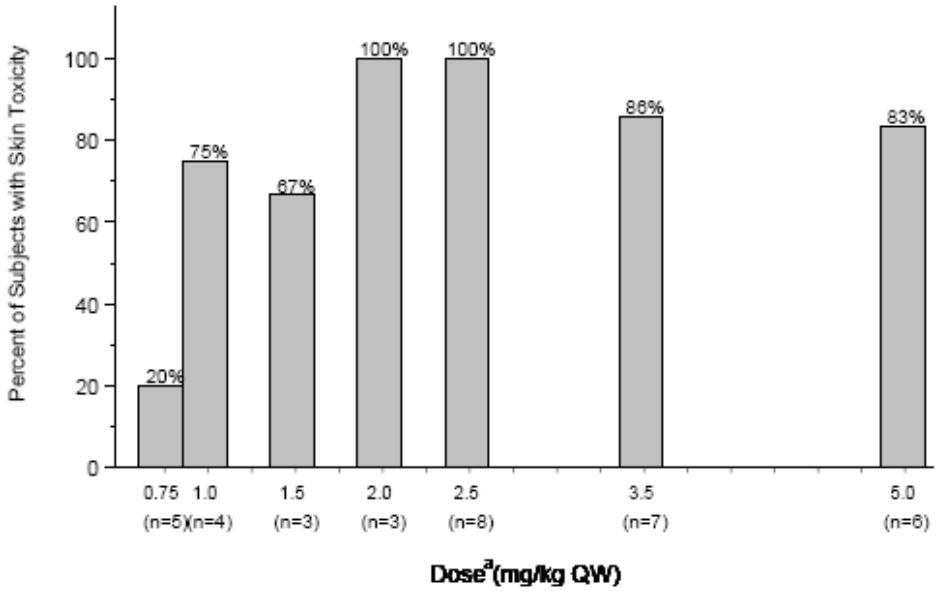
Study ID	No. of study centres	Design	Study posology[1]	Primary study objective	Subjects	Treatment duration	Diagnosis inclusion criteria[2]	Primary endpoint
Controlled study – monotherapy								
20020408	81	Phase III, randomised, open–label	Panitumumab 6 mg/kg IV every 2 weeks; CHO 2 kl	Assess whether panitumumab plus best supportive care (BSC) improves progression–free survival compared with BSC alone in patients with metastatic colorectal cancer who failed standard chemotherapy	463 (complete)	Until disease progression, intolerance or other reason (death, withdrawal etc.)	mCRC; disease progression during or after prior fluoropyridine, irinotecan and oxaliplatin, ≥ 1% EGFR+	Progression free survival
Uncontrolled studies – monotherapy								
20030194	81	Phase II, open–label, single arm, extension of 20020408	Panitumumab 6 mg/kg IV every 2 weeks; CHO 2 kl	Assess the safety of monotherapy panitumumab in patients with metastatic colorectal cancer who had progressed in the BSC arm of Study 20020408	175 (ongoing)	Until disease progression, intolerance or other reason (death, withdrawal etc.)	mCRC progression on BSC arm of 20020408/EGFR status from 20020408 BSC arm baseline	Safety
20030167	24	Phase II, open–label, single arm	Panitumumab 6 mg/kg IV every 2 weeks; hybridoma	Assess the objective response rate through week 16 and the duration of response	92 (ongoing)	Until disease progression, intolerance or other reason (death, withdrawal etc.)	mCRC; failed therapy with fluoropyrimidine, irinotecan, and oxaliplatin, ≥ 10% EGFR+	Objective tumour response
20030250	59	Phase II, open–label, single arm	Panitumumab 6 mg/kg IV every 2 weeks; CHO 2 kl	Assess the effect of treatment with panitumumab monotherapy on the objective tumour response rate through week 16 and on the duration of response	88 (ongoing)	Until disease progression, intolerance or other reason (death, withdrawal etc.)	mCRC; failed therapy with fluoropyrimidine, irinotecan, and oxaliplatin; < 10% (including < 1%) EGFR+	Objective tumour response
20025405	29	Phase II, open–label, single arm	Panitumumab 2.5 mg/kg IV every 2 weeks; CHO 2 kl	Assess the efficacy and safety of panitumumab as monotherapy	150 (complete)	Until disease progression, intolerance or other reason (death, withdrawal etc.)	mCRC; failed therapy with a fluoropyrimidine plus either irinotecan or oxaliplatin or both, ≥ 10% EGFR+	Objective tumour response

1 IV – intravenous
2 mCRC c metastatic colorectal cancer; EGFR – epidermal growth factor receptor; BSC – best supportive care

- Dose response study(ies)

Results from a Phase I study (20030138) and a Phase II study (20020374) were the basis for the selection of the dose regimen of panitumumab. Skin rash incidence and severity was used as an on-target pharmacodynamic marker for EGFR blockade.

Figure 6. Study 20030138: Incidence of skin toxicities during the treatment period in study



The incidence (Figure 6) and severity of skin rash increased as dose increased from 1 to 2.5 mg/kg once a week, reaching an apparent plateau at 2.5 mg/kg once a week.

Also, at 2.5 mg/kg once a week the time-averaged panitumumab clearance value approached the clearance value for endogenous IgG2, indicating that EGF-mediated clearance was saturated.

The dose schedule of 6 mg/kg every two weeks (and 9 mg/kg every three weeks) were selected from modelling of pharmacokinetic data from Study 20030138, in order to achieve steady-state through panitumumab concentrations (C_{min}) comparable to those obtained with 2.5 mg/kg once a week in Study 20025405.

- Main study

Study 20020408 was conducted as a pivotal clinical study in metastatic CRC with the following title: "An open–label, randomised, phase 3 clinical trials of ABX–EGF plus best supportive care *vs.* best supportive care in patients with metastatic colorectal cancer". Patients with progression in the best supportive care (BSC) alone–arm were allowed to cross over to receive panitumumab in an open-label extension study (Study 2003194).

METHODS

Study Participants

This was a multicentre study conducted at 81 centres in Europe, Canada, Australia, and New Zealand.

Main inclusion criteria were:

- metastatic colorectal carcinoma
- ECOG performance status of 0, 1 or 2
- documented evidence of disease progression during or after treatment with a fluoropyrimidine, irinotecan, and oxaliplatin for metastatic colorectal cancer
- tumour expressing EGFR by immunohistochemistry (membrane staining was to be positive in ≥ 1% of evaluated tumour cells)

Main exclusion criteria were:
- use of systemic chemotherapy or radiotherapy within 30 days before randomisation
- prior EGFR targeting agents
- prior anti–tumour therapies including prior experimental agents or approved anti–tumour small molecules and biologics with short serum half–life (< 1 week) within 30 days before randomisation, or prior experimental or approved proteins/antibodies with longer serum half–life (e.g., bevacizumab) within 3 months before randomisation
- chemotherapy other than fluoropyrimidine (or raltitrexed), irinotecan, or oxaliplatin for colorectal carcinoma in accordance with the regimens specified (leucovorin and levamisole were not considered as chemotherapy in this exclusion criterion)

Treatments
The eligible patients were allocated to one of the two treatment arms:
- Arm 1: 6 mg/kg panitumumab intravenous once every two weeks in a minimum of 100 ml normal saline, over 60 to 90 minutes (depending upon volume) and BSC
- Arm 2: BSC comprised any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational agents or anti-neoplastic chemotherapy

The cycles continued until disease progression, inability to tolerate panitumumab or other reason for discontinuation. Patients in BSC alone arm had the option to receive panitumumab 6 mg/kg once every two weeks in an open–label extension study (Study 20030194) after disease progression, determined by the investigator.

Objectives
The primary objective of this study was to assess whether panitumumab plus BSC improves progression–free survival compared with BSC alone in patients with metastatic colorectal cancer who failed standard chemotherapy.

Secondary objectives were to evaluate overall survival, objective response, duration of response, time-to-response, time-to-disease progression, time-to-treatment failure, duration of stable disease, patient-reported outcomes and the safety profile of panitumumab plus BSC compared with BSC alone.

Outcomes/endpoints
Primary outcome measure
The primary outcome measure was progression–free survival which was defined as the time from randomisation to the date of the first observed progression or death.

Secondary outcome measures
- Overall survival: time from randomisation to death
- Best objective response over time: the best disease status from randomisation through the end of the study
- Duration of response: for responders as the time from the first response to either disease progression or death due to disease progression
- Time-to-response: time from randomisation to first partial or complete response, subsequently confirmed ≥ 4 weeks after the criteria for response were first met
- Time-to-disease progression: time from randomisation to disease progression or death due to disease progression
- Time-to-treatment failure: time from randomisation to the time a decision was made to withdraw from the treatment phase for any reason
- Duration of stable disease: patients whose best response was stable disease as the time from randomisation to disease progression or death due to disease progression
- Quality of life measured by time–adjusted area under the curve for EUROQOL EQ–5D index and time–adjusted AUC for NCCN/FACT CRC subscale.

Patients were evaluated for tumour response according to the modified Response Evaluation Criteria In Solid Tumours (RECIST) at Weeks 8, 12, 24, 32, 40, and 48 and thereafter every 3 months until disease progression. Patients with symptoms suggestive of disease progression were evaluated for tumour status at the time the symptoms occurred. Tumour responses were to be confirmed no less than 4 weeks after the criteria for response were first met. In addition to the investigator's assessments, scans of all patients evaluated for tumour response were evaluated by a masked Independent Review Committee (IRC). The primary efficacy analysis was based on the masked IRC data.

Table 11. Study 20020408: Overview of the definitions and uses of the different datasets

Dataset	Description	Analysed parameters
ITT	Consented and randomised patients	Primary efficacy analysis of all efficacy endpoints
Adjudicated prior failures	All consented and randomised patients who were determined by the independent eligibility review committee to have developed progressive disease or relapsed during or after prior fluoropyrimidine, irinotecan, and oxaliplatin chemotherapy at an adequate overall exposure per the protocol	Secondary analyses of all efficacy endpoints
Per Protocol	Patients in the adjudicated prior failures analysis set who did not have any selected, important, predefined protocol deviations thought to potentially impact the efficacy analyses	Sensitivity analyses of progression–free survival and overall survival

Sample size
The sample size was estimated to achieve > 90% power for a 2–sided 1% significance level, given a hazard ratio (panitumumab plus BSC:BSC) of 0.67, which can be translated into a 50% relative median increase in progression–free survival (2.50 *vs.* 3.75 months) or a 14% absolute increase in the 6–month progression–free rate (19% *vs.* 33%). To achieve the sample–size goal, at least 362 patients in total were required to have either documented evidence of objective progression by the modified-RECIST criteria assessed by IRC or to have died. It was estimated that a total of 430 patients would be required.

Randomisation
Patients were randomly assigned in a 1:1 ratio to receive panitumumab plus BSC or BSC alone. Randomisation was stratified by ECOG performance status (0 or 1 *vs.* 2) and geographic region (Western Europe *vs.* Central and Eastern Europe *vs.* rest of the world).

Blinding (masking)
This was an open–label study. Masking was considered by the applicant not possible because of the expected skin–related toxicities related to panitumumab. Access to the data was restricted to a minimum number of individuals and masked data were reviewed by the IRC for the event–based progression–free survival analysis.

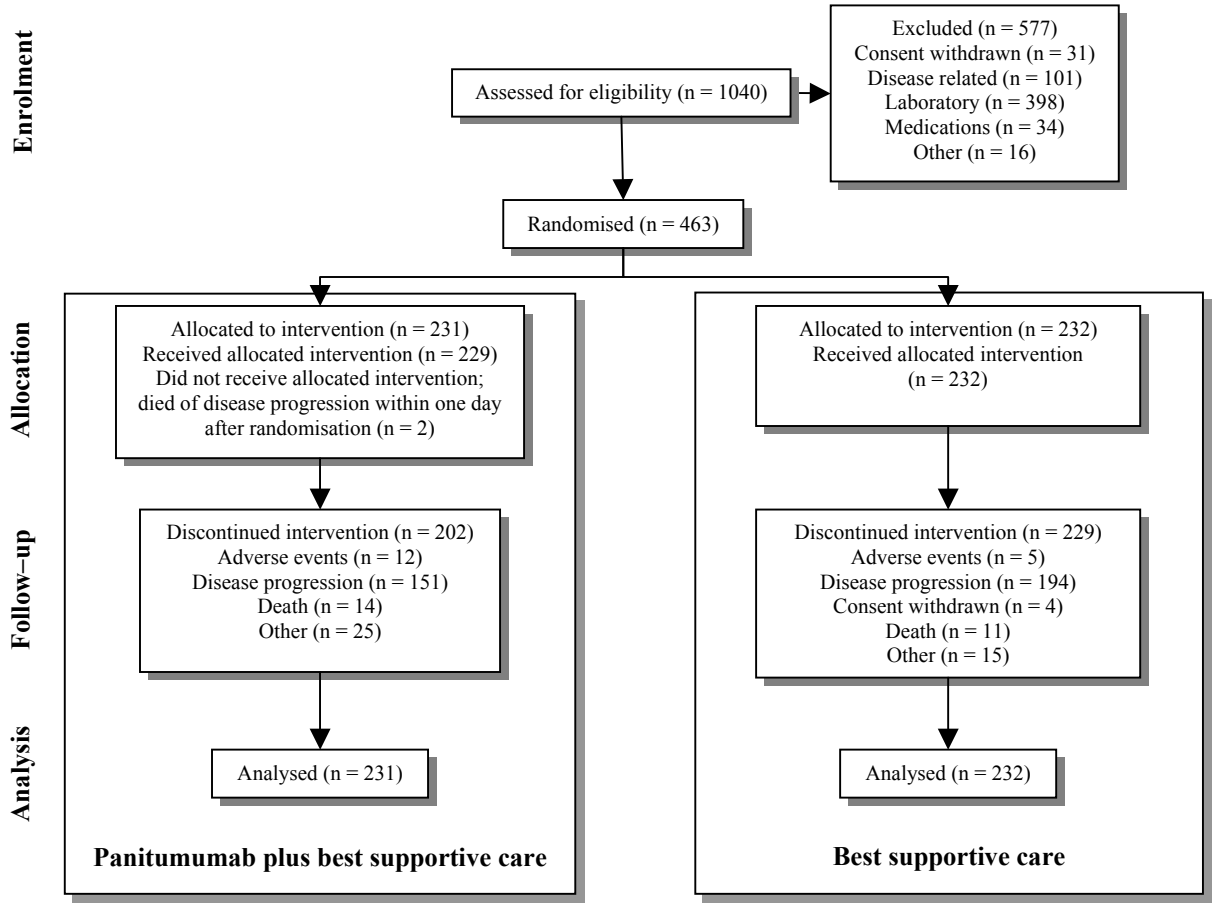
Statistical methods
The primary endpoint was progression–free survival which was compared by a stratified log rank test. The stratification factors were ECOG performance status and geographic region.

If the log–rank test for progression–free survival was significant, the co–secondary endpoints of survival and best objective response rate over time were analysed simultaneously. Survival was analysed at the 4% significance level, while response rate was analysed at the 1% significance level. Hazard ratios and corresponding 95% confidence intervals were estimated by Cox' proportional hazards model.

After completion of the 2–year long-term follow–up, descriptive statistics will be provided for all data collected. For continuous endpoints, the mean, standard error (SE; for efficacy, pharmacokinetic, and quality of life endpoints), standard deviation (SD; for other measures), median, 25^{th}, 75^{th} percentile, minimum, and maximum are provided. For discrete data, the frequency and percent distributions are provided.

RESULTS

Participant flow



Recruitment

The enrolment period was from 16 January 2004 to 16 March 2005 and the cut–off date for clinical data was 30 June 2005.

Most patients were enrolled at study centres in Western Europe (77% panitumumab plus BSC, 78% BSC alone). One investigational centre was the highest–enrolling centre, with 63 patients (14%) overall: 35 patients (15%) in the panitumumab plus BSC group and 28 patients (12%) in the BSC alone group. The other study centres enrolled between < 1% and 7% of patients overall.

Conduct of the study

The protocol for this study, originally dated 12 September 2003, was amended 4 times. All the amendments were in effect prior to the data cut–off date (Table 12).

Amendments

Table 12. Study 20020408: Summary of the major protocol amendments

Amendment	Major changes
25 October 2003 (n = 0)[1]	– RECIST criteria were modified, in consultation with the central imaging laboratory conducting the blinded review (RadPharm, Princeton, NJ), to be consistent with current medical practice – The Week–4 tumour assessment was removed, and it was clarified that patients with symptoms suggestive of disease progression should be evaluated for tumour response at the time the symptoms occurred – The grading system for skin–related toxicities was changed from NCI CTC version 2.0 to CTCAE version 3.0 (with sponsor's modifications), based on previous experience with version 2.0 and a lack of descriptive terms to grade these events effectively) – Modifications to inclusion/exclusion criteria, study procedures, and other sections were made to improve clarity
07 June 2004 (n = 99)[1]	– The definition of BSC was modified to include antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery or any symptomatic therapy as clinically indicated – Patients were allowed to remain on study treatment beyond 48 weeks until disease progression or inability to tolerate panitumumab – Tumour assessments occurring every 3 months until disease progression were added after Week 48 – Membrane staining criteria used for the determination of EGFR expression in tumour cells was changed from ≥10% to ≥1% of evaluated tumour cells, based on label information from the recently FDA–approved anti–EGFR antibody, cetuximab – An inclusion criterion was added that patients must have received at least 2 but no more than 3 prior lines of chemotherapy – Modifications to inclusion/exclusion criteria, study procedures, and statistical methods were made to improve clarity
01 February 2005 (n = 382)[1]	– The primary analysis set for the efficacy analyses was changed from the Adjudicated Prior Failures analysis set to the ITT analysis set, as the ITT set was more representative of the target population and maintained the balance achieved through randomisation. This change reduced the estimated sample size from 600 to 430 randomised patients – The timing of the primary analysis was based on the number of disease progression events rather than a predefined number of patients followed for a specific period of time, which ensures statistical power is achieved – The efficacy analysis set was replaced with a Per Protocol analysis set, which provided a more appropriate analysis set for the planned sensitivity analyses – The timing of the analyses for tumour tissue biomarkers was changed to occur after the primary analysis of this study and, as such, may be analysed separately
26 April 2005 (n = 463)[1]	– The analysis of tumour tissue biomarkers (see above) was expanded to include investigation of EGFR gene amplification using fluorescence in–situ hybridisation analyses, using existing tumour biopsies

BSC – best supportive care; EGFR – epidermal growth factor receptor

1 Number of patients enrolled at the given date

Protocol deviations

Table 13. Study 20020408: The most important protocol deviations

Category	Deviation	Panitumumab plus BSC (n = 231)	BSC alone (n = 232)
Eligibility	Prior therapies that did not have protocol– specified washout times	6 (3%)	10 (4%)
	Prior chemotherapy criteria not per protocol	12 (5%)	7 (3%)
	Radiographic evidence of disease progression is > 6 months	4 (2%)	1 (0%)
	EGFR membrane staining below protocol specified criteria of ≥ 10% of tumour cells (before Amendment 2)	5 (2%)	6 (3%)
	Screening ECOG performed prior to informed consent	7 (3%)	6 (3%)
Screening lab tests study drug	Study–specific tests drawn prior to informed consent or not done per protocol	6 (3%)	7 (3%)
	Dose not re–instated per protocol	10 (4%)	–
	Start and/or stop time for infusion is unknown	31 (13%)	–
	Weight changed by > 10% and dose was not adjusted	7 (3%)	–
Antibody samples	Baseline sample not done	6 (3%)	7 (3%)
	Follow–up sample collected < 21 days from last dose	29 (13%)	3 (1%)
	End of study sample not collected	87 (38%)	69 (30%)

EGFR – epidermal growth factor; ECOG – Eastern cooperative oncology group performance status

BSC – best supportive care; Panit. – panitumumab; -: 0 (0%)

Baseline data

In the ITT population, except for ECOG status, the two treatment groups were well balanced with regard to demographic data and disease characteristics (Tables 14, 15 and 16). Baseline demographic and disease characteristics for the other populations (the Adjudicated Prior Failures, Per Protocol populations) were similar to the ITT population.

