17 March 2011
EMA/546839/2011
Human Medicines Development and Evaluation

Assessment report

Vectibix

panitumumab

Procedure No.: EMEA/H/C/000741/II/0017

Note

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

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Invented name/name:	Vectibix
International non-proprietary name/common name:	panitumumab

Indication summary (as last approved):	Treatment of metastatic colorectal carcinoma
Marketing authorisation holder:	Amgen Europe B.V.

1. Scope of the variation and changes to the dossier

Scope of the variation:	To extend the metastatic colorectal cancer indication to include the use of panitumumab in combination with FOLFOX in first line treatment and with FOLFIRI in second line treatment after failure of first-line fluoropyrimidine-based chemotherapy (excluding irinotecan), in patients with wild-type KRAS (Kirsten rat sarcoma) tumours based on safety and efficacy results from two pivotal phase 3 clinical studies (20050203 and 20050181) and other supportive clinical studies. Further amendments to the product information were made, in particular a contraindication against use of panitumumab in combination with FOLFOX in patients with mutant KRAS tumour status and special warnings that KRAS mutation status must always be determined prior to administration of panitumumab
Rapporteur: Co-Rapporteur:	Robert James Hemmings Eva Skovlund
For the re-examination: Rapporteur: Co-Rapporteur:	 Concepcion Prieto Yerro Jens Ersbøll
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	1, 2 and 5

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2. Steps taken for the assessment

Step	Step date
Submission date:	16 April 2010
Start of procedure:	25 April 2010
Rapporteur's assessment report circulated on:	21 June 2010
Co-Rapporteur's assessment report circulated on:	18 June 2010
Rapporteur's and Co-Rapporteur's joint updated assessment report circulated on:	16 July 2010
Request for supplementary information and extension of timetable adopted by the CHMP on :	22 July 2010
MAH's responses submitted to the CHMP on :	18 October 2010
Rapporteur's and Co-Rapporteur's joint assessment report on the MAH's responses circulated on:	26 November 2010
2nd Request for supplementary information and extension of timetable adopted by the CHMP on :	16 December 2010
The Integrated Summary Report of the GCP inspection carried out at the following sites of study 2005011, Leningrad Regional Oncology Dispensary, Institute of Oncology Vilnus University, University Multiprofile Hospital for Active Treatment 'Queen Joanna' Sofia and PPD Global Ltd, between 20 October 2010 and 20 December 2010 was issued on:	31 January 2011
MAH's responsesto the 2nd RSI submitted to the CHMP on :	15 February 2011
Rapporteur's and Co-Rapporteur's joint assessment report on the MAH's responses circulated on:	28 February 2011
An Oral explanation to the CHMP took place on :	15 March 2011
CHMP opinion:	17 March 2011

2.1. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Jens Ersbøll

- The applicant submitted written notice to the EMA on 30 March 2011 to request a re-examination of the Vectibix EMEA/H/C/000741/II/0017 CHMP opinion of 18 March 2011
- During its meeting on 11-14 April 2011, the CHMP appointed Concepcion Prieto Yerro as Rapporteur and Jens Ersbøll as Co-Rapporteur

- The applicant submitted the detailed grounds for the re-examination on 11 May 2011. The re-examination procedure started on 12 May 2011
- The Rapporteur's Assessment Report was circulated to all CHMP members on 08 June 2011. The Co-Rapporteur's Assessment Report was circulated to all CHMP members on 09 June 2011
- During a meeting of the SAG-Oncology on 10 June 2011, experts were convened to consider the grounds for re-examination
- The Rapporteurs circulated the Joint Addendum Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 14 June 2011
- During the CHMP meeting on 21 June 2011, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP
- During the meeting on 20-23 June 2011, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the variation to the terms of the marketing authorisation

3. Scientific discussion

3.1. Introduction

Panitumumab, a recombinant fully human IgG2 monoclonal antibody, binds with high affinity and specificity to the human Epidermal Growth Factor Receptor (EGFR), a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases. EGFR promotes cell growth in normal epithelial tissues and is expressed on a variety of tumour cells.

Panitumumab binds to the ligand binding domain of EGFR and inhibits receptor autophosphorylation induced by all known EGFR ligands. Binding of panitumumab to EGFR results in internalisation of the receptor, inhibition of cell growth, induction of apoptosis and decreased interleukin 8 (IL-8) and vascular endothelial growth factor (VEGF) production. The KRAS (Kirsten rat sarcoma 2 viral oncogene homologue) gene encodes a small, GTP-binding protein involved in signal transduction. A variety of stimuli, including that from the EGFR activates KRAS which in turn stimulates other intracellular proteins to promote cell proliferation, cell survival and angiogenesis. Activating mutations in the KRAS gene occur frequently in a variety of human tumours and have been implicated in both oncogenesis and tumour progression. KRAS mutations have been shown to be a negative predictive biomarker for anti-EGFR therapy.

Vectibix (panitumumab) was first authorised in the EU on 03 December 2007. Based on available data at the time of the application, panitumumab was granted a conditional marketing authorisation 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.

Amgen Europe B.V. submitted an application for a type II variation in April 2010 to extend the indication of Vectibix to 1st- and 2nd-line combinations with chemotherapy and proposed to revise the wording of the Vectibix indication as follows:

treatment of patients with wild-type KRAS metastatic colorectal cancer (mCRC)

- in combination with chemotherapy

- as monotherapy in patients after the failure of standard chemotherapy.

In their response to the first CHMP request for supplementary information, the MAH revised the wording of the proposed indication in combination with chemotherapy as follows:

- in combination with oxaliplatin- or irinotecan-based chemotherapy

After the second CHMP request for supplementary information, the MAH further revised the wording of the proposed indication in combination with chemotherapy as follows:

- in combination with FOLFOX or irinotecan-based chemotherapy.

3.2. Quality aspects

No new data related to pharmaceutical quality were submitted with this variation application, which is considered acceptable.

3.3. Non-clinical aspects

No new non-clinical data were submitted with this variation application, which is considered acceptable.

3.4. Clinical aspects

3.4.1. Introduction

Colorectal cancer (CRC) is the third most common cancer, comprising approximately 11% of all new cancers worldwide (Jemal et al, 2010). Of newly diagnosed patients, 15% to 25% have metastatic disease at diagnosis (Kindler and Shulman, 2001) and up to 50% of all patients eventually develop metastatic disease (Kindler and Shulman, 2001; McLeod et al, 2000). The 5-year survival rate is only 11% in patients with metastatic disease (Kindler and Shulman, 2001; Pazdur et al, 1999). Aside from cases of potentially resectable metastatic disease, mCRC cannot be cured with currently available chemotherapy regimens, and most patients will have progressive disease through multiple lines of therapy. In addition, some patients experience unacceptable toxicity when treated with other currently available agents. Thus, there remains a significant unmet medical need for alternative, effective treatment options for patients with mCRC.

The treatment of advanced colorectal cancer has evolved significantly in recent years. Over the past decade, treatment outcomes for patients with mCRC have improved due to the introduction of new agents. These improvements were made in a step-wise fashion and they have resulted in increases in median OS from approximately 12 months with bolus 5-fluorouracil (5-FU) alone to over 20 months with sequential combinations of irinotecan, oxaliplatin, and fluoropyrimidine chemotherapy. Oxaliplatin-based chemotherapy regimens (e.g. FOLFOX) and irinotecan-based chemotherapy regimens (eg, FOLFIRI) are currently recognised in clinical practice guidelines as the standard of care for initial and second-line treatment of mCRC in patients with good (ECOG 0/1) performance status (National Comprehensive Cancer Network, 2009; UK NICE, 2005; Tournigand et al, 2004). Studies have shown that in combination with 5-FU, oxaliplatin- and irinotecan-containing regimens are effective in both the initial and second-line settings, regardless of the sequence of administration (National Comprehensive Cancer Network, 2010; Tournigand et al, 2004).

The two key Phase III studies supporting this extension of indication were studies 20050203 (1st line treatment) and 20050181 (2nd line treatment) where panitumumab was combined with FOLFOX and FOLFIRI chemotherapies, respectively. Both pivotal phase III studies were conducted in a large number of centres (overall > 300) in Western, Central and Eastern Europe, Latin America, Australia, Canada, USA, South Africa, and Japan. The majority of patients were European, but patients were allocated to two geographic regions as defined by the MAH: Western Europe together with North America and Australia in one region and Central-Eastern Europe together with Latin America, South Africa and Japan in the Rest-Of-World (ROW) region.

Provision of the Clinical Study Reports (CSRs) for these studies fulfilled specific obligations SOB 005, 006, 009, 010, 012 (as a duplicate of 010 after its deadline was extended), 011 and 013 of the Vectibix conditional marketing authorization as a monotherapy treatment for mCRC.

A tabular overview of all clinical studies supporting the use of panitumumab in combination with chemotherapy for the treatment of wild-type KRAS mCRC is presented in the following Table 1.