Table 14. Study 20020408: Demographics characteristics (ITT)

	Panitumumab plus BSC (n = 231)	**BSC alone (n = 232)**	**Total (n = 463)**
Gender			
Men	146 (63%)	148 (64%)	294 (63%)
Women	85 (37%)	84 (36%)	169 (37%)
Race/ethnicity			
White or Caucasian	229 (99%)	228 (98%)	457 (99%)
Other	2 (1%)	4 (2%)	6 (3%)
Baseline age – years			
Mean ± SD	61.2 ± 10.3	61.4 ± 10.8	61.3 ± 10.5
Median (Q1 – Q3)	62 (55 – 68)	63 (55 – 69)	62 (55 – 69)
Baseline by age group			
< 65 years	135 (58%)	141 (61%)	276 (60%)
≥ 65 years	96 (42%)	91 (39%)	187 (40%)
< 75 years	209 (90%)	211 (91%)	420 (91%)
≥ 75 years	22 (10%)	21 (9%)	43 (9%)
Baseline weight – kg			
Mean ± SD	72.6 ± 16.0	74.3 ± 15.8	73.4 ± 15.9
Median (Q1 – Q3)	72 (61 – 82)	72.6 (63 – 83)	72.0

BSC – best supportive care; SD – standard deviation

Table 15. Study 20020408: Baseline disease characteristics (ITT)

	Panitumumab plus BSC (n = 231)	BSC alone (n = 232)	Total (n = 463)
Primary diagnosis			
Colon cancer	153 (66%)	157 (68%)	310 (67%)
Rectal cancer	78 (34%)	75 (32%)	153 (33%)
Months since primary diagnosis			
n	215	209	424
Mean ± SD	31.1 ± 22.2	30.9 ± 19.5	31.0 ± 20.9
Median (Q1 – Q3)	25.0 (16.7 – 36.9)	25.2 (16.3 – 41.3)	25.1 (16.6 – 39.2)
Months since metastatic disease diagnosis[1]			
n	201	202	403
Mean ± SD	22.1 ± 13.2	21.7 ± 11.0	21.9 ± 12.2
Median (Q1 – Q3)	18.9 (14.1 – 26.2)	19.3 (14.0 – 27.0)	19.1 (14.0 – 26.6)
ECOG performance status			
0	107 (46%)	80 (34%)	187 (40%)
1	94 (41%)	115 (50%)	209 (45%)
2	29 (13%)	35 (15%)	64 (14%)
3	1 (0%)	2 (1%)	3 (1%)
Sites of disease			
Liver	178 (77%)	194 (84%)	372 (80%)
Lung	147 (64%)	139 (60%)	286 (62%)
Lymph nodes	52 (23%)	66 (28%)	118 (25%)
Abdomen	37 (16%)	39 (17%)	76 (16%)
Pelvic site	22 (10%)	17 (7%)	39 (8%)
Chest	12 (5%)	10 (4%)	22 (5%)
Bone	10 (4%)	7 (3%)	17 (4%)
Gastrointestinal	10 (4%)	5 (2%)	15 (3%)
Other	27 (11%)	22 (10%)	36 (8%)
Number of sites of disease			
1	64 (28%)	53 (23%)	117 (25%)
2	97 (42%)	108 (47%)	205 (44%)
3	45 (19%)	51 (22%)	96 (21%)
4	23 (10%)	13 (6%)	36 (8%)
5	2 (1%)	5 (2%)	7 (2%)
CEA – ug/l			
n	221	218	439
Mean ± SD	809.0 ± 1720.7	671.8 ± 1858.1	740.9 ± 1789.6
Median (Q1 – Q3)	167.7 (40 – 774)	160.4 (22 – 476)	161.3 (32 – 660)
Elevated CEA above normal	212 (92%)	214 (92%)	426 (92%)

BSC – best supportive care; CEA –carcinoembryonic antigen; ECOG – Eastern cooperative oncology group performance status; SD - standard deviation

1 Date of randomisation minus date of primary diagnosis or metastatic disease

Table 16. Study 20020408: Sequence of prior treatment with irinotecan and oxaliplatin (ITT)

	Panitumumab plus BSC (n = 231)	BSC alone (n = 232)
Lines of prior chemotherapy – median (range)	2 (1 – 5)	2 (2 – 6)
Irinotecan only	2 (1%)	0 (0%)
Sequence of prior irinotecan and oxaliplatin	229 (99%)	232 (100%)
Irinotecan before oxaliplatin	113 (49%)	108 (47%)
Irinotecan after oxaliplatin	115 (50%)	119 (51%)
Irinotecan in combination with oxaliplatin	1 (0%)	5 (2%)

BSC – best supportive care

Most patients in the panitumumab plus BSC and BSC alone groups had a partial response (29% and 33%, respectively) or stable disease (45% and 41%, respectively) as their best response to any previous line of chemotherapy. The percentages of patients with an objective response or stable disease decreased with increasing lines of chemotherapy and most patients in the panitumumab plus BSC and BSC alone groups had progressive disease as their best response to the last line of chemotherapy (58% and 57%, respectively). Medical history was generally similar between treatment groups. In both treatment groups, the median percentage of tumour cells with positive EGFR membrane staining was 20%. The percentage of patients with positive EGFR membrane staining in < 10% of tumour cells was similar in the panitumumab plus BSC group (26%) and BSC alone group (25%). A higher percentage of patients had positive membrane staining in > 35% of tumour cells in the panitumumab plus BSC group (40%) than in the BSC alone group (31%).

The IRC identified and measured target lesions at baseline for 95% of patients in the panitumumab plus BSC group and 91% of patients in the BSC alone group; the remaining patients had only non-target lesions or no lesions evaluated by the IRC at baseline. The median sum of target lesion diameters was lower in the panitumumab plus BSC group (179.5 mm) than in the BSC alone group (193.0 mm), although the means were similar (198.2 and 198.4 mm, respectively).

Numbers analysed

The primary efficacy analysis of all efficacy endpoints was conducted using the ITT population. Secondary analyses of all efficacy endpoints were conducted using the Adjudicated prior failures population. The Per Protocol population was used in sensitivity analyses of progression–free survival and overall survival for protocol deviations.

Table 17. Study 20020408: Study patient populations

Patient population	Panitumumab plus BSC	BSC alone
ITT	231 (100%)	232 (100%)
Adjudicated prior failures	179 (77%)	173 (75%)
Per Protocol	171 (74%)	166 (72%)

BSC – best supportive care

Outcomes and estimation

Primary endpoint

Progression–free survival (ITT population)

With a median follow–up of approximately 20 weeks, 193 patients (84%) in the panitumumab plus BSC group and 208 patients (90%) in the BSC alone group had disease progression per modified RECIST criteria by IRC or died due to any reasons. A statistically significant improvement in progression–free survival was observed for patients in the panitumumab plus BSC group compared with the BSC alone group ($p < 0.0001$, stratified log–rank test).

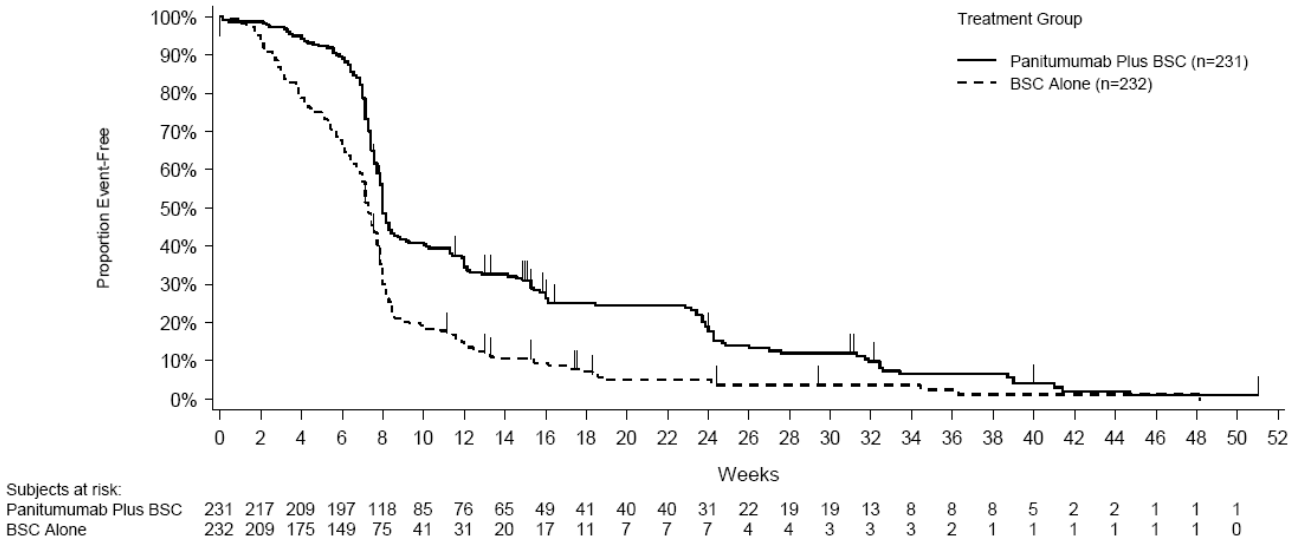
Table 18. Study 20020408: Summary of the primary analysis of progression–free survival (ITT, IRC assessment)

	Panitumumab plus BSC (n = 231)	BSC alone (n = 232)
Patients with events	193 (84%)	208 (90%)
Disease progression	161 (70%)	184 (79%)
Death, any cause	32 (14%)	24 (10%)
Patients censored	38 (16%)	24 (10%)
Kaplan–Meier's quartiles (weeks)		
Median (Q1 – Q3)	8.0 (7.9 – 8.4)	7.3 (7.1 – 7.7)
Primary analysis		
Log–rank test stratified by ECOG and region		
H_0: panitumumab plus BSC and BSC alone are equal		
P–value	< 0.0001	
Secondary analysis		
Hazard ratio (95% CI)[1]	0.542 (0.443 – 0.663)	

BSC – best supportive care; CI – confidence interval

1 The Cox proportional hazards model including treatment is adjusted for covariates ECOG performance status (0 or 1, 2 or 3) and region (Western Europe, Eastern and Central Europe, Rest of the World); Hazard ratios are presented as panitumumab plus BSC:BSC alone

Figure 7. Study 20020408: Kaplan–Meier plot of PFS (ITT, IRC assessment)



Secondary endpoints

Overall survival (ITT population)

Most of the deaths occurred during long–term follow–up (29% panitumumab plus BSC group, 20% BSC alone group) or during Study 20030194 (22%) after patients in the BSC arm had crossed over to receive panitumumab monotherapy. A high percentage of patients in the BSC group (75%) had radiographic disease progression by investigator assessment and crossed over into Study 20030194.

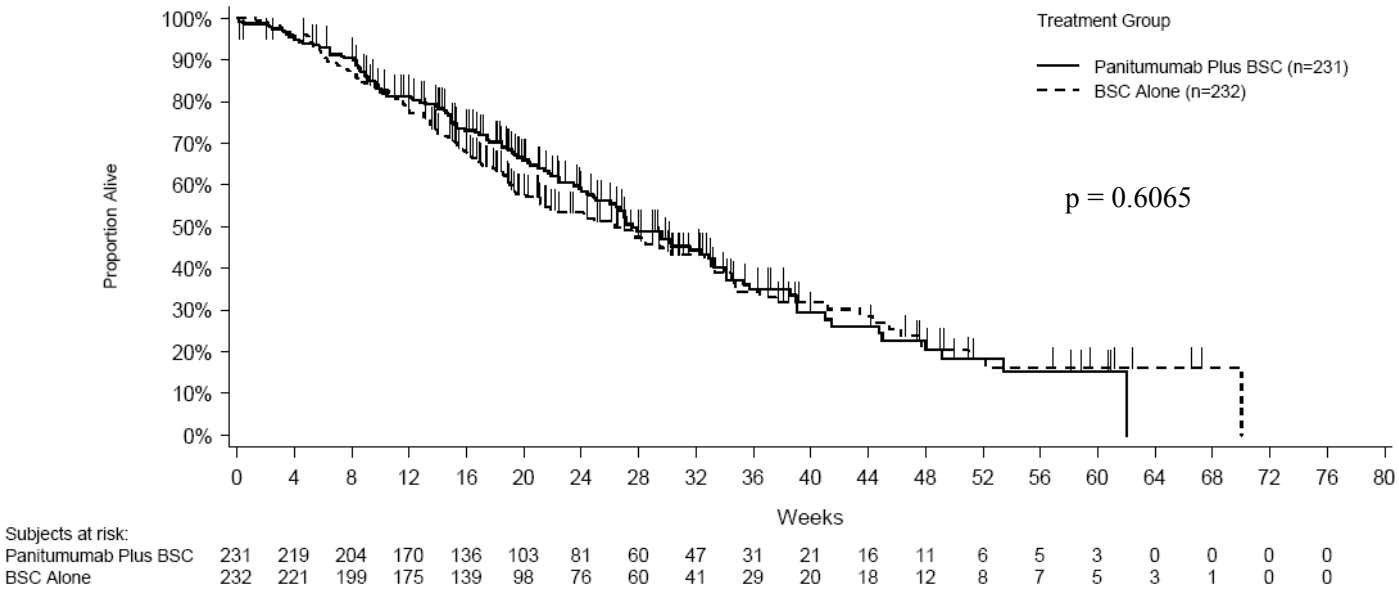
Table 19. Study 20020408: Summary of the analysis of survival at the time of the primary analysis of progression-free survival (ITT)

	Panitumumab plus BSC (n = 231)	BSC alone (n = 232)
Patients who have died (any cause)	119 (52%)	131 (56%)
Patients censored	112 (48%)	101 (44%)
Kaplan–Meier quartiles (months)		
Median (Q1 – Q3)	6.3 (3.4 – 10.3)	6.0 (3.1 – 10.6)
Primary analysis		
Log–rank test stratified by ECOG and region		
H_0: Times in panitumumab plus BSC and BSC alone are equal	0.6065	
Secondary analysis		
H_0: Times in panitumumab plus BSC and BSC alone are equal		
Hazard ratio (95% CI)[1]	0.931 (0.726 – 1.194)	

BSC – best supportive care; ECOG – Eastern cooperative oncology group performance status; CI – confidence interval

1 The Cox proportional hazards model including treatment is adjusted for covariates ECOG performance status (0 or 1, 2 or 3) and region (Western Europe, Eastern and Central Europe, Rest of the World); Hazard ratios are presented as panitumumab plus BSC:BSC alone

Figure 8. Study 20020408: Kaplan–Meier plot over survival time (ITT)



Best objective response rate over time

In the ITT population, 19 patients (8%) in the panitumumab plus BSC group had an objective response per modified RECIST criteria assessed by the IRC; all were partial responses compared with no patient in the BSC alone group. Additionally, 64 patients (28%) in the panitumumab plus BSC group and 24 patients (10%) in the BSC alone group had a best response of stable disease.

Table 20. Study 20020408: Summary of primary analysis of objective response rate

	Panitumumab plus BSC (n = 231)	BSC alone (n = 232)
Best objective response		
Complete response	0 (0%)	0 (0%)
Partial response	19 (8%)	0 (0%)
Stable response	64 (28%)	24 (10%)
Disease progression	113 (49%)	156 (80%)
Patient responding		
Rate (95% CI)	8.23 (5.02 – 12.55)	0.00 (0.00 – 1.58)
Primary analysis – Odds ratio adjusted for ECOG and region[1]		
99% CI	NA (3.94 – NA)	
P–value from stratified exact test of H_0: odds ratio=1	< 0.0001	
Sensitivity analysis: Unadjusted odds ratio[1]		
99% CI	Na (3.90 – Na)	
P–value from unstratified exact test of H_0: Odds ratio=1	< 0.0001	

BSC – best supportive care; CI Confidence interval; NA – not available

1 The odds ratio is defined as the odds of having an objective response in the panitumumab plus arm relative to the odds on the BSC alone arm

Quality of life

At Week 5, EUROQOL EQ–5D data were available for 91% of patients in the panitumumab plus BSC group and 70% of patients in the BSC alone group; by Week 17, data were available for 30% and 4% of patients, respectively. The amount of available data at Weeks 5 and 17 for the NCCN/FACT CRC subscale was very similar to that of the EUROQOL EQ–5D.

The panitumumab plus BSC group had a lower time–adjusted AUC for the DLQI92 (which assesses the frequency and impact of skin conditions on the patient, including bother and embarrassment), indicating that these patients had more frequent skin symptoms (i.e., itchy, sore, painful skin) and were more embarrassed and bothered by their skin condition than patients in the BSC alone group. These results are consistent with the higher incidence of skin– and eye–related adverse events in the panitumumab plus BSC group. Although patients in the panitumumab plus BSC group were

negatively affected by skin toxicity relative to the BSC alone group, no statistically significant or clinically meaningful differences in overall quality of life were observed between treatment groups.

Table 21. Study 20020408: Summary of the analysis of the time adjusted area under the curve (ITT)

	Panitumumab plus BSC (n = 207)	BSC alone (n = 184)	Differences between study arms (n = 391)
Time adjusted AUC for EUROQOL EQ–5D Index			
Week 8 through to 16 with imputation			
L.S. adjusted mean ± SE	0.519 ± 0.058	0.462 ± 0.059	0.057 ± 0.030
95% CI	0.405 – 0.633	0.346 – 0.578	–0.002 – 0.117
Time adjusted AUC for NCCN/FACT CRC subscale			
Week 8 through to 16 with imputation			
L.S. adjusted mean ± SE	60.1 ± 5.1	56.0 ± 5.2	4.2 ± 2.7
95% CI	50.1 – 70.2	45.8 – 66.2	–1.1 – 9.4

BSC – best supportive care; L. S. – least squares

Time-to-disease progression

In the ITT population, 189 patients (82%) in the panitumumab plus BSC group and 208 patients (90%) in the BSC alone group had disease progression per modified RECIST criteria assessed by the IRC or died of disease progression. The median time-to-disease progression was 8.0 weeks (95% CI: 7.9–8.7) in the panitumumab plus BSC group and 7.3 weeks (95% CI: 7.1–7.7) in the BSC alone group.

Time-to-treatment failure

In the ITT population, 202 patients (87%) in the panitumumab plus BSC group and 229 patients (99%) in the BSC group had ended the treatment period. The median time to treatment failure was 9.0 weeks (95% CI: 8.3–12.0) in the panitumumab plus BSC group and 7.1 weeks (95% CI: 6.4–7.6) in the BSC alone group.

Duration of stable disease

For the 64 patients (28%) in the panitumumab plus BSC group and 24 patients (10%) in the BSC alone group who had a best response of stable disease in the ITT population, the median duration of stable disease was 23.7 weeks (95% CI: 16.0–24.3) and 17.3 weeks (95% CI: 15.4–24.1), respectively.

Duration of response and time-to-response

Of the 19 patients (8%) in the panitumumab plus BSC group who had a partial response assessed by the IRC, 10 patients (53%) later had disease progression and one patient died. The median duration of response was 17.0 weeks (95% CI: 16.4–25.3). The maximum duration of response was 40.4 weeks. The median follow–up time for censored patients (progressive disease not confirmed by the IRC, on treatment at cut–off) was 17.9 weeks. For those patients who had an objective response, the median time to response was 7.9 weeks (95% CI: 7.3–8.1).

Ancillary analyses

Prospective sensitivity analyses

Progression–free survival

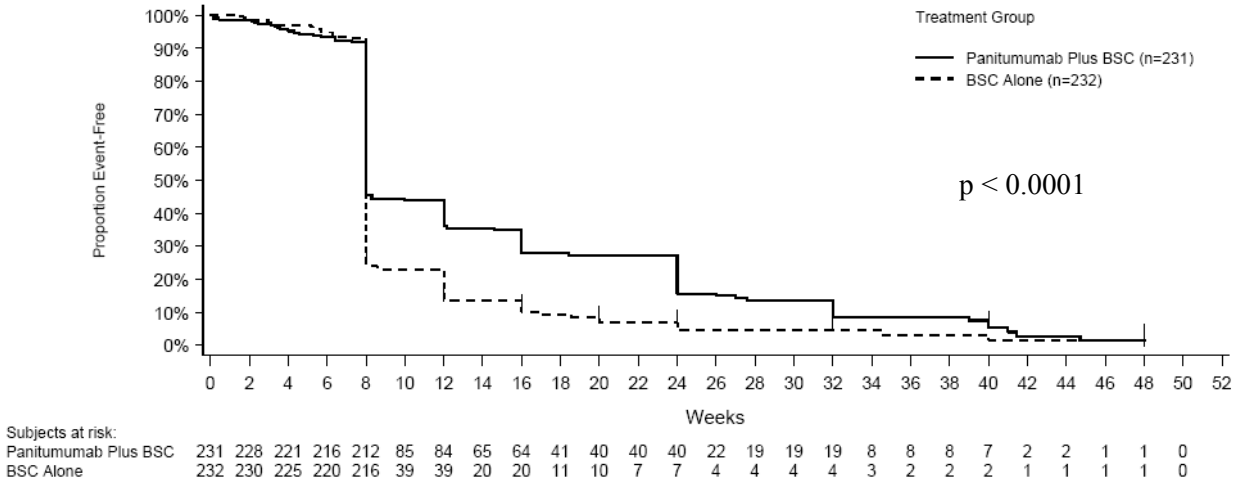
Several prospectively defined sensitivity analyses were conducted to evaluate the robustness of the results for progression–free survival, overall survival (OS) and objective response rate (ORR). Consistent results were observed in prospectively–defined sensitivity analyses.

Post–hoc sensitivity analyses

Progression–free survival

Before Week 8, the percentage of patients with unscheduled assessments was 59% in the BSC alone group and 36% in the panitumumab plus BSC group. To evaluate potential bias based on the timing of unscheduled tumour assessments, a post–hoc sensitivity analysis was conducted in which events of disease progression confirmed by the IRC were moved to the day of the closest scheduled assessment time in both treatment groups (deaths were not moved). The treatment effect size in this analysis (hazard ratio = 0.605, 95% CI: 0.491–0.745) was smaller than that observed in the primary analysis.

Figure 9. Study 20020408: Kaplan–Meier plot of PFS moving the radiographic times to the closest scheduled visit (ITT, IRC assessment)



Subgroup–analyses

Progression–free survival

Exploratory analyses of prospectively defined potential prognostic factors for progression–free survival in the ITT population (i.e., ECOG performance status, geographic region, EGFR membrane staining in tumour cells, age, gender, race, primary tumour diagnosis and progression during or after the last prior chemotherapy regimen), independent of treatment group, indicated that ECOG performance status and age had a significant effect on progression–free survival. Patients with an ECOG status of 0 or 1 were less likely to have disease progression or death relative to patients with an ECOG status of 2 or 3 ($p < 0.001$, log rank test), regardless of treatment. In addition, patients ≥ 65 years of age were less likely to have disease progression or death relative to patients < 65 years of age ($p = 0.055$, log-rank test), regardless of treatment. Similar results were observed in a multivariate Cox proportional hazards model adjusting for randomised treatment.

Overall survival

Exploratory subgroup analyses of the ITT population indicated that, as was observed for progression-free survival, an ECOG performance status of 0 or 1 was associated with a significantly lower death event rate than an ECOG status of 2 or 3 ($p < 0.001$, log–rank test), independent of treatment group. In addition, EGFR membrane staining of 3+ at baseline was associated with a significantly higher death event rate than no 3+ staining ($p = 0.012$, log–rank test), independent of treatment group. This effect of EGFR membrane staining was statistically significant only in the panitumumab plus BSC group. Maximum integument and eye toxicity was possibly associated with survival, with a lower death rate for patients with more severe toxicity. This effect was only observed in the panitumumab plus BSC group; in the BSC alone group, the effect was reversed.

- Clinical studies in special populations

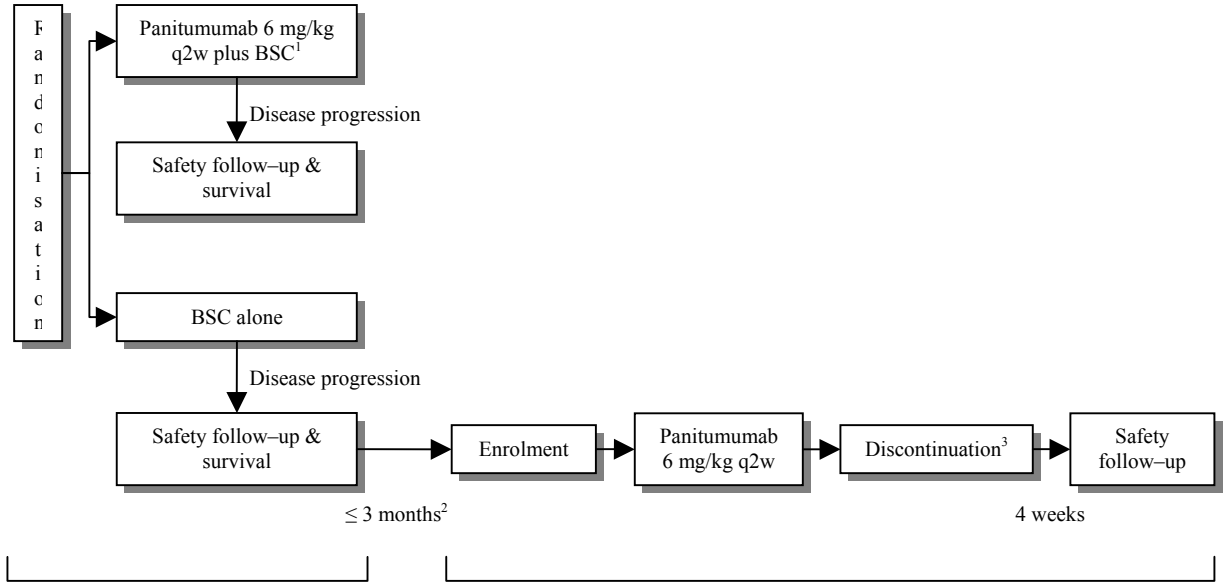
No data are available to evaluate safety in patients with renal, hepatic impairment, paediatric patients and pregnant women.

- Supportive study(ies)

Study 20020194

Study 20020194 was an open–label, single arm extension study to assess the safety of panitumumab monotherapy in patients with metastatic colorectal cancer who had progressed in the BSC arm of Study 20020408 (Figure 10). Panitumumab was administered without pre-medication. However, throughout the study, investigators could prescribe any concomitant medications or treatments deemed necessary, except investigational agents, anti–EGFR targeting agents other than panitumumab, experimental or approved anti–tumour therapies (e.g., bevacizumab), chemotherapy or radiotherapy.

Figure 10. Study 20020194: Study design



1 q2w – every second week; BSC – best supportive care
2 If > 3 months, a separate screening visit was required. All eligibility criteria were assessed before enrolment
3 Discontinuation due to disease progression, unacceptable toxicity, death, or request of patient or investigator

Participants

One hundred eighty-one (181) patients were screened, of which 175 patients were enrolled. ECOG performance status and CEA levels had increased since the time of enrolment into Study 20020408. For other demographics and disease baseline characteristics, the data are in consistent with the data from Study 20020408.

Outcomes/Endpoints

Efficacy endpoints

- progression-free survival time
- objective response rate
- duration of response
- time-to-response
- duration of stable disease
- survival time
- time-to-treatment failure

Patients were evaluated for tumour response using modified-RECIST criteria every 8 weeks from the first dose of panitumumab and at the time of suspected disease progression. Local assessment was used for the primary analysis of response rate. Tumour responses were to be confirmed by repeat assessments no less than 4 weeks after the criteria for response were first met. Time-to-disease progression was neither a pre-specified efficacy endpoint in the protocol nor in the statistical analysis plan. The efficacy endpoints were analysed using the investigators' assessment for the efficacy analysis.

Results

Fifty–nine of the 175 patients (34%) withdrew during the treatment period for reasons other than disease progression. This incidence was higher than that observed in the panitumumab plus BSC group of Study 20020408 (22%). Similar to Study 20020408, the most common of these reasons were adverse events (11 [8%]), death (19 [14%]) and "other" (including clinical/symptomatic disease progression, 23 [17%]).

The median follow–up time (Q1–Q3) was 10.7 weeks (7.4–18.3). The median follow-up time for censored patients was 8.0 weeks, which is shorter than in Study 20020408 (17.9 weeks).

The efficacy results are shown in Table 22.

Table 22. Study 20020194: Summary of efficacy endpoints

	Panitumumab plus BSC Study 20030194 (n = 174[a])	Panitumumab plus BSC Study 20020408 (n = 231)
Progression–free survival (weeks)		
Patients who progressed/died	126 (72%)	193 (84%)
Median time (95% CI)	8.1 (8.0-12.4)	8.0 (7.9–8.4)
Overall survival (months)		
Patients who died	51 (29%)	119 (52%)
Median time (95% CI)	6.8 (5.6–NA)	6.3 (5.7–7.7)
Objective tumour response		
Patient responding	17 (10%)	19 (8%)
Rate (95% CI) –%	9.77 (5.80–15.18)	8.23 (5.02–12.55)
Duration of response (weeks)		
Median time (95% CI)	16.3 (16.0–16.9)	17.0 (16.4–25.3)
Time to response (weeks)		
n	17 (100%)	19 (100%)
Mean ± SD	9.0 ± 4.3	8.9 ± 2.7
Median (Q1 – Q3)	7.9 (7.6–8.1)	7.9 (7.1–10.6)
Time-to-disease progression (weeks)		
Median time (95% CI)	8.3 (8.0–12.4)	8.0 (7.9–8.7)

a One patient was not treated
NA – not available; SD – standard deviation

Study 20025405, 20030167, 20030250

Study 20025405, 20030167, 20030250 were considered as supportive studies in the treatment of metastatic CRC. These studies were Phase II, multicentre, non–comparative, open-label single-arm trials evaluating the safety and efficacy (response rate and duration of response) of panitumumab as monotherapy in patients with mCRC after failure of prior standard chemotherapy.

For all these studies, the main inclusion and exclusion criteria are presented in Table 23.

Table 23. Study 20025405, 20030167 and 20030250: Summary of study design

Study	20025405	20030167 and 20030250
Inclusion criteria		
Cancer	Pathologically confirmed colorectal adenocarcinoma metastases	Pathologically confirmed colorectal adenocarcinoma metastases
ECOG status	0 or 1	0, 1 or 2
Previously failed chemotherapy regimens	≥\ 1 treatment regimens (with or without leucovorin) and either irinotecan, oxaliplatin, or both	Received at least 2 but no more than 3 treatment regimes
Documentation of disease progression	Not available	Radiographic; during or within 6 months after the most recent chemotherapy regimen (fluoropyrimidine, irinotecan and oxaliplatin); the time between documented tumour progression and study entry was not to have exceeded 6 months
Expressing EGFR by immunohisto–chemistry	**Cohort A:** 2+ or 3+ staining (the sum of 2+ and 3+) in ≥ 10% of evaluated tumour cells **Cohort B**: 1+ staining in ≥ 10% of evaluated tumour cells, or the sum of 1+, 2+, and 3+ staining in ≥ 10% but the sum of 2+ and 3+ in < 10% of evaluated tumour cells	**Study 20030167** Membrane staining must have been positive in ≥ 10% of evaluated tumour cells **Study 20030250**Membrane staining either negative, or positive in < 10% of evaluated tumour cells
Exclusion criteria		
	Use of systemic chemotherapy, radiotherapy, or any investigational therapy with potential anti–tumour activity within 30 days before study drug initiation (3 months for experimental proteins or antibodies) Any prior EGFR–targeting agents	Use of systemic chemotherapy or radiotherapy within 30 days before enrolment prior anti–tumour therapies, including small molecules and biologics of short serum half–life (< 1 week), within 30 days before enrolment, or proteins/antibodies with longer serum half–life (e.g., bevacizumab) within 6 weeks before enrolment), prior anti–EGFR antibody therapy (small–molecule EGFR tyrosine kinase inhibitors) were permitted

- **Study 20025405**

Participants

Three hundred eighty (380) patients were screened, from which a total of 150 patients (106 into Cohort A and 44 into Cohort B) were enrolled from 17 study sites.

Treatments

Panitumumab was administered once weekly (2.5 mg/kg intravenous) for 8 consecutive weeks with a 1–week rest between each course. The maximum duration of panitumumab administration was 54 weeks, with provisions for extended treatment beyond 6 courses in the absence of disease progression or intolerability to panitumumab. Disease evaluation was performed every 9 weeks.

Sample size

As outlined in the protocol, with a sample size of 100 patients in Cohort A (high EGFR expression), this study had 80% power at the 5% significance level (2–sided) to test the null hypothesis that the response rate was 10% *vs.* the alternate hypothesis that the response rate was truly 20%. If the observed response rate was 20%, this sample size allowed estimation of response rate to within 8 percentage points with 95% confidence. With a sample size of 50 patients in Cohort B (low EGFR expression), if the observed response rate were 20%, this sample size would allow estimation of response rate to within 11 percentage points with 95% confidence.

Outcomes/endpoint

The primary endpoint

- Objective tumour response after the initial 8–week treatment period using RECIST criteria (confirmed by a scan no less than 4 weeks after the criteria for response were first met).

The secondary endpoints

- Best overall objective tumour response throughout study
- Time to disease progression
- Progression–free survival time
- Survival time

The primary analyses of efficacy were performed in all patients who had received at least one dose of study drug and were based on a centralised review of tumour scans performed by a third party.

Results
Overall, the distribution of demographics and disease characteristics are similar to the pivotal Study 20020408.

All but two patients received at least one dose of panitumumab. Eighty six percent (86%) ended treatment due to disease progression, 5% due to adverse events, 3% due to death and 4% due to patient refusal and other reasons.

Median follow–up time (from the first dose of panitumumab to last physician consult) in the whole dataset was 7 months (range: 0–25) for all patients. Median follow–up in Cohort A was approximately 1.5 months shorter than for Cohort B.

The objective tumour response rate after the first 8–week treatment period was 6.8% (95% CI: 3.3-12.1). Across all 148 patients, there were no complete response and 10 partial responses. Cohort B had a higher percent of responders than Cohort A (11.6% *vs.* 4.8%, respectively). The 4.8% response rate in Cohort A was not significantly different from 10% ($p = 0.085$) or from Cohort B ($p = 0.155$).

The response rate across the entire treatment period was 8.8% (95% CI: 4.8-14.6), time-to-progression was 2.6 months (95% CI: 1.9-3.7) and median survival was 8.6 months (95% CI: 5.9-9.8).

- **Studies 20030167 and 20030250**

Participants
In Study 20030167, 300 patients were screened for this study of which 93 patients were enrolled into the study from 54 study centres.

In Study 20030250, 99 patients were screened for this study of which 88 patients were enrolled from 59 study centres (24 of these centres also enrolled patients into the Study 20030167).

Treatments
Panitumumab was administered by intravenous infusion at a dose of 6 mg/kg given once every two weeks until patients developed progressive disease, were unable to tolerate panitumumab or discontinued treatment for other reasons (e.g., administrative decision).

Outcomes/endpoint
The primary efficacy endpoints (centrally assessed) were objective response rate through Week 16 (responses needed to be confirmed no less than 4 weeks after the criteria for response are first met) and duration of response.

The secondary efficacy endpoints (centrally assessed except as otherwise noted) were objective response rate throughout study, time-to-response, progression–free survival time, time-to-disease progression, time-to-treatment failure (not centrally assessed), duration of stable disease (not centrally assessed), survival time.

Patients were evaluated for tumour response (both locally and centrally) at pre-specified timepoints, Weeks 8, 12, 16, 24, 32, 40, and 48 and every 3 months thereafter during the treatment until disease progression. The primary efficacy analyses were based on a masked IRC of scans at the central imaging laboratory using modified-WHO criteria.

Results
Overall, the distribution of demographics and disease characteristics are similar to the pivotal Study 20020408.

The primary efficacy subset for the interim report is evaluable adjudicated patients defined as patients who had ≥ 20 weeks potential follow–up, were determined to be eligible by the IRC (i.e., had received prior chemotherapy at the protocol–specified dose intensity and exposure, had developed progressive disease during or after their prior chemotherapy regimen and whose time between documented tumour progression and study entry was ≥ 6 months). These datasets were composed 39 and 23 patients for Study 20030167 and 20030250, respectively. A supportive analysis was conducted on evaluable patients defined as patients who consented and enrolled patients who had ≥ 20 weeks of potential follow–up. These evaluable patients were 59 patients in Study 20030167 and 32 in Study 20030250.

In Study 20030167, 91 of the 93 enrolled patients (98%) received at least one dose of panitumumab. The two patients who did not receive treatment were both determined to be ineligible after enrolment. As of the data cut–off date for the report, 18 patients (19%) were still in the treatment period. Fifty-three patients (57%) ended treatment because of disease progression, 3% due to adverse events, 8% due to death and 5% due to protocol specified criteria.

In Study 20030250, all 88 enrolled patients received at least one dose of panitumumab. As of the data cut–off for the report, 28 (32%) patients were still in the treatment period. Forty-five (51%) of all enrolled patients ended treatment because of disease progression, 3% due to adverse events, 2% due to death and 2% due to protocol specified criteria.

In Study 20030167, protocol deviations included six patients who received bevacizumab within 6 weeks before enrolment and one who received cetuximab before enrolment. In Study 20030250, protocol deviations included 10 patients who received bevacizumab within 6 weeks before enrolment.

In both studies, the median follow–up time (from enrolment to the last on–study safety follow–up or long–term follow–up visit) was 15 weeks (range: 1–64 weeks). The median potential follow–up time was 24 weeks (range: 4-64 weeks).

The results of the primary and the main secondary efficacy endpoints are shown in Table 24.