Table 1: Summary of Key Clinical Studies for Panitumumab in Combination with Chemotherapy for Wild-Type *KRAS* mCRC

Protocol No.	Study Objectives (Primary and Secondary)	Study Design and Type of Control	Test Products; Route of administration; Dosage Regimen	Number of Patients	Diagnosis of Patients	1st or 2nd Line; Oxal vs Irino	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety Studies of Panitumumab Plus Chemotherapy in Patients With Metastatic Colorectal Cancer								
Controlled Studies – Chemotherapy								
20050203	Efficacy (PFS, OS, ORR, DOR, TTP), safety, tolerability	Phase 3 open-label, randomized, multicenter	1:1 Panitumumab 6.0 mg/kg + FOLFOX; IV; Q2W FOLFOX; IV; Q2W	Planned: 1150 Enrolled: 1183 593 Panitumumab + FOLFOX 590 FOLFOX alone	Previously untreated mCRC with either wild-type or mutant *KRAS* tumors	1st line; Oxal	Until disease progression or until unacceptable toxicity	Ongoing; Full CSR
20050181	Efficacy (OS, PFS, ORR, TTP, DOR), safety	Phase 3 multicenter, open-label, randomized	1:1 Arm 1: Panitumumab 6.0 mg/kg + FOLFIRI; IV; Q2W Arm 2: FOLFIRI; IV; Q2W	Planned: 1100 Enrolled: 1186 591 Arm 1 595 Arm 2	Previously treated mCRC	2nd line; Irino	Until disease progression or until unacceptable toxicity	Ongoing; Full CSR
Uncontrolled Studies – Chemotherapy								
20060314	Efficacy (ORR, rate of disease control, DOR, TTR, PFS, TTP, duration of stable disease, TTF, time to disease relapse following surgical intervention, resection rate), safety	Phase 2 multicenter, single-arm	Panitumumab 6.0 mg/kg + FOLFIRI; IV; Q2W	Planned: 150 Enrolled: 154	Previously untreated mCRC with either wild-type or mutant *KRAS* tumors	1st line; Irino	Until disease progression	Ongoing; Full CSR
20050184	Safety (incidence of ≥ G2 skin toxicities of interest), efficacy	Phase 2 multicenter, open-label, randomized	1:1 Panitumumab 6.0 mg/kg + FOLFIRI; IV; Q2W Panitumumab 9.0 mg/kg + irinotecan; IV; Q3W	Planned: 100 Enrolled: 95	mCRC with failed 1st line treatment due to disease progression or toxicity	2nd line; Irino	Until disease progression, unacceptable AE, death, withdrawal, or loss to follow-up	Complete: Full CSR
20060277	Efficacy (ORR, best response, PFS, rate of disease control DOR, OS, TTF, TTP, TTR), safety	Phase 2 multicenter, open-label, single-arm	Panitumumab 6.0 mg/kg + FOLFIRI; IV; Q2W	Planned: 110 Enrolled: 116	Previously treated mCRC	2nd line; Irino	Until disease progression, intolerability, death, or withdrawal	Complete; Full CSR
20062010	PK, safety	Phase 1 multicenter, open-label, single-arm	Panitumumab 6.0 mg/kg + irinotecan; IV; Q2W	Planned: 23 Enrolled: 28	Unresectable mCRC with no prior exposure to EGFR inhibitors	2nd line; Irino	Until disease progression or intolerability	Complete; Full CSR

CSR = clinical study report; FOLFIRI = irinotecan/5-FU/leucovorin combination chemotherapy given every 2 weeks with a 5-FU bolus followed by a 2-day 5-FU infusion; FOLFOX = oxaliplatin/5-FU/leucovorin combination chemotherapy given every 2 weeks; FU = fluorouracil; HAPA = human anti-panitumumab antibody; Irino = irinotecan; IV = intravenous; mCRC = metastatic colorectal cancer; NA = not applicable; ORR = objective response rate; Oxal = oxaliplatin; PFS = progression-free survival; PD = progressive disease; PK = pharmacokinetics; PRO = patient-reported outcomes; TTP = time to progression; QW = once weekly; Q2W = once every 2 weeks; Q3W = every 3 weeks

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has also 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.

Both pivotal phase III studies were conducted in a large number of centres worldwide. The centres were monitored by Amgen or a Contract Research Organisation (CRO) depending on their location. A few centres with high recruitment were audited by Amgen with an acceptable level of source data verification being performed; in addition, 4 centres were inspected by local Regulatory Authorities.

In both studies, the proportion of patients with important protocol deviations according to the protocol, i.e. thought to potentially impact the patient's safety or statistical analysis conclusions, was considered high, especially in the experimental arm (up to 50%). In study 20050203, efficacy results varied significantly between different geographic regions. Similarly, in study 20050181, the reporting of severe and serious adverse events varied significantly depending on the geographic region. Therefore, concerns were raised about the GCP compliance of these trials.

A GCP inspection of the CRO in the UK and of three sites of study 20050181 (in Bulgaria, Lithuania, and Russia) was conducted.

Among the deficiencies identified during the inspections two major findings were identified at the CRO site in connection with the data management, one major with regard to the safety data at the clinical investigator site in Lithuania and one major with regard to eligibility at the site in Bulgaria.

The minor findings were considered as "not having impact on the integrity of the patients or on the quality of data".

Based on these findings the inspection report concluded that the study was conducted in compliance with GCP at the sites and the CRO. It was the opinion of the inspectors that the patients in this study had received acceptable information about the conduct of the study and that the patients were well taken care of by a professional study team. No major concerns were identified during the inspections and it was the opinion of the inspectors that the data documented and reported in the study were credible. It was the recommendation of the inspectors that the results in the report could be used for evaluation and assessment of the application.

The CHMP noted that a number of weaknesses/errors were detected during the assessment of the data presented in the CSRs. It was considered that the quality control in study monitoring, data management and analysis was not of high level. However, based on the GCP inspection findings, it was accepted that these weaknesses may not have had a major impact on the overall conclusions of the trials.

3.4.2. Pharmacokinetics

Pharmacokinetic interaction studies

Drug-drug interactions with oxaliplatin and irinotecan were discussed. Panitumumab is not expected to have pharmacokinetic drug-drug interaction with oxaliplatin as their clearance mechanisms do not

overlap; therefore, no interaction study was conducted. As for irinotecan, potential pharmacokinetic interactions were addressed in the initial Marketing Authorisation Application through a cross-study comparison between panitumumab as monotherapy and as combination with IFL/FOLFIRI therapy. Based on this analysis, irinotecan did not appear to have an effect on the pharmacokinetics of panitumumab but the impact of panitumumab on the pharmacokinetics of irinotecan was inconclusive. Thus, the pharmacokinetics of irinotecan (administered at 180 mg/m^2 Q2W) and its active metabolite SN-38 were compared with and without concomitant panitumumab administration (6 mg/kg Q2W) in 19 patients with unresectable mCRC (study 20062010). The statistical summary of irinotecan and SN-38 pharmacokinetics is provided in Table 2.

Table 2: Comparisons of AUC and Cmax of Irinotecan and SN-38 With (cycle 2) and Without (Cycle 1) Panitumumab Administration

Parameter (units)	Cycle 2 [a] N	Cycle 2 [a] LSM[b]	Cycle 1[a] N	Cycle 1[a] LSM[b]	Ratio of cycle 2/cycle 1	90% Confidence Interval[c]
Irinotecan						
C_{max} (ng/mL)	19	1508	19	1539	0.980	(0.894, 1.074)
$AUC_{0\text{-last}}$ (hr*ng/mL)	19	10000	19	11149	0.897	(0.818, 0.983)
$AUC_{0\text{-inf}}$ (hr*ng/mL)	19	10100	19	11248	0.898	(0.819, 0.985)
SN-38						
C_{max} (ng/mL)	19	21.3	19	25.9	0.823	(0.731, 0.926)
$AUC_{0\text{-last}}$ (hr*ng/mL)	19	252.3	19	287.7	0.877	(0.788, 0.976)
$AUC_{0\text{-inf}}$ (hr*ng/mL)	16	282.0	17	326.0	0.865	(0.773, 0.968)

3.4.3. Discussion on clinical pharmacology

Due to the high variability of irinotecan concentrations (CV > 30%) it was hypothesised that panitumumab would not have a clinically important effect on the pharmacokinetics of irinotecan if the 90% CIs of the ratio of geometric means for the Cmax and AUC values for irinotecan with and without concomitant panitumumab administration fell within the interval of 0.70 – 1.43.

Actual results showed that the 90% CIs of the ratios for irinotecan lay within the 0.80 – 1.25 interval and only the lower limit of the 90% CIs of the ratios for SN-38 was slightly lower than 0.80; of note, SN-38 concentrations were significantly lower when irinotecan was combined with panitumumab (higher limit of the CIs below 1).

3.4.4. Conclusions on clinical pharmacology

Overall, the conclusion that panitumumab did not have any impact of clinical significance on irinotecan and SN-38 concentrations was endorsed.

3.5. Clinical efficacy

3.5.1. Dose response studies

No dose-response studies were submitted.

3.5.2. Main studies

Two pivotal Phase III studies supported this extension of indication, namely study 2005023 (1st line treatment) and study 20050181 (2nd line treatment) in which panitumumab was combined with FOLFOX and FOLFIRI chemotherapies, respectively.

Study 20050203 (1st line)

This was a multicentre, randomised, open-label, comparative study to evaluate the efficacy of panitumumab in combination with FOLFOX chemotherapy (oxaliplatin/5-fluorouracil/leucovorin) relative to FOLFOX alone in patients with previously untreated metastatic adenocarcinoma of the colon or rectum.