Table 24. Studies 20030167 and 20030250: Results from Evaluable Adjudicated (EA) and the Evaluable (E) patients

	Study 20030167		Study 20030250	
	EA (n = 39)	E (n = 59)	EA (n = 23)	E (n = 32)
Objective Response rate through Week 16				
Responders	3	3	3	3
Rate (95% CI)	7.7 (1.6–20.9)	5.1 (1.1–14.1)	13.0 (2.8–33.6)	9.4 (2.0–25.0)
Duration of response for the responders (weeks)	4.1, 12.4, 14.0	4.1, 12.4, 14.0	10.1, 12.1, 16.1	10.1, 12.1, 16.1
Objective response rate throughout study				
Responders	3	3	3	3
Rate (95% CI)	7.7 (1.6–20.9)	5.1 (1.1–14.1)	13.0 (2.8–33.6)	9.4 (2.0–25.0)
Progression–free survival time				
Median time (95% CI)	7.6 (7.1–8.6)	7.9 (7.4–11.4)	13.3 (7.1–22.9)	8.1 (7.1–22.9)
Time-to-disease progression (weeks)				
Median time (95% CI)	7.6 (7.1–11.4)	7.9 (7.4–11.4)	8.0 (7.1–23.0)	7.9 (7.0–23.0)
Time-to-treatment failure (weeks)				
Median time (95% CI)	8.0 (7.1–15.4)	8.3 (7.4–15.4)	9.8 (8.0–16.1)	12 (8.0–16.1)

- Discussion on clinical efficacy

None of the studies focused on thorough pharmacokinetic characterisation of panitumumab in the target patient population using a commercial batch (12 kl CHO) at the proposed dose with reasonable number of patients and none had pharmacokinetics as primary purpose. The applicant has chosen to rely on argumentation for equivalence between hybridoma-derived panitumumab and 2 kl-CHO derived panitumumab and subsequent equivalence between 2 kl-CHO derived panitumumab and 12 kl-CHO derived panitumumab. The study of the bioequivalence of the two products from the manufacturing change from a hybridoma to a CHO expression system suggests that they are similar. The 90% CI did not fall within the CHMP Bioequivalence Note of Guidance recommended range

of 80-125%, certainly because of small numbers of patients. The equivalence between panitumumab from 2 kl fermentation and 12 kl fermentation seems to be the most critical regarding the pharmacokinetics and for that reason the demonstration of the equivalence should be very solid and reliable. Due to absence of a proper pharmacokinetic study and provided data from a limited number of patients, it is difficult to conclude with certainty on bioequivalence.

Panitumumab is administered intravenously. The results indicate a central volume of distribution of 42 ml/kg, which corresponds to the typical plasma volume in humans. Panitumumab is expected to be degraded into peptides and amino acids by reticulo-endothelial system (RES), like other IgG and also by receptor internalisation. The pharmacokinetics of panitumumab can be described by a 2-compartment pharmacokinetic model with dual linear (probably RES) and non-linear (probably EGFR) clearance pathways. Non-linear pharmacokinetics was observed in the dose-range 0.75-9.0 mg/kg. The time-averaged clearance value decreases with increasing dose.

Pharmacokinetic steady-state is claimed to be obtained after 3 doses at 6 mg/kg every two weeks, however not obvious from the serum concentrations-time curves of the different studies. The half-life is approximately 8 days.

No studies were designed that specifically enable estimation of intra- or inter-individual variability. It would have been appropriate to consider both intra- and between-subject variation in much more depth.

There is reasonable evidence that gender, age, hepatic function or tumour type does not affect the pharmacokinetics for panitumumab to a large extent. Renally impaired patients seem to have higher peak serum concentrations than normal patients. Some racial variation was observed, non-white patients having lower panitumumab serum concentrations at peak and trough. Body weight was found to be an influential covariate on panitumumab disposition, with increasing exposure of panitumumab with increasing body weight. There is no experience with children.

From the interactions studies, residuals from irinotecan treatment are unlikely to interfere with panitumumab after a switch from irinotecan to panitumumab.

The principal mechanism is known with acceptable certainty already. There is no overwhelming reason to believe that active protein binds other targets in a clinically relevant fashion but the possibility can of course not be excluded. The link between pharmacodynamic effect and skin toxicity seems straightforward. However, recently (ASCO 2006 Annual Meeting) it has been reported that the EGFR antagonist, nimotuzumab, YM BioSciences, was not associated with any cases of severe rash.

This application is based on one pivotal, open–label, randomised, two arms, Phase III study and four uncontrolled, single-arm, Phase II studies which were conducted with patients with metastatic colorectal cancer after failure of prior chemotherapy regimens including 5-fluorouracil, irinotecan and/or oxaliplatin.

The pivotal study was conducted at 81 centres across Europe, Canada, Australia, and New Zealand and compared panitumumab at 6 mg/kg every two weeks and best supportive care *vs.* best supportive care only. The treatment was given until disease progression, inability to tolerate investigational product or other reason for discontinuation. The study design is acceptable as no generally recognised treatment options are available for patients who have failed prior chemotherapy regimens including 5-fluorouracil, irinotecan and oxaliplatin at the start of the study.

The primary objective of this study was to assess whether panitumumab plus BSC improves progression–free survival compared with BSC alone in patients with metastatic colorectal cancer who had failed standard chemotherapy. Secondary objectives were to evaluate overall survival, objective response, duration of response, time-to-response, time-to-disease progression, time-to-treatment failure, duration of stable disease, patient–reported outcomes and the safety profile of panitumumab plus BSC compared with BSC alone.

At progression, patients in the BSC alone–arm had the option to receive panitumumab in an open-label extension study after disease progression. At the cut–off date for clinical data, a large proportion (75%) of the patients who had disease progression in the BSC alone group had crossed over to the extension study. The crossover occurred early in the study (median time-to-disease progression of 7.0 weeks). Therefore this crossover design makes interpretation of the overall survival data difficult.

In the two treatment arms, the baseline data of the recruited patients were not balanced with respect to metastatic site (liver: 77 *vs.* 84%), ECOG status (0: 46 *vs.* 34%; 1: 41 *vs.* 50%) and median tumour size (179.5 *vs.* 193.0 mm) for panitumumab plus BSC and BSC alone, respectively. Other demographic and disease characteristics were similar between the two treatment groups. Overall, the demographics and disease baseline characteristics are considered as representative of patients with advanced mCRC.

There was a statistically significant difference between the two treatments arms ($p < 0.0001$) with regard to the primary endpoint, progression–free survival. However, the difference between median progression–free survival in the two arms was only 5 days (8.0 *vs.* 7.3 weeks for panitumumab plus BSC arm and BSC alone arm, respectively). The hazard ratio, adjusted for ECOG (0 - 1 *vs*. 2+) and region, was in favour of the panitumumab plus BSC arm, 0.542 (95% CI: 0.443 – 0.663). There was a higher rate of unscheduled tumour assessments (between Weeks 0 and 8) for patients in the BSC alone group than in the panitumumab plus BSC group (59 *vs.* 36%, respectively). When corrected for this bias, the treatment effect size (hazard ratio = 0.605, 95% CI: 0.491-0.745, $p < 0.0001$) was smaller than that observed in the primary analysis. At Week 8 (first tumour assessment), 52 and 70% had progressed in panitumumab plus BSC and BSC alone groups, respectively.

No significant difference in overall survival between the two treatment arms ($p = 0.6065$) was detected. The median overall survival time was 6.3 and 6.0 months for panitumumab plus BSC arm and BSC alone arm, respectively. Partial response was detected in 19 patients (8%) in the panitumumab plus BSC and none in the BSC alone groups and none of the patients had complete response. No significant difference was observed in the Quality of Life assessment.

The efficacy results from the four uncontrolled, monotherapy Phase II studies which included similar patient populations supported the efficacy results from the pivotal study. However, it is difficult to compare across these supportive studies and the pivotal study as there are different eligibility criteria, different methods of evaluation of tumour response (modified-RECIST and WHO criteria), timepoints for tumour assessments, primary endpoints and panitumumab production procedure (hybridoma *vs*. CHO). The general picture is that there is anti-tumour efficacy but the response rate is low. Only partial response was seen.

Overall, the data from the pivotal study showed statistically significant difference between the panitumumab plus BSC and BSC alone arms with respect to progression–free survival. However, together with the small difference in median progression–free survival (0.7 week) and no significant difference in overall survival, concerns remain regarding the clinical relevance of panitumumab treatment effect.

The high mortality rate in advanced mCRC, with one-year survival of 43% (supported by results of the pivotal where approximately 50% of patients had died by Week 28), would have been ideal condition for using overall survival as the primary endpoint.. Overall mortality would have been a more convincing primary endpoint, particularly as this was an open-label design.

There is also a problem with quantifying the size of the benefit in terms of median progression-free survival, because more than 50% of patients on both groups experienced progression before the first scheduled assessment visit. The scheduling of the first visit was probably related to a general underestimation of the severity of the patient population. When powering the study the median progression-free survival on best supportive care was estimated to be about 2.5 months but in fact it was much shorter. This makes the study less sensitive to detect differences than it would have been if an earlier visit had been included, increasing the confidence that the highly significant benefit seen is

real. But it does mean that summarising the results using median progression-free survival would not be appropriate.

Panitumumab affected cell growth of some EGFR positive tumour cell lines *in vitro* but not the growth of those with no or negligible EGFR. The expression level of EGFR in a subset of human tumour xenografts did not predict a response to panitumumab. However the applicant assumed the mechanism of action would justify the adopted EGFR binary classification of positive or negative tumours and that efficacy would be reflected in the EGFR receptor data. This assumption was proven to be false, as EGFR status did not correlate with efficacy. It would have been more informative to recruit patients with a range of EGFR expression, including negative.

Clinical safety

Safety evaluations of panitumumab have included analyses of 15 clinical studies in patients (n = 1304) with a variety of solid tumours (Table 25). Among those studies, 10 clinical studies of panitumumab monotherapy have enrolled patients (n = 789) in the target patient population (i.e., with metastatic carcinoma of the colon or rectum after failure of prior standard chemotherapy).

The applicant provided an update of safety data from clinical studies in which panitumumab was administered as monotherapy in the target patient population which includes 131 new patients (a total of 920 patients and a longer follow-up time from 137 patients who remained on study at the time of the application submission). Thus, the median length of follow-up for this updated mCRC monotherapy set was 21 weeks compared with 17 weeks of those described in the original submission. Overall, these updated safety results confirmed the conclusions previously presented in this section.

Endpoint evaluated for analyses of safety data:

<u>Adverse events and deaths</u>
- incidence and severity of adverse events
- deaths on treatment or within 30 days of treatment
- deaths within 60 days of treatment and deaths occurring at any time post-treatment
- adverse events leading to discontinuation, dose alterations or interruption of panitumumab

<u>Study drug exposure</u>
- study drug exposure and incidence of dose changes
- chemotherapy exposure
- infusion duration

Table 25. Overview of the clinical trials

Study	Phase	Indication[1]	Design	No of patients	Treatment[2]	Drug regimen[3]
20020408	III	mCRC	Open–label, randomised two arms	463	Panitumumab + BSC *vs.* BSC alone	6 mg/kg/q2w
20030194	–	Extended treatment of Study 20020408	Open–label single arm	175	Panitumumab alone	6 mg/kg/q2w
20030167	II	mCRC	Open–label single arm	93	Panitumumab alone	6 mg/kg/q2w
20030250	II	mCRC	Open–label single arm	88	Panitumumab alone	6 mg/kg/q2w
20025405	II	mCRC	Open–label single arm	150	Panitumumab alone	2.5 mg/kg/qw
20020374	II	Renal	Open–label single arm	195	Panitumumab alone	1.0–2.5 mg/kg/qw
20020375	–	Extended treatment of Studies 20020374 and 20040116	Open–label single arm	11	Panitumumab alone	2.5 mg/kg/qw or 6 mg/kg/q2w or 9 mg/kg/q3w
20025408	II	NSCLC	Open–label single arm	9	Panitumumab alone	2.5 mg/kg/qw
20030110	II	Prostate	Open–label single arm	33	Panitumumab alone	2.5 mg/kg/qw
20030138	I	Renal, prostate, pancreatic, NSCLC, CRC, oesophageal	Open–label single arm	97	Panitumumab alone	0.01–9.0 mg/kg/(qw–q3w)
20030251	I	Solid tumours	Open–label single arm	57	Panitumumab alone	6 mg/kg/q2w or 9 kg/mg/q3w
20040116	I	Renal, prostate, pancreatic, NSCLC, CRC, oesophageal	Open–label single arm	20	Panitumumab alone	0.01–9.0 mg/kg/(qw–q3w)
20040192	I	Solid tumours	Open–label single arm	12	Panitumumab alone	2.5 mg/kg/qw or 6 mg/kg/q2w or 9 mg/kg/q3w
20025404	II	NSCLC	Open–label, randomised two arms	194	Panitumumab + paclitaxel+carboplatin *vs.* paclitaxel+carboplatin	1.0–2.5 mg/kg/qw
20025409	II	mCRC	Open–label single arm	43	Panitumumab+IFL/FOLFIRI	2.5 mg/kg/qw

1 CRC – colorectal cancer; mCRC – metastatic colorectal cancer; NSCLC – non–small lung cancer
2 IFL/FOLFIRI – irinotecan+5–FU+leucovorin
3 qw – weekly; q2w – every two week; q3w – every three week

- Patient exposure

The exposure to panitumumab is summarised in Tables 26 and 27.

Table 26. Number of patients who received at least one dose of panitumumab

	All patients[1]	mCRC monotherapy[2]	All monotherapy[3]	All combination therapy[4]
Panitumumab–treated patients	1304	789	1130	174
Dosing Regimen				
2.5 mg/kg qw	493 (38%)	157 (20%)	332 (29%)	161 (93%)
6.0 mg/kg q2w	660 (51%)	608 (77%)	660 (58%)	0 (0%)
9.0 mg/kg q3w	23 (2%)	20 (3%)	23 (2%)	0 (0%)
Other	128 (10%)	4 (<1%)	115 (10%)	13 (7%)

mCRC – metastatic colorectal cancer; qw – weekly; q2w – every second week; q3w – every third week

1 Includes all patients from all 15 studies. Totals for "All patients" include the All monotherapy set plus the All combination therapy set

2 Includes all patients with mCRC who received at least 1 dose of panitumumab as a single agent

3 Includes all patients (including those with mCRC or other solid tumours) who received at least one dose of panitumumab as a single agent

4 Includes all patients who received at least 1 dose of panitumumab in combination with an irinotecan- or paclitaxel/carboplatin-based chemotherapy regimen

Table 27. Summary of exposure to panitumumab

	mCRC monotherapy dataset (n = 789)	All monotherapy dataset (n = 1130)
Number of infusions	6091	9809
Number of infusions per patient		
Mean ± SD	7.7 ± 7.0	8.9 ± 9.1
Median (Q1–Q3)	5.0 (4.0–9.0)	6.0 (4.0–11.0)
Number of infusions per patient		
1–4	362 (46%)	471 (42%)
5–8	206 (26%)	312 (28%)
9–12	90 (11%)	117 (10%)
13–16	76 (10%)	113 (10%)
17–20	12 (2%)	25 (2%)
21–24	20 (3%)	38 (3%)
≥ 25	23 (3%)	54 (5%)
Duration of infusion delivered – minutes		
Mean ± SD	61.32 ± 7.69	61.99 ± 10.20
Median (Q1–Q3)	60.00 (60.00–60.00)	60.00 (60.00–60.00)
Weight–adjusted cumulative dose – mg/kg		
Mean ± SD	36.23 ± 26.09	33.36 ± 27.34
Median (Q1–Q3)	24.49 (18.56–48.93)	24.12 (17.64–43.38)
Average weight–adjusted dose delivered – mg/kg/infusion		
Mean ± SD	5.31 ± 1.58	4.54 ± 1.99
Median (Q1–Q3)	5.99 (5.28–6.10)	5.88 (2.50–6.05)

SD – standard deviation; mCRC – metastatic colorectal cancer

Long–term exposure to panitumumab (i.e., ≥ 6 months) was limited as most studies were ongoing at the time of data cut–off and patients in these studies had an advanced stage of disease and progressed relatively quickly, resulting in discontinuation of treatment. Most patients (91%) in the mCRC monotherapy patient population received < 6 months of panitumumab exposure. Data from long–term exposure (≥ 6 months) is available for 74 patients (9%) in the mCRC monotherapy patient population and 18 among these 74 patients had received ≥ 9 months of exposure. The median follow–up time for the mCRC monotherapy patient population was 17.0 weeks, with a range of 1 to 111 weeks.

Table 28 displays the patient baseline demographic and disease characteristics for mCRC monotherapy and all monotherapy patient populations.

Table 28. Key patient demographics and baseline disease characteristics

Parameters	mCRC monotherapy dataset (n = 789)	All monotherapy dataset (n = 1130)
Gender		
Men	476 (60%)	730 (65%)
Women	313 (40%)	400 (35%)
Race/ethnicity		
White or Caucasian	707 (90%)	1007 (89%)
Black or African American	38 (5%)	53 (5%)
Hispanic	18 (2%)	37 (3%)
Asian	12 (2%)	16 (1%)
Japanese	11 (1%)	13 (1%)
Other	3 (0%)	4 (0%)
Baseline age (years)		
Mean ± SD	60.4 ± 11.1	60.7 ± 11.0
Median (Q1–Q3)	61.0 (53.0–68.0)	61.0 (53.0–69.0)
Baseline geriatric age group		
< 65 years	497 (63%)	700 (62%)
≥ 65 years	292 (37%)	430 (38%)
< 75 years	711 (90%)	1011 (89%)
≥ 75 years	78 (10%)	119 (11%)
Region		
United States	376 (48%)	715 (63%)
Western Europe	311 (39%)	311 (28%)
Central Eastern Europe	33 (4%)	33 (3%)
Japan	10 (1%)	12 (1%)
Rest of the World	59 (7%)	59 (5%)
Primary tumour type		
Colon	544 (69%)	544 (48%)
Rectal	235 (30%)	235 (21%)
Colorectal	10 (1%)	10 (1%)
Renal	0 (0%)	214 (19%)
Prostate	0 (0%)	57 (5%)
Non–small lung cancer	0 (0%)	33 (3%)
Other	0 (0%)	37 (3%)
Months since metastatic diagnosis		
Mean ± SD	22.4 ± 12.5	33.5 ± 29.6
Median (Q1–Q3)	19.7 (14.1–27.0)	24.9 (15.3–41.8)
ECOG performance status		
0	293 (37%)	483 (43%)
1	417 (53%)	561 (50%)
2	78 (10%)	85 (8%)
3	1 (0%)	1 (0%)
Number of prior lines of therapy		
Not collected/unknown	129 (16%)	429 (38%)
Collected	660 (84%)	701 (62%)
1–2	305 (46%)	333 (29%)
3–4	344 (52%)	350 (31%)
≥ 5	11 (2%)	18 (2%)

BSC – best supportive care; ECOG – Eastern cooperative oncology group performance status; mCRC – metastatic colorectal cancer

- Adverse events

A summary of adverse events and adverse reactions is provided in Table 29 for mCRC monotherapy and All monotherapy patient populations.

Table 29. Summary of adverse events and reactions

Adverse events	mCRC monotherapy (n = 789)	All monotherapy (n = 1130)
Patients with any adverse event	789 (100%)	1126 (100%)
Worst Grade of 3	276 (35%)	377 (33%)
Worst Grade of 4	26 (3%)	42 (4%)
Worst Grade of 5	126 (16%)	149 (13%)
Any serious	289 (37%)	384 (34%)
Leading to permanent discontinuation of study drug or removal from study	84 (11%)	155 (14%)
Not serious	29 (4%)	61 (5%)
Serious	56 (7%)	106 (9%)
Patients with any treatment–related adverse event	737 (93%)	1049 (93%)
Worst Grade of 3	130 (16%)	182 (16%)
Worst Grade of 4	8 (1%)	10 (1%)
Worst Grade of 5	2 (0%)	2 (0%)
Any serious	33 (4%)	44 (4%)
Leading to permanent discontinuation of study drug or removal from study	23 (3%)	42 (4%)
Not serious	17 (2%)	36 (3%)
Serious	6 (1%)	8 (1%)

mCRC – metastatic colorectal cancer

Table 30 gives the list of most common adverse events by decreasing order for mCRC monotherapy patient population.

Table 30. mCRC monotherapy dataset: Patient incidence of common adverse events

Events	Any Grade (≥ 5%) (n = 789)[1]	Grade 3 or higher (≥ 2%) (n = 789)[2]
Patients with any adverse event	789 (100%)	428 (54%)
Dermatitis acneiform	412 (52%)	39 (5%)
Pruritus	390 (49%)	13 (2%)
Erythema	389 (49%)	33 (4%)
Rash	300 (38%)	22 (3%)
Fatigue	260 (33%)	43 (5%)
Nausea	226 (29%)	16 (2%)
Diarrhoea	208 (26%)	15 (2%)
Skin exfoliation	178 (23%)	NA
Vomiting	164 (21%)	24 83%)
Constipation	155 (20%)	12 (2%)
Abdominal pain	154 (20%)	38 (5%)
Paronychia	149 (19%)	NA
Anorexia	148 (19%)	18 (2%)
Disease progression[3]	128 (16%)	120 (15%)
Dry skin	124 (16%)	NA
Skin fissures	124 (16%)	NA
Dyspnoea	114 (14%)	31 (4%)
Pyrexia	114 (14%)	NA
Cough	105 (13%)	NA
Oedema peripheral	88 (11%)	NA
Asthenia	84 (11%)	17 (2%)
Back pain	83 (11%)	15 (2%)
Stomatitis	70 (9%)	NA
Insomnia	65 (8%)	NA
Abdominal pain upper	59 (7%)	NA
Anxiety	56 (7%)	NA
Nail disorder	55 (7%)	NA
Arthralgia	50 (6%)	NA
Pain in extremity	49 (6%)	NA
Weight decreased	48 (6%)	NA
Depression	46 (6%)	NA
Headache	43 (5%)	NA
Rash pustular	43 (5%)	NA
Dyspepsia	42 (5%)	NA
Anaemia	40 (5%)	NA
Epistaxis	40 (5%)	NA
Chills	38 (5%)	NA
Decreased appetite	38 (5%)	NA
Conjunctivitis	37 (5%)	NA
General physical health deterioration	37 (5%)	26 (3%)
Jaundice	37 (5%)	19 (2%)
Urinary tract infection	37 (5%)	NA
Ascites	36 (5%)	19 (2%)
Dehydration	36 (5%)	12 (2%)
Hypomagnesaemia	NA	12 (2%)

1 Patient incidence of common (≥ 5%) adverse events, NA: – incidence < 5%
2 Patient incidence of common Grade 3 or higher adverse events, NA – incidence < 2%
3 Adverse event terms indicative of progression of the underlying malignancy were grouped under the term "disease progression"

The most common adverse events and reactions from the mCRC monotherapy patient population were skin adverse events followed by gastro-intestinal adverse events. These findings were also observed in the other datasets: All patients, All monotherapy for adverse events or reactions.

Table 31 gives the comparative (active *vs.* no active treatment) list of most common adverse events by decreasing order for Study 20040408.

Table 31. Study 20040408: Patient incidence of adverse events with difference > 5% by treatment groups

	Panit. plus BSC (n = 299)	BSC alone (n = 234)	Difference between the treatment arms
Patients with at least one adverse event	229 (100%)	202 (86%)	27 (14%)
Erythema	146 (64%)	2 (1%)	144 (63%)
Dermatitis acneiform	142 (62%)	2 (1%)	140 (61%)
Pruritus	130 (57%)	5 (2%)	125 (55%)
Skin exfoliation	56 (24%)	0 (0%)	56 (24%)
Paronychia	55 (24%)	0 (0%)	55 (24%)
Rash	46 (20%)	2 (1%)	44 (19%)
Skin fissures	45 (20%)	1 (0%)	44 (19%)
Constipation	44 (19%)	21 (9%)	23 (10%)
Diarrhoea	48 (21%)	26 (11%)	22 (10%)
Fatigue	55 (24%)	34 (15%)	21 (9%)
Dry skin	21 (9%)	0 (0%)	21 (9%)
Nail disorder	20 (9%)	0 (0%)	20 (9%)
Acne	19 (8%)	0 (0%)	19 (8%)
General physical health deterioration	23 (10%)	8 (3%)	15 (7%)
Nausea	50 (22%)	36 (15%)	14 (6%)
Vomiting	42 (18%)	28 (12%)	14 (6%)
Cough	31 (14%)	17 (7%)	14 (6%)
Abdominal pain	52 (23%)	39 (17%)	13 (6%)
Colorectal cancer metastatic	29 (13%)	17 (7%)	12 (5%)
Mucosal inflammation	14 (6%)	2 (1%)	12 (5%)
Stomatitis	14 (6%)	2 (1%)	12 (5%)
Growth of eyelashes	12 (5%)	0 (0%)	12 (5%)

Targeted adverse events: Adverse events of special interest in the setting of panitumumab administration include integument and eye toxicities, stomatitis/oral mucositis, diarrhoea, hypomagnesaemia, hypocalcaemia, pulmonary toxicity, vascular toxicity cardiac toxicity and infusion reactions occurred with a similar incidence and severity in the mCRC monotherapy and All monotherapy patient population, are detailed below.

Eight percent (8%) of patients required a temporary interruption and/or reduction of the panitumumab dose as a result of an integument– or eye–related toxicity. However, panitumumab administration was resumed after improvement of skin toxicity in 72% of these patients. Two percent (2%) of patients permanently discontinued panitumumab administration for integument- and eye-related toxicities. Forty patients (5%) had Grade 3 acneiform rash and one patient was reported to have “acne” that was life threatening in severity. The median time to first symptom of acneiform rash was 27 days (95% CI: 21 28) and the median duration of toxicity was 102 days (95% CI: 85–126).

Stomatitis/oral mucositis events were mild or moderate in 98% of patients yielding an overall incidence of Grade 3 or 4 stomatitis–type adverse events of 0.3%. However, one case of life-threatening fungal stomatitis occurred approximately one month after panitumumab was discontinued. The patient later died due to fatal systemic mycosis. The event was not considered related to panitumumab by the investigator.

Diarrhoea as adverse events were reported in 29% of patients and were considered related to panitumumab in 13% of patients. Most patients (93%) with diarrhoea had events mild or moderate in intensity. Fifteen patients (2%) had diarrhoea classified as severe. No patient had life–threatening or fatal diarrhoea. Six patients (1%) had events of diarrhoea by this definition that was serious; only one patient was considered related to panitumumab. Diarrhoea rarely led to modification of panitumumab administration: dose alteration and study discontinuation due to diarrhoea each occurred in one patient (< 1%) and none interrupted panitumumab treatment because of diarrhoea.

Overall, 39% of patients with normal magnesium levels at baseline had decreases in serum magnesium levels of any grade. Grade 3 or 4 levels were observed in 5% of patients. Most of the decreases in serum magnesium were asymptomatic and the hypomagnesaemia generally responded promptly to intravenous administration of magnesium. No causal relationship was apparent between

hypomagnesaemia and cardiac toxicity. Five patients (0.8%) had concurrent severe hypomagnesaemia and hypocalcaemia. In 3 of these cases, the hypomagnesaemia preceded the hypocalcaemia by at least one day. The median duration of the concurrent Grade 3 events was 8 days (range: 4-49).

Most treatment–related pulmonary adverse events were mild or moderate in intensity and most patients with treatment–related pulmonary adverse events had pulmonary metastases at study entry, and approximately half of the pulmonary adverse events were ongoing after discontinuation of panitumumab. One severe treatment-related adverse event was reported (dyspnoea); this patient experienced dyspnoea 30 minutes after the first panitumumab infusion. No Grade 4 or 5 pulmonary adverse events were considered by the investigator to be treatment related. Interstitial lung disease was not identified as a complication in any patient.

The majority of the cardiac adverse events were either mild or moderate in intensity. Five patients (< 1%) experienced adverse events associated with cardiac function that led to either discontinuation or interruption of treatment, while no event led to an alteration of the dose. Most of the 12 patients with serious adverse events associated with cardiac function had either a prior history of the same event occurring at some time prior to study enrolment or a history of predisposing cardiovascular co-morbidity and/or risk factors; nearly half of these patients had both prior event history as well as additional risk factors. Fatal events were reported for two patients and an additional two patients had Grade 4 (i.e., life-threatening) events associated with cardiac function. There did not appear to be a relationship between the incidence of cardiac adverse events and duration of exposure, length of follow-up, dosing regimen, panitumumab cell line or manufacturing scale nor did severity of the cardiac toxicities appear to be influenced by these factors.

The overall patient incidence of oedema, venous and arterial vascular adverse events was 19%. About 4% of these were Grade 3 or higher and 2% were considered to be related to study drug. In Study 20020408, this incidence was similar as in the mCRC monotherapy patient population in panitumumab group (21%) but higher than the BSC alone group (10%). Three percent (3%) of patients experienced serious vascular adverse events, all of which could be explained by predisposing medical problems such as hypercoagulable state associated with adenocarcinoma, advanced age or the pre-existing history or medical complications. Seven patients (1%) were discontinued prematurely due to vascular adverse events, one vascular adverse event led to dose interruption and one led to dose alteration.

Adverse events defined as vascular toxicity was experienced by 16 patients and were considered related to study drug: oedema peripheral (8 patients), pulmonary embolism (3 patients), hypertension (2 patients) and cerebrovascular accident, deep vein thrombosis, oedema and thrombophlebitis superficial (1 patient each). The adverse events were mild (5 patients), moderate (6 patients), severe (1 patient), life–threatening (2 patients, both pulmonary embolism) and fatal (1 patient with cerebrovascular accident and 1 with pulmonary embolism).

No potential infusion reaction was life–threatening or fatal. Most of the symptoms of potential infusion reactions were mild in intensity, occurred during the panitumumab infusion, resolved without treatment and were isolated occurrences without alteration or interruption of panitumumab administration.

Immunological events: As a human antibody, an immunological response is possible to the panitumumab molecule. In addition, during the CHO manufacturing process an extra sequence of light chain can be translated. This extra sequence may emerge as a pre-monomer peak before the panitumumab peak that is approximately 1% of the main peak. Immunogenicity to both panitumumab and the pre-monomer were evaluated.

An acid dissociation ELISA was used as a screening immunogenicity assay, an immunodepletion assay as confirmation, a bioassay to test for neutralising activity and a Biocore based assay for isotyping and affinity testing. Table 32 presents these results.

Table 32. Immunological events detected by ELISA and Biacore bio sensor immunoassays

Immunoassay	Baseline	Patients with ≥ 1 post–dose sample	Patients with follow-up assessments[1]
Acid dissociation bridging ELISA, n/total	5/636 (0.8%)	3/447 (0.7%)[2]	2/197 (1.0%)[3]
Biacore biosensor immunoassay, n/total	16/636 (2.5%)	19/447 (4.3%)[4]	4/197 (2.0)

1 Collected at least 21 days after the last panitumumab infusion
2 One patient tested positive for neutralizing antibodies in the in vitro biological assay in a post–dose sample
3 One of these two patients with follow–up samples tested positive for pre–existing antibodies at baseline
4 Two of the patients with post–dose samples tested positive for pre–existing antibodies at baseline

When compared to patients who did not develop antibodies, no relationship between the presence of anti–panitumumab antibodies and pharmacokinetics, efficacy and safety has been observed.

- Serious adverse event/deaths/other significant events

Table 33 displays the patient incidence (≥ 1%) with serious adverse events unrelated and related to study treatment for the mCRC monotherapy patient population.

Table 33. mCRC monotherapy dataset: Patient incidence of serious adverse events with difference > 5% by treatment groups

Serious adverse events	All SAE (≥ 1%) (n = 789[1])	Treatment–related (n = 789)
Patients with any adverse event	289 (37%)	33 (4%)
Disease progression[2]	122 (15%)	–
General physical health deterioration	22 (3%)	–
Abdominal pain	18 (2%)	–
Intestinal obstruction	18 (2%)	1 (0%)
Dehydration	15 (2%)	4 (1%)
Dyspnoea	14 (2%)	2 (0%)
Vomiting	13 (2%)	–
Small intestinal obstruction	11 (1%)	–
Ascites	10 (1%)	–
Hepatic failure	10 (1%)	–
Pleural effusion	9 (1%)	–
Pulmonary embolism	8 (1%)	3 (0%)
Pyrexia	8 (1%)	–
Back pain	7 (1%)	1 (0%)
Hypomagnesaemia	7 (1%)	7 (1%)
Jaundice	7 (1%)	–
Anaemia	6 (1%)	–
Asthenia	6 (1%)	1 (0%)
Constipation	6 (1%)	–
Gastrointestinal obstruction	6 (1%)	–
Nausea	6 (1%)	1 (0%)
Anorexia	5 (1%)	–
Deep vein thrombosis	5 (1%)	1 (0%)
Diarrhoea	5 (1%)	1 (0%)
Oedema peripheral	5 (1%)	–
Rectal haemorrhage	5 (1%)	1 (0%)
Respiratory failure	5 (1%)	–
Catheter site infection	4 (1%)	1 (0%)
Cerebrovascular accident	4 (1%)	1 (0%)
Convulsion	4 (1%)	–
Epilepsy	4 (1%)	–
Fatigue	4 (1%)	–
Hepatic encephalopathy	4 (1%)	4 (1%)
Hyperbilirubinaemia	4 (1%)	–
Hypersensitivity	4 (1%)	–
Pneumonia	4 (1%)	–
Sepsis	4 (1%)	–
Urinary tract infection	4 (1%)	–
Hypocalcaemia	NA	2 (0%)
Acute myocardial infarction	NA	1 (0%)
Adverse drug reaction	NA	1 (0%)
Chills	NA	1 (0%)
Dermatitis acneiform	NA	1 (0%)
Flushing	NA	1 (0%)
Haematemesis	NA	1 (0%)
Haematuria	NA	1 (0%)
International normalised ratio increased	NA	1 (0%)
Myocardial infarction	NA	1 (0%)
Nerve compression	NA	1 (0%)
Paronychia	NA	1 (0%)
Petechiae	NA	1 (0%)
Prothrombin time prolonged	NA	1 (0%)
Renal failure acute	NA	1 (0%)
Skin toxicity	NA	1 (0%)
Vocal cord paralysis	NA	1 (0%)
Wheezing	NA	1 (0%)

1 Patient incidence of common (≥ 1%) serious adverse events, NA: – incidence < 1%; SAE – serious adverse event

2 Adverse event terms indicative of progression of the underlying malignancy were grouped under the term "disease progression"

The incidence and type of serious adverse events in the All monotherapy patient population were consistent with those in the mCRC monotherapy patient population.

Deaths

Table 34 displays the number and percent of the reasons of deaths that occurred on study or within 30 days of the last dose of panitumumab for mCRC monotherapy and All monotherapy patient populations.

Table 34. mCRC and All monotherapy datasets: Reasons of deaths

	mCRC monotherapy[1] (n = 789)	All monotherapy (n = 1130)
Patients who died on study[2]	115 (15%)	134 (12%)
Disease progression	101 (13%)	118 (10%)
Respiratory failure	2 (0%)	2 (0%)
Cardiac arrest	1 (0%)	1 (0%)
Cerebrovascular accident	1 (0%)	1 (0%)
Dyspnoea exacerbated	1 (0%)	1 (0%)
Gastrointestinal haemorrhage	1 (0%)	2 (0%)
Hepatic failure	1 (0%)	1 (0%)
Intestinal perforation	1 (0%)	1 (0%)
Myocardial infarction	1 (0%)	1 (0%)
Pleural effusion	1 (0%)	1 (0%)
Pneumonia	1 (0%)	1 (0%)
Pulmonary embolism	1 (0%)	2 (0%)
Sepsis	1 (0%)	1 (0%)
Small intestinal obstruction	1 (0%)	1 (0%)

mCRC monotherapy patient population
Most other non–disease progression causes of death also appeared to be related to the underlying primary malignancy (such as hepatic failure, intestinal perforation, pleural effusion, small intestinal obstruction). Of the 14 non-disease progression deaths in the mCRC monotherapy population two were considered to be possibly related to panitumumab by the investigator: pulmonary embolism in one patient and myocardial infarction in another.

An additional 69 deaths in the mCRC monotherapy population occurred between 31 and 60 days after the last dose of panitumumab. Fifty–six (81%) of these deaths were due to disease progression. Non-disease progression deaths included respiratory failure, systemic mycosis resulting from mucositis and “unknown” (one patient each) and for 10 deaths the cause was not reported at the report cut-off date.

All monotherapy patient population
In the 1,130 patients in the monotherapy patient population, 134 (12%) died during panitumumab treatment or within 30 days of the last dose. Disease progression was reported as the cause of death in 118 patients. There were an additional 85 deaths that occurred between 31 and 60 days after the last dose of panitumumab and all of these deaths were considered to be caused by disease progression.

- Laboratory findings

Table 35 presents overall patient incidence of the laboratory adverse events together with incidence of Grade 3 or worst, fatal, serious and related adverse events for mCRC monotherapy patient population.

Table 35. mCRC monotherapy dataset: Summary of incidence of laboratory adverse events

Adverse event	Incidence (n = 789)	Incidence worst Grade ≥ 3	AE Grade ≥ 3[1]		
			Fatal	Serious	Related
Patients with at least 1 laboratory adverse event[3]	178 (23%)	82 (10%)	–	35 (4%)[3]	46 (6%)[4]
Blood and lymphatic system disorders					
Anaemia	40 (5%)	11 (1%)	–	6 (1%)	2 (0%)
Febrile neutropenia	2 (0%)	2 (0%)	–	1 (0%)	–
Thrombocytopenia	1 (0%)	1 (0%)	–	–	–
Hepatobiliary disorders					
Jaundice	37 (5%)	19 (2%)	–	7 (1%)	1 (0%)
Hyperbilirubinemia	8 (1%)	8 (1%)	–	4 (1%)	–
Jaundice cholestatic	1 (0%)	1 (0%)	–	1 (0%)	–
Jaundice extra-hepatic obstructive	1 (0%)	1 (0%)	–	1 (0%)	–
Hepatotoxicity	1 (0%)	1 (0%)	–	–	–
Infections and infestations					
Bacteraemia	1 (0%)	1 (0%)	–	1 (0%)	–
Investigations					
Bilirubin increased	5 (1%)	5 (1%)	–	1 (0%)	–
Prothrombin time prolonged	5 (1%)	4 (1%)	–	1 (0%)	1 (0%)
Aspartate aminotransferase increased	4 (1%)	1 (0%)	–	–	–
Blood urine present	4 (1%)	1 (0%)	–	–	1 (0%)
Alanine aminotransferase increased	2 (0%)	1 (0%)	–	–	–
Blood magnesium decreased	2 (0%)	1 (0%)	–	–	2 (0%)
Blood creatinine increased	1 (0%)	1 (0%)	–	–	–
Blood culture positive	1 (0%)	1 (0%)	–	–	–
C–reactive protein increased	1 (0%)	1 (0%)	–	–	–
Metabolism and nutrition disorders					
Hypomagnesaemia	35 (4%)	12 (2%)	–	7 (1%)	30 (4%)
Hypokalaemia	31 (4%)	10 (1%)	–	1 (0%)	8 (1%)
Hypocalcaemia	10 (1%)	5 (1%)	–	2 (0%)	5 (1%)
Hyperglycemias	6 (1%)	1 (0%)	–	1 (0%)	–
Hyperkalaemia	4 (1%)	2 (0%)	–	1 (0%)	–
Hypoglycaemia	3 (0%)	1 (0%)	–	1 (0%)	–
Hypercalcaemia	2 (0%)	1 (0%)	–	1 (0%)	–
Hypoalbuminemia	2 (0%)	1 (0%)	–	–	–
Hypophosphataemia	1 (0%)	1 (0%)	–	–	–
Lactic acidosis	1 (0%)	1 (0%)	–	–	–
Renal and urinary disorders					
Haematuria	23 (3%)	5 (1%)	–	3 (0%)	2 (0%)

1 –: 0 (0%)
2 For any adverse event, a patient may be counted more than once across categories
3 In addition, 4 patients experienced serious adverse events (anaemia by two patients and hypomagnesaemia, hypoglycaemia, and haematuria by one patient each) which were < Grade 3 in severity
4 In addition, 32 patients experienced related adverse events which were < Grade 3 in severity

- Safety in special populations

Adverse event profile in patients with or without hepatic impairment from the mCRC monotherapy patient population is summarised in Table 36.