Methods

Study Participants

Main inclusion criteria

- men and women 18 years of age or older

- with histologically or cytologically confirmed adenocarcinoma of the colon or rectum

- with at least 1 unidimensionally measurable lesion of at least 20 mm per modified RECIST guidelines

- with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2

- with available paraffin-embedded tumour tissue from the primary tumour or metastasis

Main exclusion criteria

- history of or known presence of central nervous system metastases

- prior therapies including but not limited to chemotherapy, oxaliplatin, EGFR inhibitors, radiotherapy (≤ 14 days before randomization), or other investigational therapies (≤ 30 days before randomisation)

Treatments

One cycle of chemotherapy lasted 14 days.

Panitumumab was administered on *Day 1* of each cycle just prior to the administration of chemotherapy as an intravenous infusion at a dose of 6 mg/kg until patients developed disease progression or were unable to tolerate panitumumab.

The components of FOLFOX regimen (oxaliplatin, 5-FU, and LV) were obtained by each site according to routine institutional practice. The FOLFOX regimen was as follows:

- *Day 1*: oxaliplatin 85 mg/m^2 + LV 200 mg/m^2 racemate (or 100 mg/m^2 *l*-LV) IV infusion, followed by 5-FU 400 mg/m^2 IV bolus, followed by 5-FU 600 mg/m^2 as a 22-hour continuous IV infusion;

- *Day 2*: same as *Day 1* without oxaliplatin.

A standardised protocol was provided to adjust (i.e. withhold, reduce, or delay) the doses of panitumumab or chemotherapy in case of emergent toxicities. Patients receiving panitumumab plus FOLFOX who demonstrated objective response or who had stable disease but became intolerant to chemotherapy or panitumumab could continue panitumumab or chemotherapy, respectively, until disease progression or intolerance to study treatment.

Objectives

The primary objective was to assess whether panitumumab in combination with FOLFOX chemotherapy improved progression-free survival (PFS) compared to FOLFOX alone as first-line therapy for mCRC among patients with wild-type *KRAS* tumours and patients with mutant *KRAS* tumours.

Secondary objectives included evaluation of overall survival (OS), objective response rate (ORR), duration of response, time to progression, and safety and tolerability among patients with wild-type *KRAS* (WT) tumours and patients with mutant *KRAS* (MK) tumours.

Tertiary objectives were to evaluate time to response and patient-reported outcomes among patients with wild-type *KRAS* tumours and patients with mutant *KRAS* tumours and exploratory objectives were to investigate potential biomarker development based on assessment of blood cells, tumour cells and the proposed mechanism of action of the study drug among patients with wild-type *KRAS* tumours and patients with mutant *KRAS* tumours.

Outcomes/endpoints

Primary efficacy endpoint

Progression-free survival (PFS) by central radiological assessment, defined as the time from randomisation to disease progression per modified Response Evaluation Criteria in Solid Tumours (RECIST) criteria or death. Patients were to be evaluated every 8 weeks until disease progression. In addition to the investigator's assessments, scans for tumour response of all patients were centrally evaluated by a blinded panel of at least 2 blinded independent radiologists. The central review of radiographic data by the Independent Review Committee (IRC) was used for the primary analysis of efficacy to reduce potential bias resulting from the open-label nature of the study.

Secondary efficacy endpoints

Overall survival (OS) defined as the time from randomization to death; patients who were alive at the analysis data cut-off were censored at their last contact date.

Objective response rate (ORR) by central radiological assessment defined as the incidence of either a confirmed complete or partial response (CR or PR) while on the first-line treatment per modified RECIST, as determined by blinded independent central review

Time to progression defined as time from randomisation date to date of disease progression

Duration of response calculated only for those patients with a confirmed CR or PR as the time from the first CR or PR (subsequently confirmed within no less than 4 weeks) to first observed disease progression

Incidence of adverse events and significant laboratory changes

Tertiary efficacy endpoints

Time to response

Patient-reported outcomes (EQ-5D health state index score, EQ-5D overall health rating)

Sample size

Sample size considerations were focused on ensuring sufficient power in the wild-type KRAS stratum alone. It was estimated that 1150 patients (575 per arm) were needed to be randomized over 19 months (with about 900 from the original protocol and about 250 from the enrolment extension, with

14 months under the original protocol and 5 months for the enrolment extension) with a minimum follow-up of approximately 12 months to achieve 380 events for PFS in the Wild-type KRAS efficacy analysis set. With wild-type KRAS prevalence of 55% and a KRAS expected evaluation rate of 90%, 1150 randomized patients would produce about 570 patients that would be tested as wild-type KRAS and about 466 patients that would be tested as mutant KRAS.

Randomisation

Patients were randomly assigned in a 1:1 ratio to receive panitumumab plus FOLFOX or FOLFOX alone. Randomisation was centralised and stratified by geographic region (Western Europe, Canada, and Australia vs. Rest of World) and ECOG performance status (0 or 1 vs. 2).

Blinding (masking)

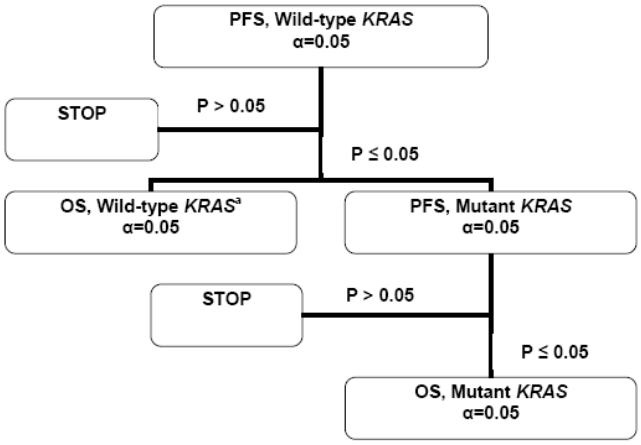
The study was open-label, as blinding was not possible because of expected skin-related toxicities in patients receiving panitumumab. To minimize bias in this non-blinded study, tumour assessment based on independent central review was used for the analysis of the primary endpoint.

Statistical methods

The goals of the statistical analysis of the study were to show whether there was an increase in PFS in patients treated with panitumumab plus FOLFOX versus FOLFOX alone:

- in the Wild-type KRAS Efficacy Analysis Set (primary)
- in the Mutant KRAS Efficacy Analysis Set (secondary).

A hierarchical testing procedure for PFS and OS in two primary analysis populations was designed as follows.



The data cut-off date for the primary analysis was set based on the date by which the PFS event goal (380 events: central radiology progressive disease or death) was projected to be achieved. To allow estimation of the median survival time, the primary analysis for overall survival was to occur when at least 50% of patients had an event.

Results

Participant flow

Out of 1378 patients screened, **1183** patients were randomised and included in the ITT Analysis Set; 593 were randomized to panitumumab plus FOLFOX and 590 to FOLFOX alone.

At the cut-off date of August 2009 most patients had discontinued all treatment:

- *In the Wild-type group*, 305 (94%) in the P+FX arm and 321 (97%) in the FX arm. Panitumumab was discontinued in 306 (94%) patients, with the most common reason being disease progression (158 [49%]). FOLFOX was discontinued in 628 (96%) patients: 307 (94%) in the P+FX and 321 (97%) in the FX arm. Among the patients who discontinued FOLFOX, the reason was disease progression for 147 (45%) patients in the P+FX arm and 170 (51%) patients in the FX arm.
- *In the Mutant KRAS group*: 202 (91%) in the P+FX arm and 198 (90%) in the FX arm. FOLFOX was discontinued in 400 (91%) patients (202 [91%] P+FX, 198 [90%] FX alone). The most common reason for ending FOLFOX was disease progression (126 [57%] P+FX, 119 [54%] FX alone). Panitumumab was discontinued in 202 (91%) patients, 126 (57%) because of disease progression.

The other main reasons for treatment discontinuations were adverse event (11 to 16% of the patients depending on the treatment arm and KRAS group) and patient request (6 to 16% of the patients).

There were slightly more patients with protocol deviations considered important as per protocol, i.e. thought to potentially impact the patient's safety or statistical analysis conclusions, in the P+FX arm (44%) than in the FX alone group (39%). The most common were "other treatment compliance", e.g. chemotherapy not per protocol (14%) or dosing in spite of neutropenia (33%), and "off-schedule study procedures" (13%).

Recruitment

The first patient was randomised on 23 August 2006 and the last patient was enrolled on 01 February 2008. Data cut-off date was 30 September 2008 for the PFS analysis and 28 August 2009 for the OS analysis.

Conduct of the study

The two pivotal Phase III studies in mCRC (20050203 and 20050181) were ongoing at the time of the retrospective analysis of KRAS in the pivotal monotherapy trial (Study 20020408), which demonstrated that the treatment effect of panitumumab as a single agent is confined to patients with wild-type KRAS mCRC (initial Marketing Authorisation Application). Subsequently, the protocols and statistical analysis plans (SAPs) for both studies were amended twice such that the treatment effect of panitumumab in combination with chemotherapy could be prospectively analysed by tumour KRAS status. The initial study protocol of study 20050203, dated 09 March 2006, was first amendment on 10 October 2007, before the enrolment period ended and prior to any interim efficacy analysis, so that a sufficient number of patients would be enrolled to enable adequate statistical power for analysis within the wild-type KRAS sub-population. The second amendment occurred on 21 January 2009, prior to any formal efficacy analysis or knowledge of patient KRAS tumour status and after input on Protocol 20050181 was received from the FDA and CHMP regarding implementation of data analysis according to KRAS status.