Table 36. mCRC monotherapy dataset: Summary of adverse events by hepatic impairment at baseline

	Hepatic Impairment at Baseline	
	Yes (n = 37)	No (n = 737)
Patients with any adverse event	37 (100%)	737 (100%)
Worst Grade of 3	8 (22%)	267 (36%)
Worst Grade of 4	0 (0%)	25 (3%)
Worst Grade of 5	18 (49%)	105 (14%)
Any serious	20 (54%)	263 (36%)
Leading to permanent study drug discontinuation or removal from study	6 (16%)	78 (11%)
Not serious	2 (5%)	27 (4%)
Serious	4 (11%)	52 (7%)
Patients with any treatment-related adverse event	31 (84%)	693 (94%)
Worst Grade of 3	7 (19%)	122 (17%)
Worst Grade of 4	0 (0%)	8 (1%)
Worst Grade of 5	0 (0%)	2 (0%)
Any Serious	2 (5%)	30 (4%)
Leading to permanent study drug discontinuation or removal from study	2 (5%)	21 (3%)
Not serious	2 (5%)	15 (2%)
Serious	0 (0%)	6 (1%)

No data are available to evaluate safety in patients with renal impairment, paediatric patients and pregnant women. No notable differences were observed in the overall adverse event profile when assessed by gender, age, race, primary tumour type, cell line used for panitumumab manufacturing or dosing regimen, although patients ≥ 75 years of age had a slightly higher incidence (19% [15/78 patients]) of fatal adverse events than the mCRC monotherapy patient population as a whole (16% [111/711 patients]).

- Safety related to drug-drug interactions and other interactions

Drug metabolism and specific drug interaction studies between panitumumab and other drugs have not been performed. Limited data are presented in this application see Pharmacokinetics section of this document.

- Discontinuation due to adverse events

Figure 11 gives a synoptic view of the treatment/study discontinuation or treatment alteration due to adverse events.

Figure 11. mCRC monotherapy dataset: Summary of actions taken with respect to panitumumab administration resulting from an adverse event

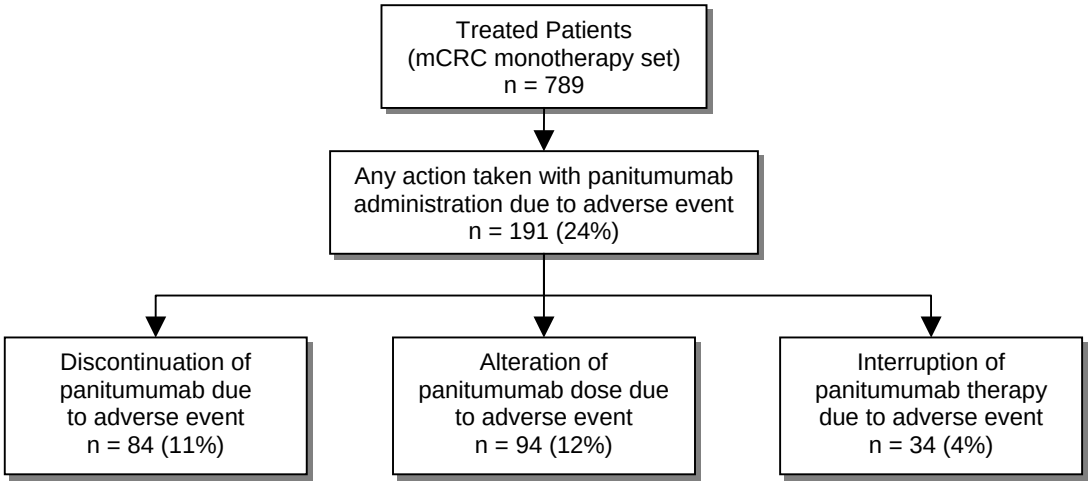


Table 37 provides detailed information on the 84 patients who experienced adverse events leading to permanent panitumumab discontinuation.

Table 37. mCRC monotherapy dataset: Patient incidence of adverse events leading to permanent discontinuation

Adverse events	n = 789
Patients with any adverse event	84 (11%)
Disease progression	18 (2%)
Dermatitis acneiform	6 (1%)
Erythema	4 (1%)
General physical health deterioration	4 (1%)
Nausea	4 (1%)
Rash	4 (1%)
Ascites	3 (0%)
Hyperbilirubinaemia	3 (0%)
Intestinal obstruction	3 (0%)
Pulmonary embolism	3 (0%)
Vomiting	3 (0%)
Abdominal pain	2 (0%)
Asthenia	2 (0%)
Convulsion	2 (0%)
Hepatic failure	2 (0%)
Jaundice	2 (0%)
Paronychia	2 (0%)
Pleural effusion	2 (0%)
Pneumonia	2 (0%)
Skin exfoliation	2 (0%)
Small intestinal obstruction	2 (0%)

- Combination treatment

There were 174 patients who received panitumumab (for 93% at dose of 2.5 mg/kg once a week) in combination with chemotherapy. Nineteen patients received panitumumab with IFL regimen (irinotecan, leucovorin and 5-fluorouracil), 24 with FOLFIRI regimen (irinotecan, leucovorin and 5-fluorouracil) and 131 with paclitaxel and carboplatin.

Overall, the safety profile of the combination regimens was dominated by adverse events related to the chemotherapy, with the addition of the skin toxicities attributable to panitumumab. While no clear additive effect was observed in the non-small cell lung cancer setting where panitumumab was combined with carboplatin/paclitaxel, in the mCRC setting panitumumab in combination with IFL, the incidence of severe diarrhoea was notably higher than that historically expected for this already highly GI-toxic chemotherapy regimen and one patient had an episode of Grade 4 diarrhoea that was also considered serious. Of note, panitumumab in combination with the FOLFIRI regimen using the same agents but different doses/infusion times was well tolerated with an incidence of severe diarrhoea similar to that expected from the literature for this chemotherapy regimen alone.

There were three fatal events in the all combination patient population which were considered possibly related to panitumumab therapy. The causes of the deaths were pulmonary fibrosis, gastrointestinal perforation and cerebrovascular accident. Of the 174 patients, 17 died during panitumumab treatment or within 30 days of drug discontinuation. Disease progression was the primary cause of death in eight of these. Many of the others reflected the toxicity of the chemotherapy, including pneumonia and pancytopenia or were related to malignancy, such as gastrointestinal perforation and paralytic ileus. There were a further two deaths between 31-60 days of stopping treatment caused by cardiopulmonary arrest and complications from elective surgery.

- Post-marketing experience

None, although recently approved in the USA.

- Discussion on clinical safety

Safety was assessed by review of death, discontinuation of treatment, analyses of laboratory data, vital signs, serious and non-serious adverse events. Data from 1304 patients (789 with mCRC and monotherapy, 341 with other solid tumours and monotherapy; 174 with mCRC and combination therapy) who had received at least one dose of panitumumab was included in the safety analyses. Safety assessment focused on key safety findings observed with administration of panitumumab as monotherapy (mCRC monotherapy; All monotherapy), as monotherapy is the applied regimen. The majority of the patients (77 and 58% in mCRC monotherapy and All monotherapy, respectively) received as per proposed posology (6 mg/kg every two weeks). There is limited data on long-term exposure to panitumumab (74 patients with ≥ 6 months of exposure); however, this is acceptable as the indication sought assumes a patient population with limited life expectation. Overall, the two datasets of interest are comparable with respect to demographics and disease baseline characteristics. The population included in the primary analysis for safety (mCRC monotherapy patient population) is considered representative of patients with advanced mCRC.

All patients in the mCRC monotherapy patient population had at least one adverse event during the study period. The most common (≥ 15%) adverse events were associated with the skin, including acneiform dermatitis (52%), pruritus, erythema (49% each), and rash (38%), skin exfoliation (23%), paronychia (19%) and skin fissures and dry skin (16% each) which reflect the pharmacological effect of inhibition of EGFR signalling pathway. Other common adverse events were fatigue (33%), nausea (29%), diarrhoea (26%), constipation, abdominal pain (20% each) and anorexia (19%). Approximately one-half of patients (54%) reported at least one Grade 3 or higher adverse event and the most common ones were pruritus, rash, and abdominal pain (5% each). The adverse events frequency and distribution are similar between the mCRC monotherapy and All monotherapy patient populations, except for skin exfoliation which occurred with a difference in incidence of ≥ 5% (23% vs. 17%, respectively).

The most common adverse events reported as severe, life threatening or fatal were directly attributed to the underlying cancer. Two patients had fatal adverse events (one patient with pulmonary embolism and one with cardiovascular accident and myocardial infarction) reported as related to panitumumab treatment. Additionally, eight patients (1%) had life-threatening adverse events that were considered related to panitumumab (one patient had acute myocardial infarction, three had hypomagnesaemia, one had acute renal failure, two had pulmonary embolism, and one had acne and erythema).

Due to high percentage of patients still on study, suboptimal compliance with protocol–required sample collection at follow–up, complete immunogenicity data are available for only approximately one–third of the patients enrolled. From these limited data available, there is no apparent impact the presence of anti–panitumumab antibodies on pharmacokinetics, efficacy and safety parameters.

Like other EGFR-inhibitors, the most common adverse events were related to panitumumab pharmacological effect, inhibition of the EGFR signalling pathway. However, the one fatal and two life-threatening cases of pulmonary embolism in this relatively small safety population raise concerns.

No data are available to evaluate safety profile of panitumumab in patients with renal impairment, paediatric patients and pregnant women. No notable differences were observed in panitumumab safety profile when assessed by gender, age or race.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a Risk Management Plan. A number of deficiencies originally identified were satisfactorily addressed in a revised version of the Risk Management Plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Integument and eye toxicities Stomatitis and oral mucositis	Routine pharmacovigilance Study to investigate whether pre-emptive skin treatment, as compared with reactive treatment, helps reduce the risk of clinically significant skin reactions in patients treated with panitumumab	Warning in Section 4.4 of the SPC Listed as an ADR in Section 4.8 of the SPC Risk communication will be through Direct Healthcare Professional Communication*
Pulmonary toxicities	Routine pharmacovigilance	
Hypomagnesaemia and hypocalcaemia	Routine pharmacovigilance	
Diarrhoea	Routine pharmacovigilance	
Infusion reactions	Routine pharmacovigilance	Listed as an ADR in Section 4.8 of the SPC Risk communication will be through Direct Healthcare Professional Communication*
Dehydration	Routine pharmacovigilance	
Lack of response in tumours with KRAS mutation	Routine pharmacovigilance	Risk communication will be through Direct Healthcare Professional Communication*
Important potential risks		
Vascular toxicities	Routine pharmacovigilance	Risk communication will be through Direct Healthcare Professional Communication*
Cardiac toxicities	Routine pharmacovigilance	
Wound healing	Routine pharmacovigilance	
Immunogenicity	Routine pharmacovigilance Study to investigate whether the development of anti-panitumumab antibodies is correlated with clinical consequences	Relevant information included in Section 5.1 of SPC Risk communication will be through Direct Healthcare Professional Communication*
Important missing (or limited) information		
Pregnant women	Routine pharmacovigilance	Relevant information included in Sections 4.6 and 5.3 of the SPC Risk communication will be through Direct Healthcare Professional Communication*
Lactating women	Routine pharmacovigilance	Relevant information included in Section 4.6 of the SPC Risk communication will be through Direct Healthcare Professional Communication*

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Paediatric patients	Routine pharmacovigilance A paediatric programme will be developed, initially conducting a paediatric dose finding study	Relevant information listed in Section 4.2 of the SPC Risk communication will be through Direct Healthcare Professional Communication*
Non-white patients	Routine pharmacovigilance	N/A
Patients with renal, hepatic, cardiac, or pulmonary impairment	Routine pharmacovigilance	Relevant information on renal and hepatic impairment listed in Sections 4.2 and 5.2 of the SPC Risk communication will be through Direct Healthcare Professional Communication*
Patients who receive panitumumab at a dose schedule that has not been evaluated extensively or in combination with chemotherapy	Planned/ongoing clinical studies	Alternative dosage and chemotherapy regimens will not be included in the SPC Risk communication will be through Direct Healthcare Professional Communication*
Patients with cancer type other than refractory mCRC	Planned/ongoing clinical studies	Alternative indications will not be included in the SPC Risk communication will be through Direct Healthcare Professional Communication*
Additional non-routine pharmacovigilance studies		
Biomarkers	Study to discover biomarkers that help predict responsiveness, or lack thereof, to panitumumab therapy. Such biomarkers could help identify a population of patients who are likely to benefit from panitumumab treatment and consequently improve the benefit-risk balance of the therapy.	N/A

* if appropriate

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the drug substance, have been adequately described, controlled and validated. The drug substance has been well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications have been set. The manufacturing process of the drug product has been satisfactorily described and validated. The quality of the drug product is controlled by adequate test methods and specifications. The viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

Non-clinical pharmacology and toxicology

The preclinical testing programme for panitumumab included primary and secondary pharmacology studies, assessment of cross reactivity, one safety pharmacology study, a number of repeated dose general toxicology studies and two studies assessing toxicity to reproductive function.

Panitumumab binds to the ligand-binding domain of EGFR to competitively inhibit the action of EGFR ligands to promote phosphorylation of EGFR. Where EGFR stimulation drives tumour growth, this competitive binding disrupts the EGFR ligand signal and consequently has an anti-tumour action. EGFR expression is abnormal in malignant transformations in a variety of cell types. The ability of panitumumab to inhibit growth of a range of tumour types in vitro and in vivo when these were transplanted into athymic mice has been adequately shown.

Toxicity to skin and diarrhoea was the primary toxicity of panitumumab in monkeys. These effects are also seen with other chimeric anti-EGFR antibody and with small molecule inhibitors of EGFR. It is considered directly related to the pharmacological action of drugs that inhibit EGFR signalling.

Animal studies are insufficient with respect to embryo-foetal development since foetal panitumumab exposure levels were not examined. EGF and EGFR are involved in embryo-foetal growth and development and effects on growth and development would therefore be expected. Indeed, panitumumab has been shown to be an abortifacient in cynomolgus monkeys when administered during the period of organogenesis at doses up to 6-fold the exposure of recommended human dose on a mg/kg basis. No pre- and post-natal development animal studies have been conducted with panitumumab.

Efficacy

The pivotal study compared panitumumab plus BSC to BSC alone in patients with metastatic colorectal cancer after failure of prior chemotherapy regimens containing 5-fluorouracil, irinotecan and oxaliplatin. The primary endpoint was progression-free survival, allowance of crossing over for patients in the controlled arm if they are declared progressing. The first assessment of progression was done at 8 weeks, at which time a large proportion of patients had already progressed. As this was an open-label study, more patients in the BSC arm had unscheduled visits to their physician before Week 8, allowing disease progression to be detected earlier in these patients. A very small improvement in progression-free survival, no significant difference in overall survival and a low objective response rate were observed.

Safety

Like other EGFR-inhibitors, the most common adverse events were related to the pharmacological effect (inhibition of the EGFR signalling pathway) and resulted mainly skin toxicity. The high incidence of adverse events affecting the patients' quality of life is a safety concern. Although most deaths were secondary to disease progression, there were several deaths that may have been related to the pharmacodynamic mode of action of panitumumab.

Anti-idiotypic antibodies may inhibit the mechanism of action. From these limited data available, there is no apparent impact of the presence of anti–panitumumab antibodies on pharmacokinetics, efficacy and safety parameters but this could not be totally ruled out.

User consultation

The Patient Information Leaflet (PIL) for Vectibix 20 mg/ml concentrate for solution for infusion (panitumumab) has been tested in English in accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC. The PIL for Vectibix 20 mg/ml concentrate for solution for infusion (panitumumab) was found to contain all the necessary information in a way that is accessible and understandable to those who participated in this test.

It is considered that the tested PIL meets the requirements set for User Testing.

Risk/benefit assessment

In the pivotal study, panitumumab plus best supportive care (BSC) was compared to BSC alone in patients with metastatic colorectal cancer after failure of prior chemotherapy regimens containing 5-fluorouracil, irinotecan and oxaliplatin. The primary endpoint was progression-free survival (PFS). The pivotal study was not adequately designed to demonstrate difference in overall survival as patients in the BSC arm were allowed to cross-over to the panitumumab arm when progressing, thereby confounding the comparison of overall survival between treatment groups. In late stage cancer patients with short expected lifetime, it would have been possible to run a trial without cross-over which would have allowed estimating the effect of treatment with panitumumab on overall survival.

The first assessment of progression was done at 8 weeks, at which time a large proportion of patients had already progressed. As this was an open-label study, more patients in the BSC arm had unscheduled visits to their physician before Week 8, allowing disease progression to be detected earlier in these patients. The lack of a scheduled early visit in both treatment arms leads to bias, and the overall difference in PFS is probably overestimated. Notwithstanding these methodological weaknesses, only a very small improvement in progression-free survival, no significant difference in overall survival were observed, and a low objective response rate. A clinically relevant benefit has thus not been sufficiently proven.

The most common adverse events reported as severe, life threatening or fatal were related to the underlying disease, however some deaths may have been related to panitumumab pharmacodynamic mode of action. As expected for an EGFR inhibitor, the most common adverse reactions by patient incidence were skin reactions, including acneiform dermatitis, pruritus, erythema and rash which reflect the pharmacological effect of inhibition of EGFR signalling pathway. The quality of life assessment indicated that the patients experiencing these adverse reactions were more embarrassed and disturbed by their skin condition than patients in the BSC alone group.

Of note, a study with panitumumab combined with bevacizumab and chemotherapy *vs.* bevacizumab and chemotherapy alone (PACCE), as first-line treatment of patients with metastatic CRC has been stopped due to a statistically significant reduction in PFS in patients receiving panitumumab. The addition of panitumumab in the PACCE trial also led to a considerably higher frequency of severe adverse events, including deaths. Although the study is not of direct relevance to the indication sought the safety information is of major concern, also, for the claimed indication.