Baseline data

The ratio of patients enrolled from Western Europe, Canada and Australia versus the rest of the world was approximately 56:44 in both treatment arms. Most patients were male (63%) and Caucasian (90%). The median age was 62 years with 9% of the patients being ≥ 75 years. The demographic characteristics were well balanced between treatment arms in the WT group except for a lower proportion of women in the P+FX arm (33%) than in the FX arm (38%). The same was true in the MK

group (34% vs. 42%), where there were also more elderly (≥ 60 years) patients in the P+FX arm (45%) than in the FX arm (38%).

Disease characteristics are summarised in Tables 3 & 4. Overall, they were similar in WT and MK tumours except for a slightly higher proportion of colon cancers and a higher CEA concentration in the MK group. The vast majority of patients (about 95%) had a performance status score of 0 or 1. The disease characteristics were well balanced in the WT group, with only a slight difference in ECOG status favouring the P+FX arm. In contrast, in the MK group, a few factors showed an imbalance consistent with less disease burden in the FX group with less metastatic sites, and lower LDH and CEA levels.

Table 3: Main baseline characteristics (Wild-type KRAS Efficacy Analysis Set, Study 20050203)

	Panitumumab Plus FOLFOX (N = 325)	FOLFOX Alone (N = 331)	Total (N = 656)
Primary tumor type - n(%)			
Colon cancer	214 (66)	216 (65)	430 (66)
Rectal cancer	111 (34)	115 (35)	226 (34)
Months since primary diagnosis[a]			
N	320	328	648
Mean	9.8	10.0	9.9
SD	18.1	18.3	18.2
Median	2.1	2.1	2.1
Q1, Q3	1.2, 7.4	1.3, 6.9	1.2, 7.2
Min, Max	0, 130	0, 120	0, 130
Months since metastatic disease diagnosis[a]			
N	322	328	650
Mean	2.2	2.1	2.2
SD	3.5	3.3	3.4
Median	1.5	1.5	1.5
Q1, Q3	0.8, 2.4	0.9, 2.2	0.9, 2.3
Min, Max	0, 40	0, 45	0, 45
Location of sites of metastatic disease			
Liver only	59 (18)	57 (17)	116 (18)
Liver plus other sites	224 (69)	226 (68)	450 (69)
Other sites only	40 (12)	47 (14)	87 (13)
Missing/Unknown	2 (1)	1 (0)	3 (0)
Number of sites of metastatic disease			
1	67 (21)	68 (21)	135 (21)
2	113 (35)	116 (35)	229 (35)
≥3	143 (44)	146 (44)	289 (44)
Missing/Unknown	2 (1)	1 (0)	3 (0)
ECOG performance status - n(%)			
0	191 (59)	178 (54)	369 (56)
1	114 (35)	134 (40)	248 (38)
2	20 (6)	18 (5)	38 (6)
Missing/Unknown	0 (0)	1 (0)	1 (0)
CEA[c] - ug/L			
N	319	319	638
Mean	739.4	436.2	587.8
SD	4477.2	1347.7	3307.1
Median	35.8	32.2	33.5
Q1, Q3	7.0, 203.6	8.0, 166.1	7.4, 190.0
Min, Max	0, 71000	1, 12600	0, 71000
Elevated CEA above normal range - n(%)[d]	255 (80)	255 (80)	510 (80)
Baseline LDH concentration			
< 1.5 x ULN	219 (67)	221 (67)	440 (67)
≥ 1.5 x ULN	92 (28)	97 (29)	189 (29)
Missing/Unknown	14 (4)	13 (4)	27 (4)
< 2.0 x ULN	246 (76)	249 (75)	495 (75)
≥ 2.0 x ULN	65 (20)	69 (21)	134 (20)
Missing/Unknown	14 (4)	13 (4)	27 (4)

Table 4: Main baseline characteristics (Mutant KRAS Efficacy Analysis Set, Study 20050203)

	Panitumumab Plus FOLFOX (N = 221)	FOLFOX Alone (N = 219)	Total (N = 440)
Primary tumor type - n(%)			
Colon cancer	151 (68)	160 (73)	311 (71)
Rectal cancer	70 (32)	59 (27)	129 (29)
Months since primary diagnosis[a]			
n	220	215	435
Mean	9.2	8.4	8.8
SD	19.8	15.1	17.6
Median	2.1	2.2	2.2
Q1, Q3	1.4, 6.4	1.3, 6.7	1.4, 6.4
Min, Max	0, 188	0, 96	0, 188
Months since metastatic disease diagnosis[a]			
n	217	217	434
Mean	2.0	2.5	2.3
SD	2.0	6.0	4.5
Median	1.5	1.5	1.5
Q1, Q3	1.0, 2.2	1.0, 2.2	1.0, 2.2
Min, Max	0, 16	0, 70	0, 70
Number of sites of metastatic disease			
1	39 (18)	43 (20)	82 (19)
2	70 (32)	80 (37)	150 (34)
≥3	110 (50)	95 (43)	205 (47)
Missing/Unknown	2 (1)	1 (0)	3 (1)
Location of sites of metastatic disease			
Liver only	32 (14)	36 (16)	68 (15)
Liver plus other sites	156 (71)	159 (73)	315 (72)
Other sites only	31 (14)	23 (11)	54 (12)
Missing/Unknown	2 (1)	1 (0)	3 (1)
ECOG performance status - n(%)			
0	117 (53)	122 (56)	239 (54)
1	96 (43)	87 (40)	183 (42)
2	8 (4)	9 (4)	17 (4)
4	0 (0)	1 (0)	1 (0)
CEA[c] - ug/L			
n	212	211	423
Mean	520.4	736.1	628.0
SD	1505.5	4994.1	3681.9
Median	71.3	60.6	63.3
Q1, Q3	14.6, 254.3	9.5, 296.9	11.4, 267.2
Min, Max	1, 10466	0, 71000	0, 71000
Elevated CEA above normal range - n(%)[d]	188 (89)	170 (81)	358 (85)
Baseline LDH concentration			
< 1.5 x ULN	143 (65)	156 (71)	299 (68)
≥ 1.5 x ULN	73 (33)	59 (27)	132 (30)
Missing/Unknown	5 (2)	4 (2)	9 (2)
< 2.0 x ULN	168 (76)	176 (80)	344 (78)
≥ 2.0 x ULN	48 (22)	39 (18)	87 (20)
Missing/Unknown	5 (2)	4 (2)	9 (2)

Numbers analysed

Out of 1378 patients screened, **1183** patients were randomised and included in the ITT Analysis Set; 593 were randomized to panitumumab plus FOLFOX and 590 to FOLFOX alone.

Most patients (93%) were evaluable for KRAS status (KRAS Efficacy Analysis Set): 55% of patients had wild-type KRAS tumours (Wild-type KRAS Efficacy Analysis Set) and 37% had mutant KRAS tumours (Mutant KRAS Efficacy Analysis Set). The most common reasons for unevaluable KRAS status were lack of a sample available for testing and no tumour in specimen.

Outcomes and estimation

A summary of the main efficacy results in the ***WT group*** of the primary analysis (data cut off: 30/09/2008 for PFS (primary endpoint) and ORR and 28/08/2009 for OS) and of the final analysis submitted by the MAH (data cut-off: 02/08/2010) is shown in Table 5.

Table 5: Summary of efficacy endpoints (Central Assessment, Wild-type *KRAS* Efficacy Analysis Set, Study 20050203)

	Primary Analysis		Final Analysis	
Number of Subjects	Pmab + FOLFOX n=325	FOLFOX Alone n=331	Pmab + FOLFOX n=325	FOLFOX Alone n=331
Median PFS (95% CI) (months)	9.6 (9.2, 11.1)	8.0 (7.5, 9.3)	10.0 (9.3, 11.4)	8.6 (7.5, 9.5)
Absolute Difference in Median PFS (months)	1.6		1.4	
PFS Hazard Ratio (95% CI) (stratified log-rank p-value)	0.798 (0.656 to 0.971) (p = 0.0234)		0.799 (0.674 to 0.946) (p = 0.0092)	
On-treatment PFS Hazard Ratio (60 days) (95% CI) (stratified log-rank p-value)	0.779 (0.632, 0.961) (p = 0.0194)		0.765 (0.633, 0.924) (p = 0.0054)	
Median OS (95% CI) (months)	23.9 (20.3, 28.3)	19.7 (17.6, 22.6)	23.9 (20.3, 27.7)	19.7 (17.6, 22.7)
Absolute Difference in Median OS (months)	4.2		4.2	
OS Hazard Ratio (95% CI) (stratified log-rank p-value)	0.825 (0.669 to 1.018) (p = 0.0723)		0.878 (0.728 to 1.058) (p = 0.1710)	
Overall Response Rate - % (95% CI)	55.2 (49.6, 60.8)	47.7 (42.1, 53.3)	57.1 (51.5, 62.6)	47.5 (42.0, 53.1)
P-value	0.068		0.018	

Figures 1 and 2 present the Kaplan-Meier curves for PFS and OS in the primary analysis and figure 3 presents the OS Kaplan Meier curve for the final analysis. Figures 4 and 5 present forest plots of PFS and OS results from the primary analysis in different subpopulations.

Figure 1: Kaplan-Meier Plot of PFS Time (Central Assessment, Wild-type *KRAS* Efficacy Analysis Set, Study 20050203)

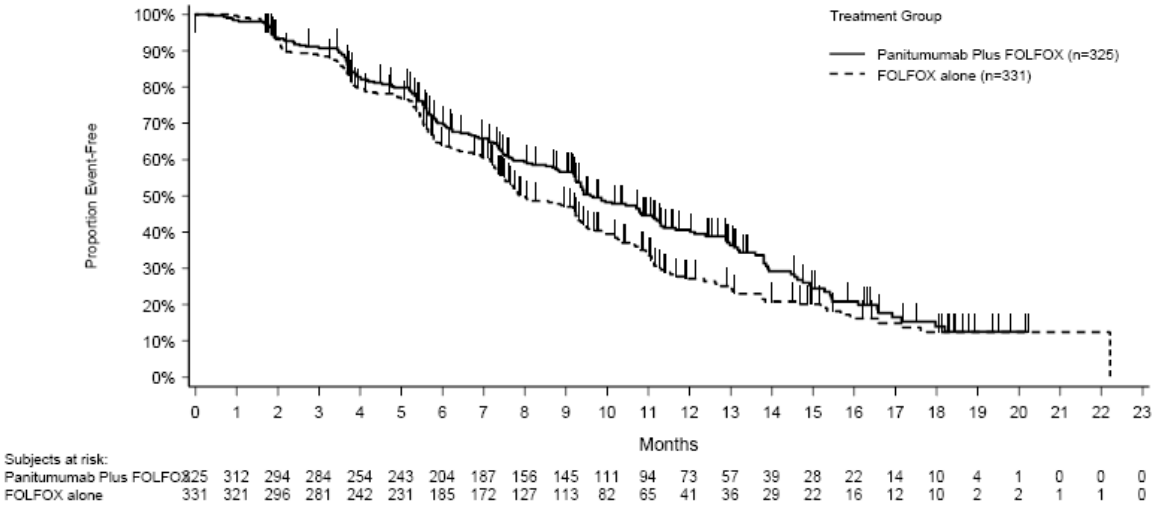


Figure 2: Kaplan-Meier Plot of OS Time (Wild-type *KRAS* Efficacy Analysis Set, Study 20050203)

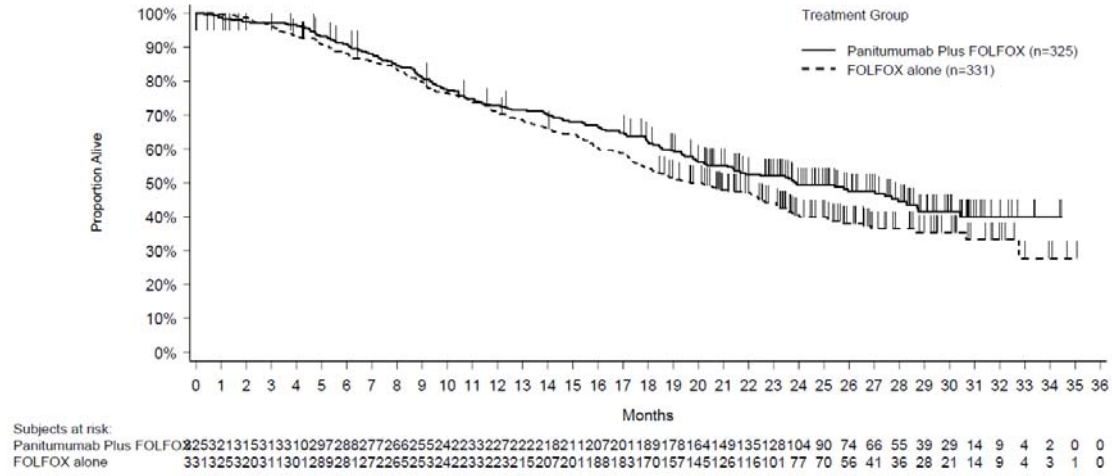


Figure 3: Kaplan-Meier Plot of Overall Survival Time (Final Analysis, Wild-type KRAS Efficacy Analysis Set, Study 20050203)

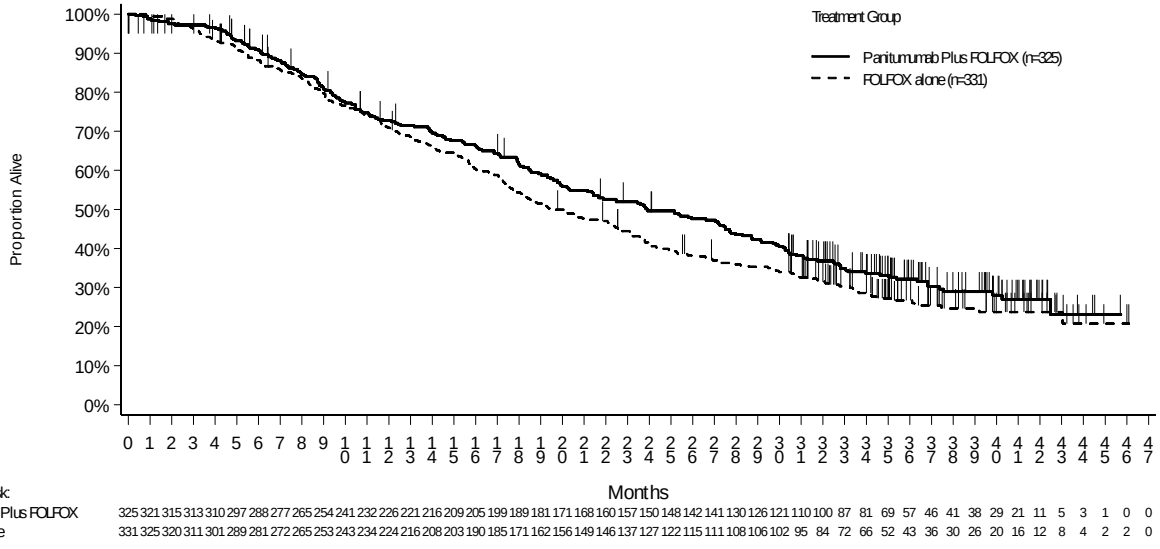


Figure 4: Forest Plot of Treatment Hazard Ratios (95% Confidence Interval) for PFS Within Subpopulations (Central Assessment, Wild-type *KRAS* Efficacy Analysis Set, Study 20050203)