In conclusion, the risk/benefit of panitumumab in the treatment of patients with metastatic colorectal cancer after failure of prior chemotherapy containing 5-fluorouracil, irinotecan and oxaliplatin is not considered favourable due to the following grounds:

- The pivotal, open-label study is difficult to interpret because the majority of patients in the BSC were switched to panitumumab early on. More patients in the BSC arm had unscheduled visits to their physician before Week 8 (first scheduled study visit), allowing disease progression to be detected earlier in these patients.
- Only a very small effect on progression-free survival has been observed, and no favourable effect has been shown in terms of overall survival or other clinical benefit endpoint.
- Treatment with panitumumab was associated with skin reactions, including acneiform dermatitis, pruritus, erythema, and poorer quality of life was reported in patients experiencing these adverse reactions. In addition, safety information from the PACCE study raised additional concerns, including increased mortality in panitumumab-treated patients.
- The clinical efficacy observed is too small to constitute a clinical benefit and does not outweigh the risks associated to treatment with panitumumab.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of in the treatment of patients with metastatic colorectal after failure of prior chemotherapy containing 5-fluorouracil, irinotecan and oxaliplatin was unfavourable and therefore did not recommend the granting of the marketing authorisation.

7. Re-examination of the CHMP opinion of 24 May 2007

Following the CHMP conclusion that the risk/benefit balance of panitumumab in the treatment of patients with metastatic colorectal cancer after failure of prior chemotherapy containing 5-fluorouracil, irinotecan and oxaliplatin was unfavourable, the applicant submitted detailed grounds for the re-examination of the grounds for refusal. The applicant presented a number of arguments regarding the grounds for refusal.

Ground #1 (design of the pivotal study). The Applicant acknowledged that:

- Study 20020408 was the first randomised study to evaluate the efficacy and safety of panitumumab against BSC in an advanced, refractory mCRC
- the study design allowed patients in the BSC group who progressed to be enrolled in Study 20030194 to receive panitumumab ("active crossover") which confounds a direct evaluation of the effect of panitumumab on overall survival
- More patients in the BSC arm had unscheduled visit before Week 8, allowing disease progression to be detected earlier in these patients.

However, sensitivity analyses were performed to facilitate the interpretation of the results in which progression (assessed by IRC) were imputed either a) at the closest scheduled assessment time or b) the next scheduled assessment time. For each method of imputation, PFS was modelled either as a continuous or discrete time variable. The results of these analyses are show in Table 38.

Table 38. Study 20020408 - PFS sensitivity analyses to address potential for time ascertainment bias

Analysis	Hazard Ratio	95% CI
Observed PFS times (primary analysis)		
Continuous time model [a]	0.54	0.44 – 0.66
Discrete time model [b]	0.53	0.43 – 0.65
Moving radiological events to closest scheduled assessment time		
Continuous time model [a]	0.60	0.49 – 0.74
Discrete time model [b]	0.53	0.40 – 0.70
Moving radiological events to next scheduled assessment time		
Continuous time model [a]	0.61	0.50 – 0.75
Discrete time model [b]	0.54	0.41 – 0.71

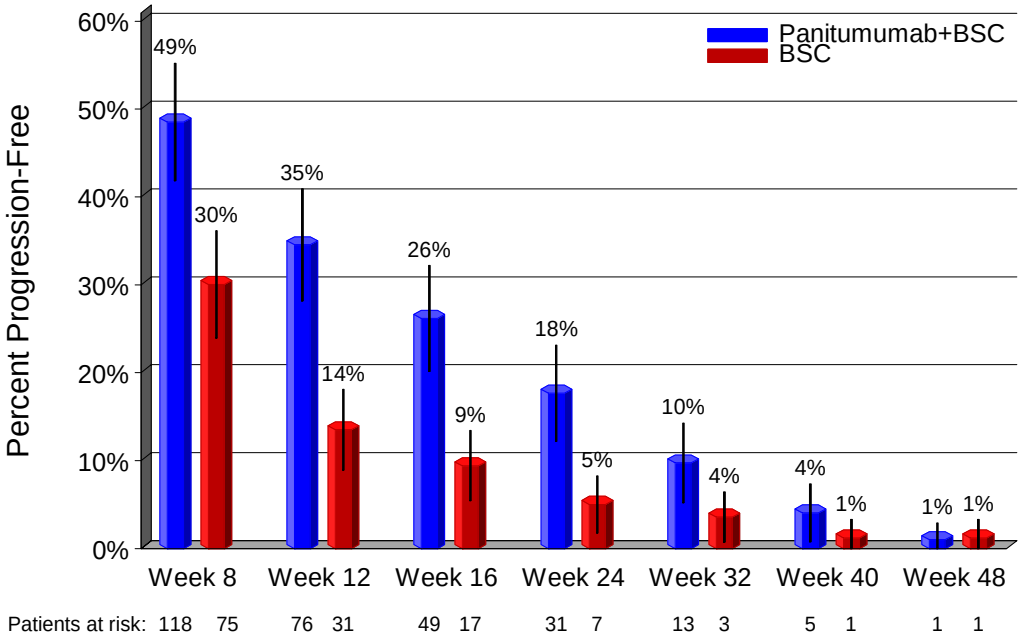
a Cox model from SAS PHREG with TIES=EXACT option
b Cox model from SAS PHREG with TIES=DISCRETE option
Note: Cox models adjusted for randomisation factors (ECOG score and geographic region)

The hazard ratio ranges for the continuous and discrete time models are very consistent with the primary analysis. Thus, even the most conservative estimate indicates the rate PFS was decreased by approximately 40% in the panitumumab group compared with BSC.

Ground #2 (treatment effect). The Applicant argued that:

- PFS was statistically significant in favour of patients receiving panitumumab (Table 18), as above-mentioned sensitivity analyses showed hazard ratios ranging from 0.53 to 0.61 (Table 38).
- There was a greater probability of being alive and progression free at Week 8 of treatment with panitumumab compared to BSC alone. A similar estimate was observed up to Week 24 post-randomisation (Figure 12).

Figure 12. Study 20020408 - Progression-free survival rates at protocol-specified disease assessment timepoints



Program: /stat/amg954/onc/20020408/analysis/ectd/stats/post_hoc/EMEA/OE/PFS/Bar_graph/PFS_bar_graph_rev2.sas
Output: graphs/PFSc.ITT.bar_graph_rev2.cgm (Date Generated:12APR07:12:25:26)

- Remaining progression free at Week 8 was strongly associated with a better survival prognosis on panitumumab (Table 39).

Table 39. Study 20020408 - Survival Prognosis at Selected Time Points by Prior Progression Status

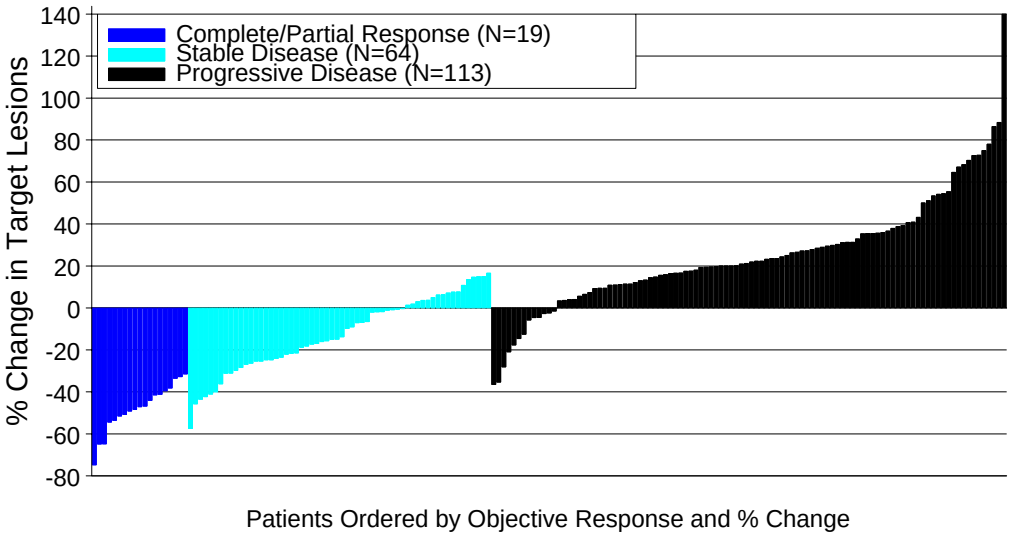
		No PD		PD		Difference	Hazard Ratio[1]
		N	Median Survival (months)	N	Median Survival (months)	Median Survival (months)	Est. (95% CI)
Week 8	Panitumumab	101	7.6	101	3.6	3.9	0.36 (0.23, 0.55)
	BSC	64	8.6	135	4.3	4.3	0.45 (0.28, 0.72)
Week 12	Panitumumab	71	7.5	98	3.3	4.2	0.27 (0.16, 0.45)
	BSC	28	NE	144	4.7	NE	0.31 (0.14, 0.69)
Week 16	Panitumumab	44	7.3	91	3.2	4.1	0.24 (0.13, 0.45)
	BSC	17	NE	120	4.3	NE	0.62 (0.27, 1.45)

1 Adjusted for randomisation factors (ECOG performance score and geographic region)

- Panitumumab had an impact on tumour burden, 42% of patients randomised to panitumumab had a decrease in target lesions compared with 3% of patients randomised to BSC (Figure 13).

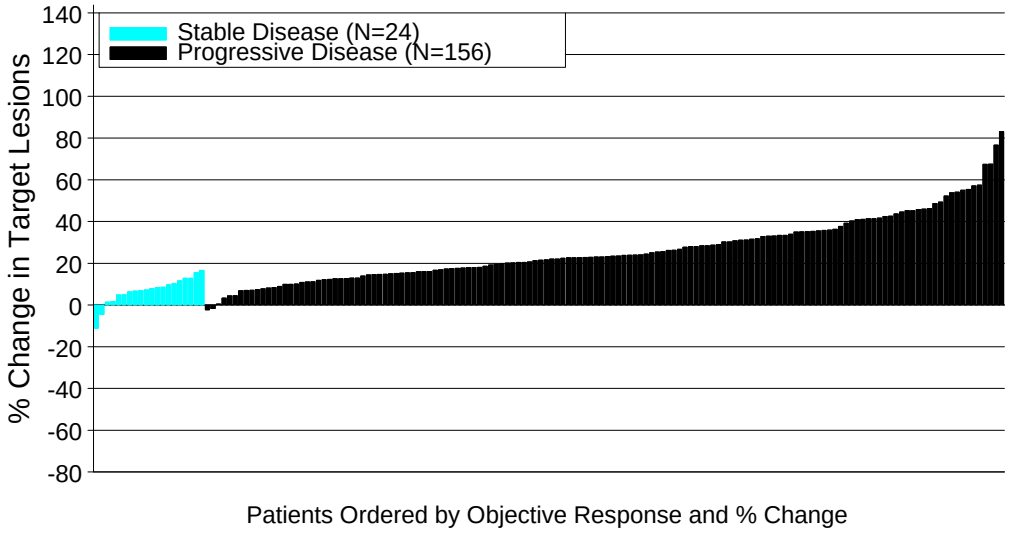
Figure 13. Study 20020408 - Maximum decrease in target lesions (ITT, IRC assessment)

Patients randomised to panitumumab



Program: /stat/amg954/onc/20020408/analysis/ectd/stats/post_hoc/EMEA/LoOI/Major1/MaxD_SLD/MaxD_SLD.sas
Output: graphs/pmab_maxd_sld.cgm (Date Generated:13MAR07:09:53:38)

Patients randomised to BSC



Program: /stat/amg954/onc/20020408/analysis/ectd/stats/post_hoc/EMEA/LoOI/Major1/MaxD_SLD/MaxD_SLD.sas
Output: graphs/bsc_maxd_sld.cgm (Date Generated:13MAR07:09:53:38)

- Due the possibility of initiating panitumumab treatment in BSC patients after progression, the Study 20020408 design did compromise any conclusion on OS improvement. However, a study using monoclonal antibody (cetuximab) in mCRC demonstrated an association between PFS and OS (Jonker et al, 2007).

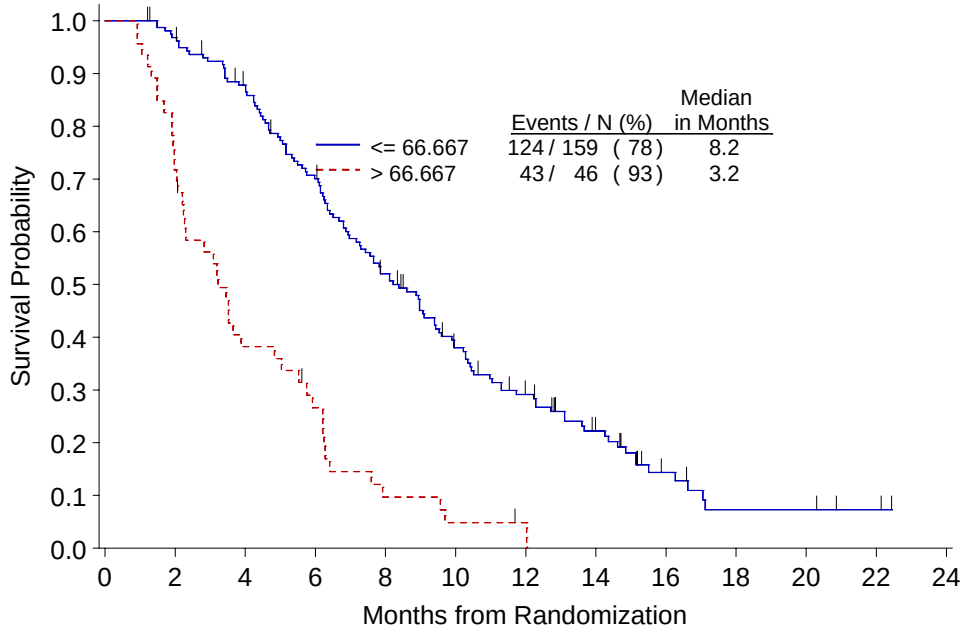
Overall, the observed magnitude of the treatment effect on PFS as measured by the hazard ratio is clinically meaningful in the targeted patient population after failure of 5-fluorouracil, irinotecan and oxaliplatin therapy and compares favourably with that observed with other agents licensed for the treatment of metastatic CRC. Additional trials of panitumumab in combination with chemotherapy are ongoing to further characterise the effect of panitumumab on OS.

Ground #3 (safety profile). The Applicant stated that:

- Treatment-related adverse events were predominantly mild-to-moderate skin toxicities, a recognised class effect of EGFR inhibitors. Approximately 75% of patients who reduced or interrupted panitumumab dosing because of a skin-related adverse event were able to subsequently reinstate their initial dose. Patients most bothered by their skin toxicity appeared to experience the

best overall outcomes (Figure 14), i.e., better PFS and better OS. Similar results have been observed with other EGFR inhibitors for worst severity of skin toxicity (Perez-Soler et al, 2005). In clinical studies, there were a low incidence of infusion reactions (none were life-threatening or fatal), even in the absence of premedication.

Figure 14. Study 20020408 - Kaplan-Meier Estimates of OS by post-baseline DLQI score



Program: /stat/amg954/onc/20020408/analysis/408survival/stats/post_hoc/EMEA/Q47/DLQI/TTD.DLQI.sas
Output: graphs/OS_DLQI.cgm (Date Generated:12DEC06:15:40:05)

- Severe, life-threatening or fatal adverse events were generally attributable to comorbid illnesses rather than to panitumumab.

- In the Study 20020408, the QoL was assessed using:
  - the NCCN/FACT CRC symptom index (FCSI) for colorectal cancer symptoms. The FCSI results were numerically in favour of panitumumab
  - the modified Dermatology Life Quality Index (mDLQI) subscale for the impact of skin toxicity. Patient treated with panitumumab had lower scores, indicating that they were more symptomatic and more embarrassed and/or bothered by their skin symptoms than were patient with BSC alone
  - the EuroQol-5D Health Index (EQ-5D Index) and the EORTC Global Health/Quality of Life Scale (EORTC Global) for the overall QoL. The results indicate that panitumumab did not have a negative impact on overall QoL.

- The PACCE study was designed to compare the efficacy (primary endpoint PFS, secondary endpoints OR rate, time to treatment failure, OS) and safety of bevacizumab and chemotherapy (oxaliplatin or irinotecan) combined or not with panitumumab for first-line treatment of mCRC.

  - Initial interim safety results were based on all 926 enrolled patients who received at least one dose of study treatment. Of these, 793 patients received oxaliplatin-based chemotherapy and 133 patients received irinotecan-based chemotherapy, the reported results are based on patients who received oxaliplatin as chemotherapy. A summary of main safety results is displayed in Table 40.

Table 40. PACCE study - Summary of main safety results

Adverse event	Pmab + Bev/Ox N=401	Bev/Ox N=392
Grade 3 or higher	89%	74%
Serious	56%	37%
Pulmonary embolism Grade 5 fatal event	1%	
Pulmonary embolism Grade 4	6%	4%
Diarrhoea and dehydration Grade 4	2%	< 1%
Diarrhoea Grade 3	21%	12%
Dehydration Grade 3	14%	4%
Infection fatal cases	< 1%	1%
Infection Grade 4	2%	2%
Infection Grade 3	15%	8%
Deaths on study	20%	15%
Deaths Grade 5 adverse events[1]	4%	3%

1: Does not include deaths attributed to disease progression (i.e., neoplasms)

- The planned interim analysis showed an unfavourable benefit for panitumumab plus bevacizumab/oxaliplatin vs. bevacizumab/oxaliplatin alone based on reduced PFS (8.8 months 95% CI: 8.3 to 9.5) versus 10.5 months 95% CI: 9.4 to 12.0, HR 1.44, p = 0.0004), on progression rate or died (ICR assessment) (147 [36%] versus 110 patients [27%], respectively), overall survival (HR 1.56 [1.11, 2.17]) and best overall response rates (ICR assessment) (39% vs. 41%, respectively).

- The interim data from two ongoing clinical trials investigating combination treatment (FOLFOX or FOLFIRI) with panitumumab do not reveal alarming trends observed in the panitumumab arm of the PACCE study (diarrhoea, dehydration, infection, pulmonary embolism or thromboembolic events). No alarming signal is revealed when pooled safety data from these studies are compared with historical safety data from other mCRC trials that included only chemotherapy (i.e., FOLFOX or FOLFIRI).