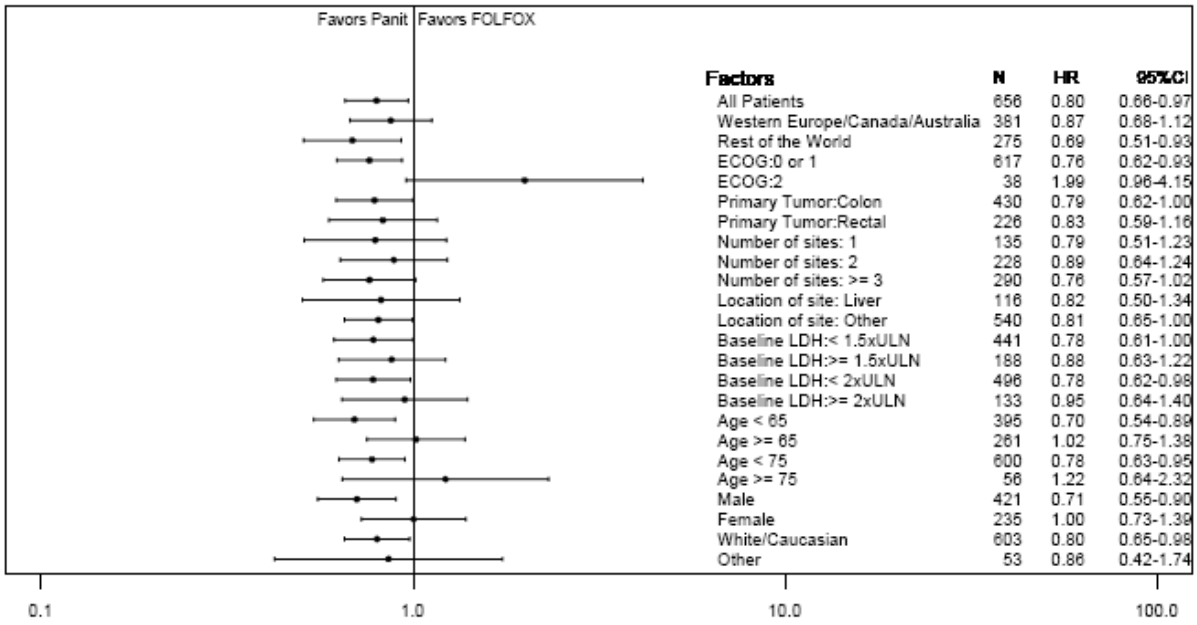
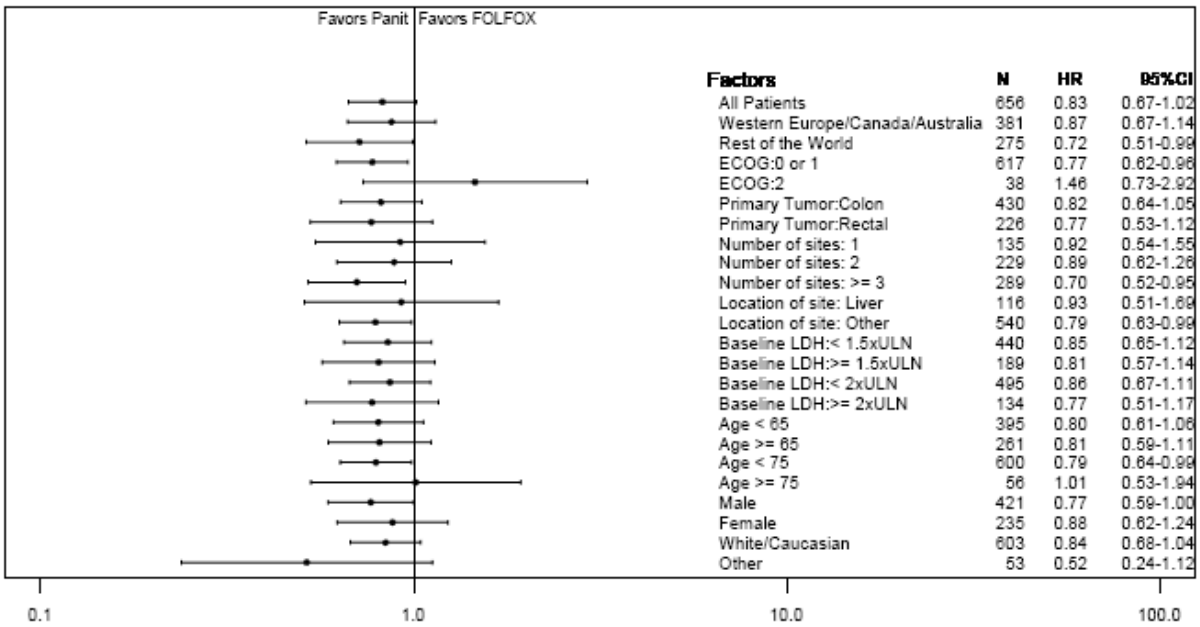


Figure 5: Forest Plot of Treatment Hazard Ratios (95% Confidence Interval) for OS Within Subpopulations (Wild-type *KRAS* Efficacy Analysis Set, Study 20050203)



The number of patients receiving subsequent anti-EGFR therapy of chemotherapy in the primary and final analysis is shown in the following Table 6.

Table 6: Subsequent therapy (Wild-type *KRAS* Efficacy Analysis Set, Study 20050203)

	Primary Analysis		Final Analysis	
Number of Subjects	Pmab + FOLFOX n=325	FOLFOX n=331	Pmab + FOLFOX n=325	FOLFOX n=331
Subjects receiving subsequent anti-EGFR therapy (n, %)	26 (8.0)	59 (17.8)	42 (12.9)	84 (25.4)
Median months from randomization to subsequent anti-EGFR therapy (Q1, Q3)	17.9 (14.0.20.9)	10.8 (7.7, 17.4)	21.5 (15.9, 29.4)	15.6 (9.4, 25.2)
Subjects receiving subsequent chemotherapy (n, %)	173 (53.2)	205 (61.9)	191 (58.8)	214 (64.7)
Median months from randomization to subsequent chemotherapy (Q1, Q3)	10.5 (7.2, 15.5)	9.7 (6.8, 13.1)	11.5 (7.5, 16.9)	10.0 (7.1, 14.1)

The main efficacy results in the ***MK group*** (primary analysis) are shown in Table 6 and Figures 6 and 7.

Table 7: Summary of efficacy endpoints (Central Assessment, Mutant KRAS Efficacy Analysis Set, Study 20050203)

	Panitumumab Plus FOLFOX		FOLFOX Alone
Progression-free survival (months)			
N	221		219
Subjects who progressed/died - n(%)	167 (76)		157 (72)
Median time (95% CI)	7.3 (6.3,8.0)		8.8 (7.7,9.4)
Log-rank test stratified by Region and ECOG score			
Normal score		2.28	
P-value		0.0227	
Hazard ratio (95% CI) stratified by Region and ECOG score		1.294 (1.036,1.616)	
Overall survival (months)			
N	221		219
Subjects who died - n(%)	152 (69)		142 (65)
Median (95% CI)	15.5 (13.1, 17.6)		19.3 (16.5, 21.8)
Log-rank test stratified by Region and ECOG score			
Normal score		1.83	
P-value		0.0678	
Hazard ratio (95% CI) stratified by Region and ECOG score		1.241 (0.984,1.566)	

	Panitumumab Plus FOLFOX		FOLFOX Alone
Objective tumour response			
N	215		211
Subject responding -n(%)	85 (40)		85 (40)
Rate (95% CI) - %	39.53 (32.95, 46.41)		40.28 (33.61, 47.24)
Difference in rates (95% CI)		-0.75 (-10.30, 8.81)	
Odds ratio (95% CI) stratified by Region and ECOG score		0.98 (0.65,1.47)	

Figure 6: Kaplan-Meier Plot of PFS Time (Central Assessment, Mutant *KRAS* Efficacy Analysis Set, Study 20050203)

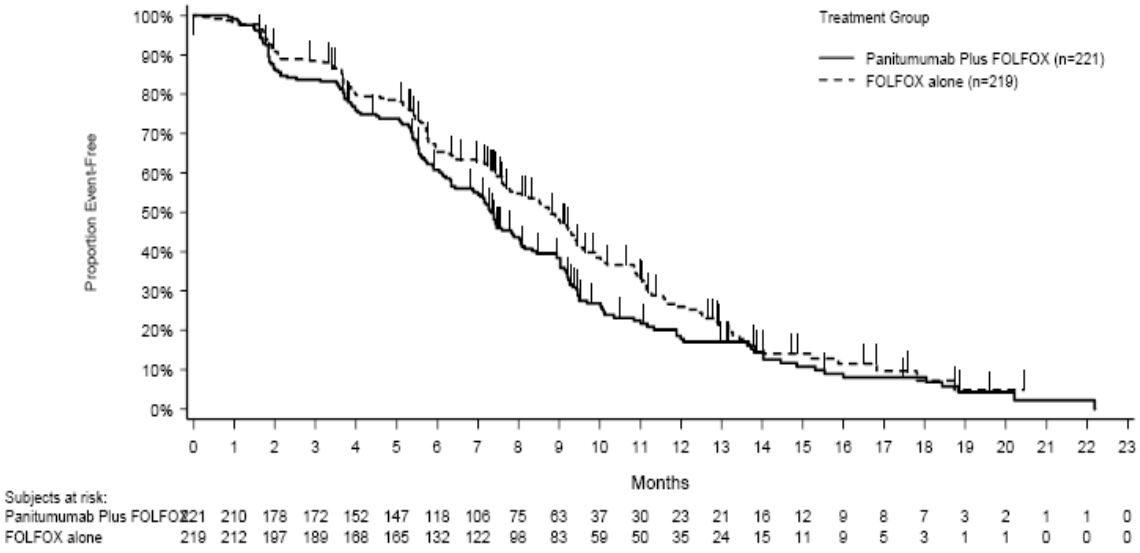
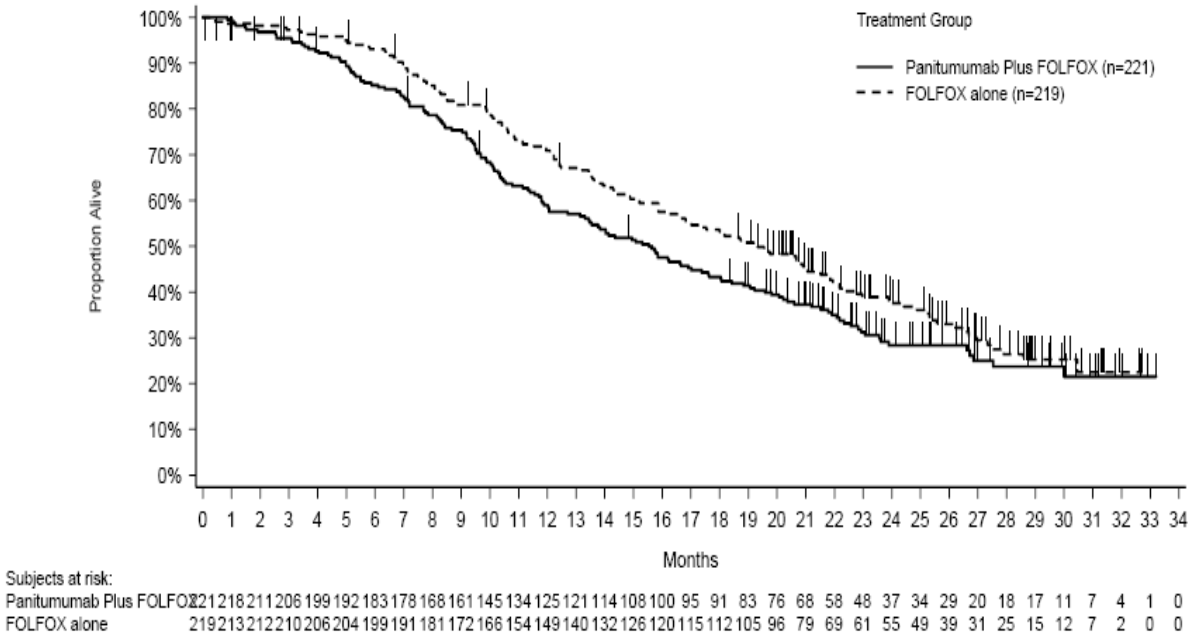


Figure 7: Kaplan-Meier Plot of OS Time (Mutant *KRAS* Efficacy Analysis Set, Study 20050203)



Finally, Patients Reported Outcomes (PRO) were assessed every 4 weeks while patients were on treatment. Approximately two-thirds of expected assessments were collected. Quality of life was not significantly affected by treatment with panitumumab. Numerically, the results were in favour of FOLFOX alone (data not shown).

Ancillary analyses

The MAH submitted a large number of ancillary analyses (data not shown).

Study 20050181 (2nd line)

This was a multicentre, randomised, open-label, comparative study to evaluate the efficacy of panitumumab in combination with FOLFIRI chemotherapy (irinotecan/5-fluorouracil/leucovorin) relative to FOLFIRI alone in patients with previously treated metastatic adenocarcinoma of the colon or rectum.

Methods

Except for previous and concomitant therapy, and the stratification factors, the design and study population of this study were the same as those of study 20050203.

Study Participants

As this was a study of second-line treatment, patients should have previously received one prior chemotherapy regimen consisting of first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) but this should have been stopped for at least 30 days before randomisation. Disease progression either while receiving or ≤ 6 months after the last dose of prior first-line therapy was to be radiographically documented per modified RECIST criteria.

Treatments

FOLFIRI chemotherapy was administered on *Day 1* of each treatment cycle at the following starting doses: irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 racemate (or 200 mg/m^2 *l*-LV), 5-FU bolus 400 mg/m^2, 5-FU infusion 2400 mg/m^2.

Objectives

The objective was to investigate and assess the treatment effect of panitumumab plus FOLFIRI on OS and/or PFS in patients receiving panitumumab plus FOLFIRI vs. FOLFIRI alone in the Wild-type KRAS Efficacy Analysis Set (primary goal) and in the Mutant KRAS Efficacy Analysis Set (secondary goal).

Outcomes/endpoints

PFS and OS were co-primary endpoints.

Sample size

The study was initially estimated to require 1100 patients to investigate the treatment effect on OS and/or PFS in the intention-to-treat (ITT) Analysis Set. Based on evidence from previous trials strongly suggesting that any clinically meaningful benefit of anti-EGFR therapy is limited to patients with wild-type KRAS tumours, the goal of the sample size considerations was to ensure adequate power to demonstrate an improvement in OS and/or PFS among patients with wild-type KRAS tumours.

Although patient follow-up time was lengthened, the original sample size goal was considered sufficient and was therefore not revised.

Randomisation

The randomisation was stratified by prior oxaliplatin exposure, prior bevacizumab exposure, and ECOG performance status.

Blinding (masking)

This was an open-label study and central radiology review was used for tumour assessments, based on the same considerations as for study 20050203.

Statistical methods

The two co-primary endpoints, PFS and OS, were analysed independently using a p-value of 0.01 and 0.04, respectively. Comparisons using the mutant KRAS efficacy analysis set were contingent on first demonstrating a significant difference in the Wild-type population.

The timing of the primary analyses of OS and PFS were event-driven based on the target OS and PFS event goal within the Wild-type KRAS Efficacy Analysis Set (380 events for both OS and PFS). To preserve trial integrity, although the analysis of PFS proceeded regardless of the OS outcome, it was not performed until the earlier of a positive interim OS analysis or the primary OS analysis.

Results

Participant flow

Out of 1345 patients screened, **1186** were enrolled into this study and included in the ITT analysis set; 591 patients were randomized to panitumumab plus FOLFIRI and 595 were randomized to FOLFIRI alone.

Almost all patients (98%) had stopped treatment at the cut-off date of 30 April 2009. The median duration of follow-up was around 40-45 weeks in the MK group and in the FOLFIRI alone (FI) arm of the WT group; it was longer in the Panitumumab + FOLFIRI (P+FI) arm of the WT group (58 weeks).

The most frequent reason for discontinuation of FOLFIRI was disease progression per investigator assessment, which was slightly more frequent in the MK group (66%) than in the WT group (59%). There were no notable differences between the treatment arms for the various reasons for discontinuation.

There were more patients with important protocol deviations in the P+FI arm (50%) than in the FI alone arm (44%). The most common deviations were "other treatment compliance" (e.g. incorrect doses of chemotherapy or dosing in spite of neutropenia) and "entry/eligibility". Protocol deviations regarding patient eligibility included absence or more than one prior chemotherapy (3%), absence of radiographically documented progressive disease (6%) or randomisation within 30 days of the last dose of chemotherapy (15%), as well as non compliance to chemotherapy or off-schedule scans.

Recruitment

The first patient was enrolled on 30 June 2006 and the last patient was enrolled on 13 March 2008. Data cut-off date was 08 April 2008 for the PFS analysis and 30 April 2009 for the OS and response analysis.

Conduct of the study

As mentioned before for study 20050203, the protocol and statistical analysis plan (SAP) for study 20050181 was amended such that the treatment effect of panitumumab in combination with chemotherapy could be prospectively analysed by tumour KRAS status. The initial study protocol, dated 29 November 2005 was amended twice (on 09 March 2006 and 04 April 2008). Amendment 1 occurred before any patients were enrolled, and amendment 2 occurred after all patients were enrolled. With the second amendment, the primary objective of this study was amended to incorporate analysis by KRAS status.

Baseline data

The ratio of patients enrolled from Western Europe, Australia and USA versus the rest of the world was 61:39 in both treatment arms. Most patients were male (61%) and Caucasian (96%). The median age was 61 years with 7% of the patients being ≥ 75 years. The demographic characteristics were well balanced between treatment arms in the WT. In the MK group, there were notably less patients ≥ 65 years in the P+FI arm (36%) than in the FI arm (45%).

Disease characteristics are summarised in Tables 8 & 9. They were well balanced in the WT group; in the MK group, there were more patients with ≥ 3 metastatic sites in the P+FI arm (52% vs. 47%).

Table 8: Main baseline characteristics (Wild-type KRAS Efficacy Analysis Set, Study 20050181)

	Panitumumab Plus FOLFIRI (N = 303)	FOLFIRI Alone (N = 294)	Total (N = 597)
Primary tumor type - n(%)			
Colon cancer	187 (62)	189 (64)	376 (63)
Rectal cancer	116 (38)	105 (36)	221 (37)
Months since primary diagnosis[a]			
n	295	284	579
Mean	17.9	19.7	18.8
SD	16.2	21.7	19.1
Median	12.3	12.1	12.3
Q1, Q3	8.3, 21.4	8.1, 23.1	8.3, 22.0
Min, Max	2, 103	3, 198	2, 198
Months since metastatic disease diagnosis[a]			
n	291	284	575
Mean	10.7	11.1	10.9
SD	6.5	7.4	7.0
Median	9.6	9.7	9.6
Q1, Q3	6.4, 13.3	6.7, 13.4	6.6, 13.3
Min, Max	1, 38	0, 50	0, 50
Number of sites of metastatic disease			
1	61 (20)	69 (23)	130 (22)
2	99 (33)	86 (29)	185 (31)
≥3	143 (47)	137 (47)	280 (47)
Missing/Unknown	0 (0)	2 (1)	2 (0)
Location of sites of metastatic disease			
Liver only	51 (17)	59 (20)	110 (18)
Liver plus other sites	205 (68)	189 (64)	394 (66)
Other sites only	47 (16)	44 (15)	91 (15)
Missing/Unknown	0 (0)	2 (1)	2 (0)
ECOG performance status - n(%)			
0	152 (50)	152 (52)	304 (51)
1	136 (45)	121 (41)	257 (43)
2	15 (5)	20 (7)	35 (6)
3	0 (0)	1 (0)	1 (0)

Table 9: Main baseline characteristics (Mutant KRAS Efficacy Analysis Set, Study 20050181)

	Panitumumab Plus FOLFIRI (N = 238)	FOLFIRI Alone (N = 248)	Total (N = 486)
Primary tumor type - n(%)			
Colon cancer	156 (66)	164 (66)	320 (66)
Rectal cancer	82 (34)	84 (34)	166 (34)
Months since primary diagnosis[a]			
n	231	234	465
Mean	18.1	15.4	16.7
SD	16.5	13.4	15.1
Median	12.2	10.9	11.6
Q1, Q3	8.6, 21.5	7.3, 17.0	8.0, 19.6
Min, Max	2, 152	2, 82	2, 152
Months since metastatic disease diagnosis[a]			
n	234	235	469
Mean	11.1	10.2	10.6
SD	7.7	7.1	7.4
Median	9.5	9.0	9.3
Q1, Q3	6.7, 12.9	6.2, 12.4	6.6, 12.7
Min, Max	0, 68	1, 80	0, 80
Number of sites of metastatic disease			
1	45 (19)	46 (19)	91 (19)
2	68 (29)	83 (33)	151 (31)
≥3	124 (52)	117 (47)	241 (50)
Missing/Unknown	1 (0)	2 (1)	3 (1)
Location of sites of metastatic disease			
Liver only	37 (16)	35 (14)	72 (15)
Liver plus other sites	166 (70)	172 (69)	338 (70)
Other sites only	34 (14)	39 (16)	73 (15)
Missing/Unknown	1 (0)	2 (1)	3 (1)
ECOG performance status - n(%)			
0	114 (48)	119 (48)	233 (48)
1	110 (46)	114 (46)	224 (46)
2	14 (6)	15 (6)	29 (6)

The two treatment arms were well balanced with respect to prior surgical resections (83-87%) and radiotherapy (16%-20%).