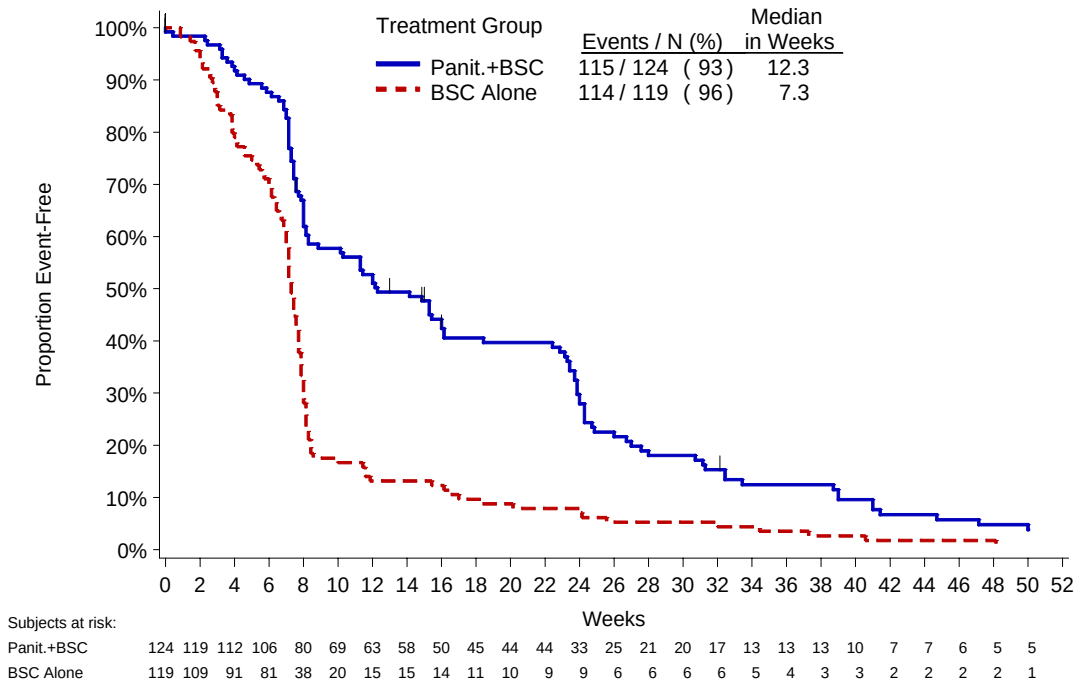
The overall safety profile and pattern of adverse events remained consistent with mCRC monotherapy compared with the ongoing post-marketing safety surveillance and clinically manageable. Moreover, PACCE study are consistent with the observed toxicity of dual pathway inhibition in combination with chemotherapy, therefore PACCE study results should not be generalised to the use of panitumumab as monotherapy.

Ground #4 (risk/benefit balance). The Applicant has identified a biomarker (KRAS) which allows selecting patients who will not benefit from panitumumab treatment.

- The median PFS in the wild type KRAS population was 12.3 weeks vs. 7.3 in the mutant type KRAS population which is a difference of 5 weeks (HR 0.45, 95% CI 0.34-0.59) (Figures 15 and 16).

Figure 15. Study 20020408 – Kaplan–Meier plot of PFS (ITT, non-time adjusted, IRC assessment)

Patient population with wild-type KRAS



Patient population with mutant-type KRAS

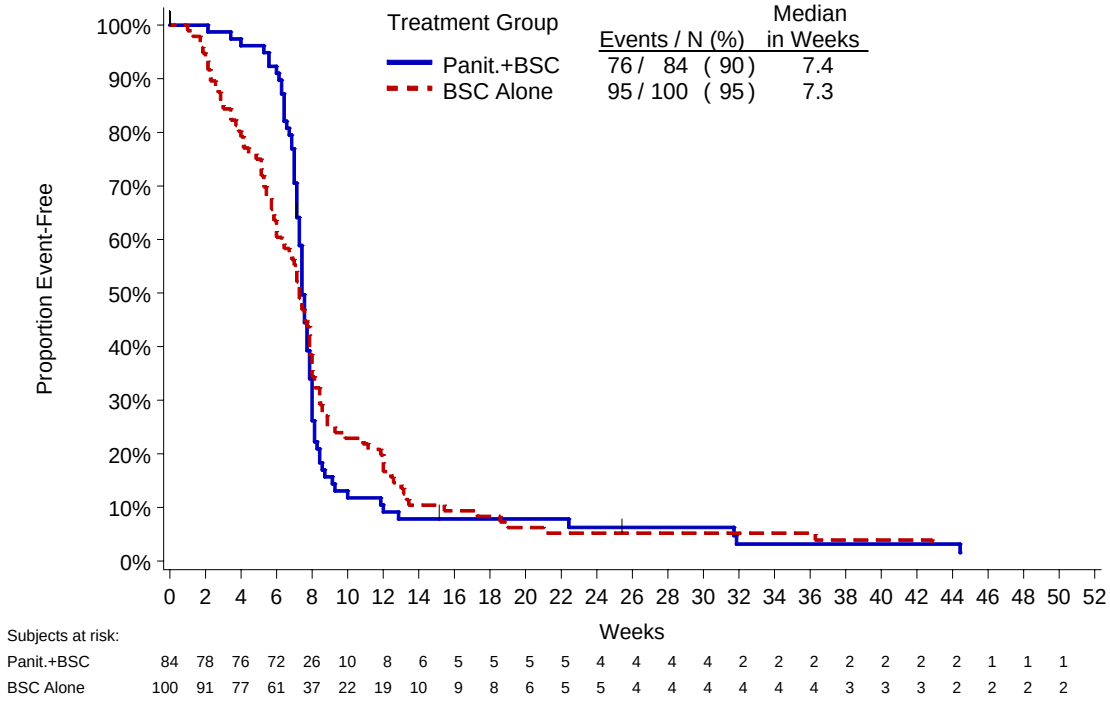
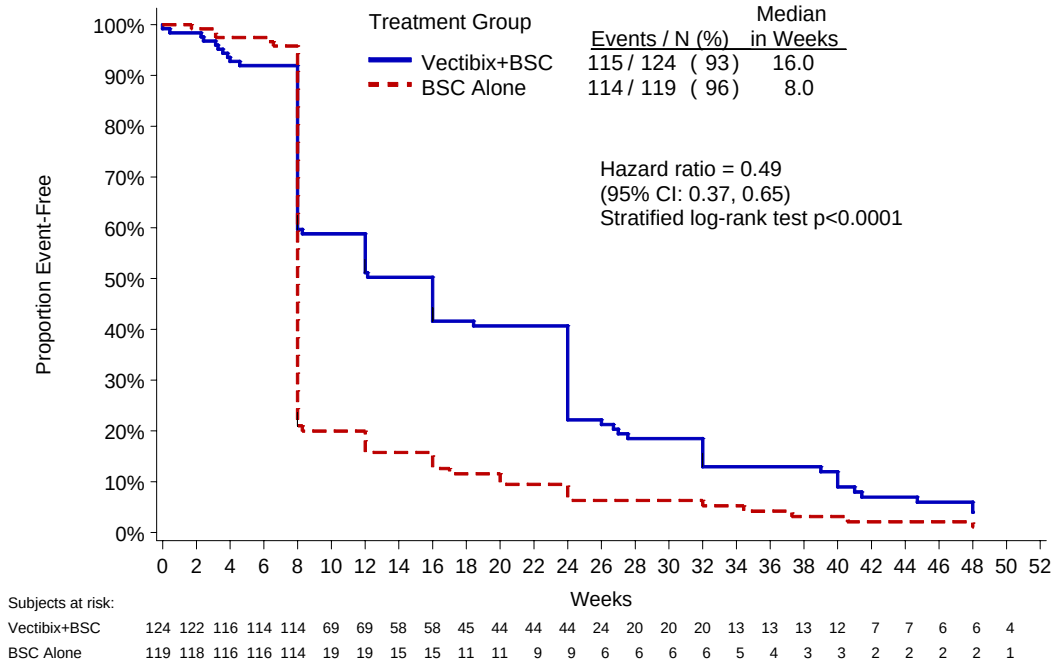


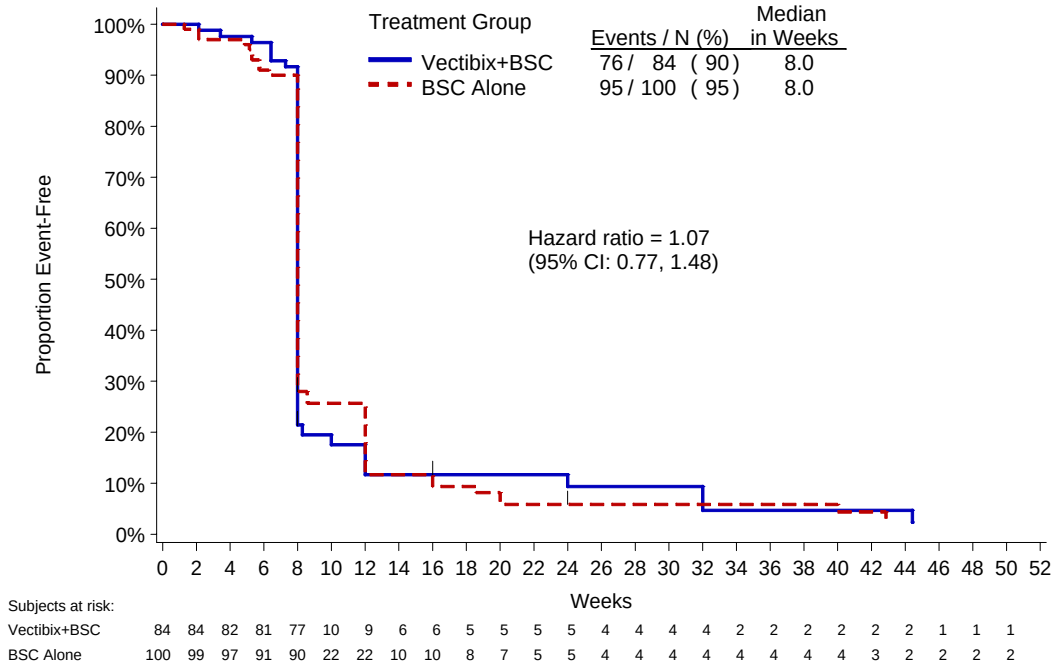
Figure 16. Study 20020408 – Kaplan–Meier plot of PFS (ITT, time adjusted, IRC assessment)

Patient population with wild-type KRAS



Unscheduled tumour assessments were moved to the nearest scheduled timepoint

Patient population with mutant-type KRAS



Unscheduled tumour assessments were moved to the nearest scheduled timepoint

- The results on PFS are supported by the OR and SD rates (assessed by the IRC) where 17 and 34% was observed in the wild-type vs. 0 and 12% in mutant-type, respectively. Beneficial treatment effect is present when maximum decrease in tumour size is considered however no effect on OS was observed in this subgroup of patients either.

- This subgroup analysis indicates that patients with wild-type KRAS receives more infusions and had a slightly increased incidence of adverse events, however the rates observed were comparable to those seen in the mCRC monotherapy dataset.

- The applicant is conducting two large pivotal, Phase III studies (Studies 20050181 and 20050203) in patients with mCRC using panitumumab in combination as first or second-line treatment. The applicant commits:

    - using that further data for confirming treatment effects in the wild-type and mutant KRAS populations
    - exploring the utility of other biomarkers that may further identify those more likely to respond.

Ground #5. From clinical efficacy and safety data presented above, the Applicant is of viewpoint that the treatment effect observed in the subpopulation of patients who had progressed on all available anticancer therapies patient and presenting with wild type KRAS phenotype is of clinical relevance with an acceptable safety profile.

The CHMP requested the SAG to answer to following 3 questions:

1. Does the observed treatment effect in terms of PFS represent a clinical benefit, taking into account:
    - concerns with the reliability of the PFS measure, in particular due to the design and conduct of the pivotal study (open-label and asymmetry of the unscheduled visit before Week 8) and
    - lack of evidence of any clinically meaningful effect on overall survival or other important clinical benefit endpoints

    Divergent views were expressed but the SAG-oncology globally considers that:

    - Overall Survival remains the most appropriate endpoint for end stage of the disease. There is no suggestion that treatment with panitumumab had any effect on important clinical endpoints such as overall survival.
    - Progression-free survival is considered to be an endpoint that is of relevance in earlier lines of the treatment. Regardless of line of treatment, PFS would require large effects in order to be considered of any benefit to the patient (PFS). Despite the statistically significant difference observed in terms of the primary endpoint PFS, the observed difference is very small and is not considered to be of clinical relevance. Small differences of this kind are, may be, partly due to chance and partly caused by imbalances of known and unknown prognostic factors. In this respect, concerns were raised on unbalanced baseline characteristics of recognised prognostic factors favouring the experimental treatment arm.

2. Does the toxicity profile of panitumumab in the claimed indication raise safety concerns? To what extent does the toxicity observed in the PACCE study, including increased mortality in panitumumab-treated patients, contribute to safety concerns for the claimed target population in this submission?

    The SAG-oncology does not consider that the safety profile of panitumumab is a major concern since it appears being not really different from those described for other EGFR inhibitors. The panitumumab toxicity is recognised to be clinically manageable by the experts. However, in the absence of a meaningful benefit, the benefit risk was considered negative.

3. Would KRAS mutation status be an appropriate bio-marker for selecting patients for initiating a treatment with panitumumab? Would further data be necessary to support this observation or to fully demonstrate that KRAS mutation status is a relevant bio-marker for patient selection?

    The results of the post-hoc analyses on KRAS being a possible biomarker for selection of patients to be treated with panitumumab are interesting but remain exploratory findings which need to be confirmed by results of prospective, well-designed, well-conducted study(ies). From a pharmacological point of view this remains a possible theory but there are no data to confirm it.

Overall conclusion on grounds for re-examination
The pivotal trial showed an effect on PFS that is considered small, but of a comparable magnitude to those observed in other studies which have supported recent regulatory approvals for other anticancer drugs as irinotecan, oxaliplatin, bevacizumab, or cetuximab.

For Study 20020408, additional analysis results showed a statistically significant larger panitumumab treatment effect on PFS in patients with the wild-type KRAS compared with patients with the mutant-type.

Most common adverse events observed in clinical trials of panitumumab monotherapy or in combination with chemotherapy were skin rash, it is a well-known side effect of EGFR inhibitors. These effects were manageable since 75% of patients who reduced or interrupted panitumumab dosing because of a skin-related adverse event were able to subsequently reinstate their initial dose. Moreover, measures of overall Quality of Life do not indicate that panitumumab has a clear positive impact on Quality of Life.

Finally, results taken from the PACCE study should be interpreted with caution in the context of panitumumab being used together with bevacizumab-containing chemotherapy. These results should not be generalised to include the use of panitumumab in combination with chemotherapy regimens alone or the monotherapy settings.

Adverse reactions reported in clinical trials are described in the Summary of Product Characteristics.

Overall, the additional arguments and analyses presented indicate that the benefit-risk profile of panitumumab is marginally positive in the treatment of patients with metastatic colorectal cancer after failure of prior chemotherapy containing 5-fluorouracil, irinotecan and oxaliplatin. However, the inability to select patients that respond to treatment is a pitfall of available options in this setting. Additional efficacy analyses provided indicated an interaction of panitumumab with KRAS mutation status. Although this interaction is being investigated further in prospective trials, this interaction allows selecting patients for treatment with panitumumab and the indication should be restricted based on this criterion. The ability to select patients that might benefit from treatment with this type of agent is considered a major therapeutic advantage to those affected.

In addition, the applicant has agreed to provide a prospective statistical analysis plan describing the analysis of a wild-type KRAS subpopulation in ongoing Phase 3 trials. The applicant has also committed to explore and report the utility of other biomarkers that may further identify those more likely to respond and to provide additional data on Quality of Life using a validated scale. Finally, the applicant has committed to ensure the availability of KRAS test kit.

Thus, concerning the grounds for negative opinion, having considered the additional arguments and analyses presented by the applicant and the answers from the SAG, the CHMP concluded that:

- Based on sensitivity analyses presented, unscheduled visits are unlikely to alter the conclusions in terms of the statistically significant effect observed in terms of PFS and major bias can be excluded.
- A small but statistically significant effect in terms of progression-free survival has been observed and efficacy can be considered demonstrated even in the absence of a statistically significant difference in terms of overall survival.
- The safety profile of panitumumab is not a major concern and appears to be similar from that described for other EGFR inhibitors. The toxicity of panitumumab is recognised to be clinically manageable.
- The clinical efficacy observed is small but a positive benefit-risk profile can be established in a restricted indication.

The CHMP considered the need to provide additional information to refine the understanding about the interaction of panitumumab with KRAS mutation status in prospective studies, and having

consulted with the applicant considered the granting of a marketing authorisation subject to specific obligations to be reviewed annually by the Agency.

The CHMP considers that Vectibix falls within the scope of Regulation (EC) No 507/2006, with particular reference to Article 2, based on the following grounds. Vectibix aims at the treatment of metastatic colorectal cancer which a seriously debilitating and life-threatening disease.

The CHMP considers that Vectibix fulfils the requirements of Article 4 of Regulation (EC) No 507/2006 based on the following grounds:

(a) The main clinical efficacy data for Vectibix are based on a randomized trial of Vectibix plus best supportive care *vs.* best supportive care in patients with metastatic colorectal carcinoma. Vectibix was administered as monotherapy at the recommended dose of 6 mg/kg of bodyweight given once every two weeks. Patients to be included had to have documented evidence of disease progression during or after treatment with a fluoropyrimidine, irinotecan and oxaliplatin for metastatic colorectal carcinoma. In this randomised, controlled, clinical trial, a statistically significant improvement in progression-free survival has been observed among Vectibix treated patients compared with those who received best supportive care alone. In an analysis adjusting for potential bias from unscheduled assessments, based on all patients, the rate of disease progression or death in patients who received Vectibix was reduced by 40% relative to patients who received best supportive care alone. Additional retrospective efficacy analyses studied the association between *KRAS* mutation status determined in archived paraffin embedded tumour tissue and clinical outcome. In the *KRAS* wild-type subgroup, the rate of disease progression or death in patients who received Vectibix was reduced by 51% relative to patients that received best supportive care alone. No significant treatment effect was observed in the *KRAS* mutant group. The safety profile in the *KRAS* wild-type subgroup was considered acceptable. Thus, the benefit-risk profile of Vectibix monotherapy, as defined in Article 1(28a) of Directive 2001/83/EC, is positive in the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.
(b) Studies (20050181 and 20050203) to provide a better understanding of the role of the interaction between panitumumab and *KRAS* mutation status are ongoing and it is expected that results will be submitted in the agreed timeframe as specific obligations to be reviewed on a yearly basis. Ongoing trials, although conducted in different clinical settings from the proposed indication, will provide valuable information about the impact on the benefit-risk profile of the interaction between treatment effect of panitumumab and *KRAS* mutation status. Therefore, it is likely that the applicant will be in a position to provide the comprehensive clinical data.
(c) There are few treatment options available for patients with metastatic colorectal carcinoma after failure of prior chemotherapy containing 5-fluorouracil, irinotecan and oxaliplatin. Cetuximab, which acts as a signal transduction inhibitor of EGFR is approved for use in combination with irinotecan in patients with EGFR expressing metastatic colorectal cancer who have failed prior irinotecan therapy. Patients treated with chemotherapy and monoclonal antibodies tend to progress after a certain time and their only treatment option is best supportive care. The inability to select patients that respond to treatment is a pitfall of available treatment options in this setting. The retrospective analyses presented for Vectibix monotherapy indicated an interaction between treatment effect of panitumumab and *KRAS* mutation status. In the *KRAS* wild-type subgroup, the rate of disease progression or death in patients who received Vectibix was reduced by 51% relative to patients that received best supportive care. No significant treatment effect was observed in the *KRAS* mutant group. This interaction allows to select patients for treatment with panitumumab and to exclude patients that are unlikely to benefit from this type of treatment and for whom other options might be available. The ability to select patients with metastatic colorectal carcinoma who are likely to benefit from Vectibix monotherapy treatment, allowing physicians to make an informed decision about the best treatment options for patients having failed a number of previous combination regimens, is considered a major therapeutic advantage. Therefore, Vectibix will address an unmet medical need.
(d) In view of the favourable benefit-risk profile in the restricted indication, and the fact that the additional data required only concern the interaction between panitumumab and *KRAS* mutation,

the immediate availability on the market outweighs the risk inherent in the fact that additional data are still required.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk/benefit balance of Vectibix as monotherapy for the treatment of patients with EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens was favourable and therefore recommended the granting of the conditional marketing authorisation, subject to the following specific obligations: to provide results of ongoing studies 20050181 and 20050203.