In the *WT group*, prior chemotherapy in the P+FI and FI included fluorouracil (74% vs. 71%), folinic acid (55% vs. 50%), oxaliplatin (67% vs. 65%), bevacizumab (18% vs. 20%). The median time to progression on prior therapy was 6.7 months (95% CI: 6.2, 7.4) in the P+FI arm and 7.1 months (95% CI: 6.4, 7.8) in the FI arm.

In the *MK group*, prior chemotherapy in the P+FI and FI included fluorouracil (73% vs. 64%), folinic acid (54% vs. 46%), oxaliplatin (69% vs. 68%) and bevacizumab (19% vs. 17%). The median time to progression on prior therapy was 6.9 months (95% CI: 6.3, 8.0) in the P+FI arm and 6.7 months (95% CI: 5.9, 7.4) in the FI arm.

Numbers analysed

Out of 1345 patients screened, **1186** were enrolled into this study and included in the ITT analysis set; 591 patients were randomized to panitumumab plus FOLFIRI and 595 were randomized to FOLFIRI alone. Most patients (91%) were evaluable for KRAS status. The most frequent reasons that patients were not evaluable were lack of tumour in the specimen or insufficient quality of DNA recovered from the specimen for testing. Similar percentages of patients in the panitumumab plus FOLFIRI arm and FOLFIRI alone arm had wild-type KRAS tumours (51% and 49%) or mutant KRAS tumours (40% and 42%).

Outcomes and estimation

A summary of the main efficacy results in the ***WT group*** of the primary analysis (data cut off: 08/04/2008 for PFS and 30/04/2009 for OS and ORR) and of the final analysis submitted by the MAH (data cut-off: 02/09/2010) is shown in Table 10 and Figures 8, 9 and 10. Figures 11 and 12 present forest plots of PFS and OS results from the primary analysis in different subpopulations.

Table 10: Summary of efficacy endpoints (Central Assessment, Wild-type group, Study 20050181)

	Primary Analysis		Final Analysis	
Number of Subjects	Pmab + FOLFIRI n=303	FOLFIRI Alone n=294	Pmab + FOLFIRI n=303	FOLFIRI Alone n=294
Median PFS (95% CI) (months)	5.9 (5.5, 6.7)	3.9 (3.7, 5.3)	6.7 (5.8, 7.4)	4.9 (3.8, 5.5)
Absolute Difference in Median PFS (months)	2.0		1.8	
PFS Hazard Ratio (95% CI)a (stratified log-rank p-value)	0.732 (0.593 to 0.903) (p = 0.0036)		0.820 (0.692 to 0.972) (p = 0.0231)	
On-treatment PFS Hazard Ratio (60 days) (95% CI) (stratified log-rank p-value)	0.684 (0.548, 0.854) (p = 0.0008)		0.726 (0.600, 0.878) (p = 0.0010)	
Median OS (95% CI) (months)	14.5 (13.0, 16.0)	12.5 (11.2, 14.2)	14.5 (13.0, 16.1)	12.5 (11.2, 14.2)
Absolute Difference in Median OS (months)	2.0		2.0	
OS Hazard Ratio (95% CI) (stratified log-rank p-value)	0.854 (0.702 to 1.039) (p = 0.1154)		0.922 (0.775 to 1.098) (p = 0.3660)	
Overall Response Rate - % (95% CI)	35.4 (29.9, 41.1)	9.8 (6.6, 13.9)	36.0 (30.6, 41.8)	9.8 (6.6, 13.8)
P-value	< 0.0001		< 0.0001	

Figure 8: Kaplan-Meier Plot of PFS Time (Primary analysis, Central Assessment, Wild-type *KRAS* Efficacy Analysis Set, Study 20050181)

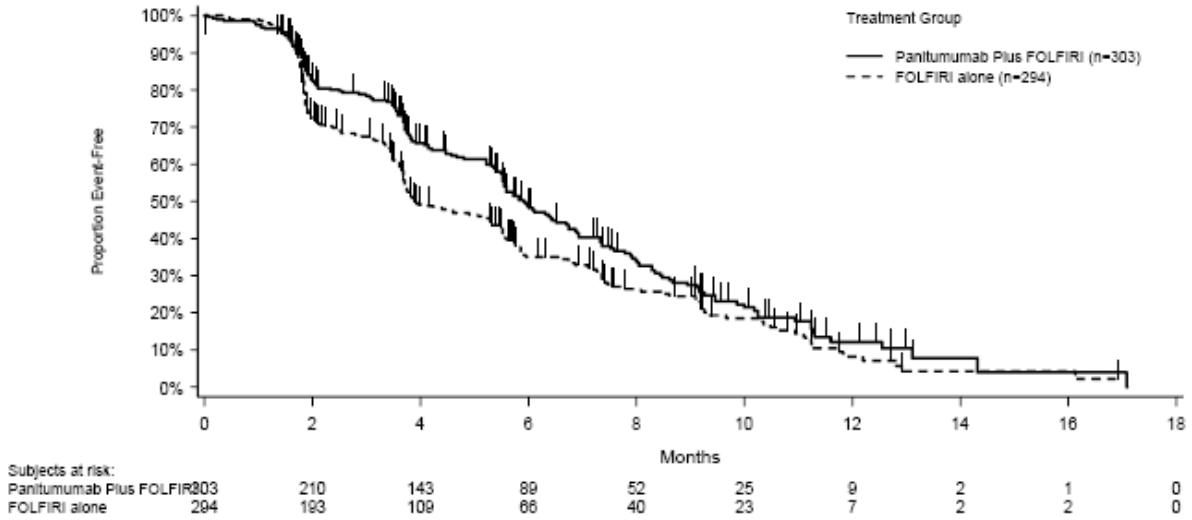


Figure 9: Kaplan-Meier Plot of OS Time (Primary analysis, Wild-type *KRAS* Efficacy Analysis Set, Study 20050181)

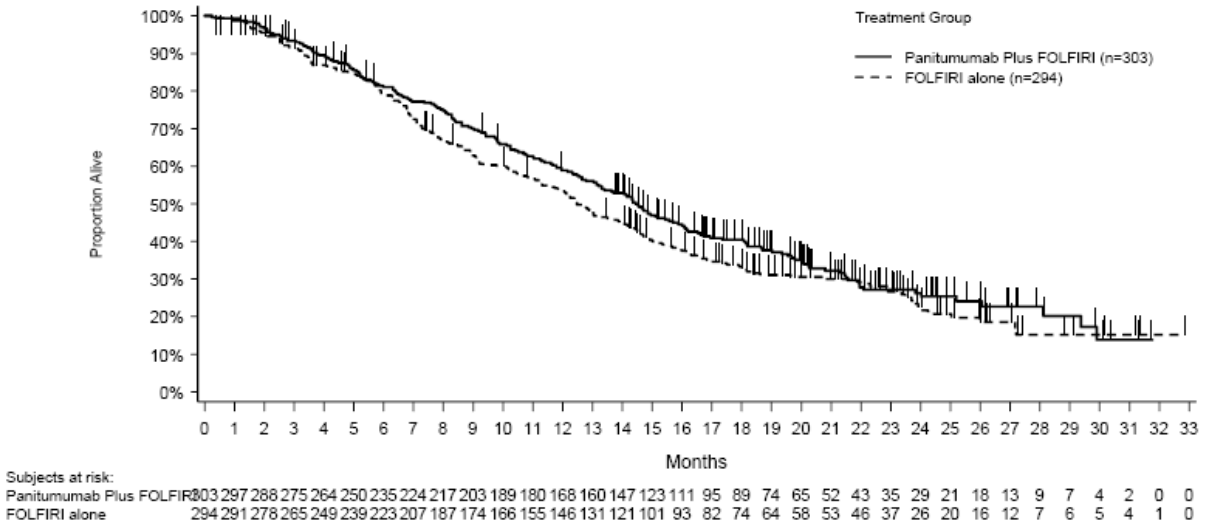


Figure 10: Kaplan-Meier Plot of OS Time (Final analysis, Wild-type *KRAS* Efficacy Analysis Set, Study 20050181)

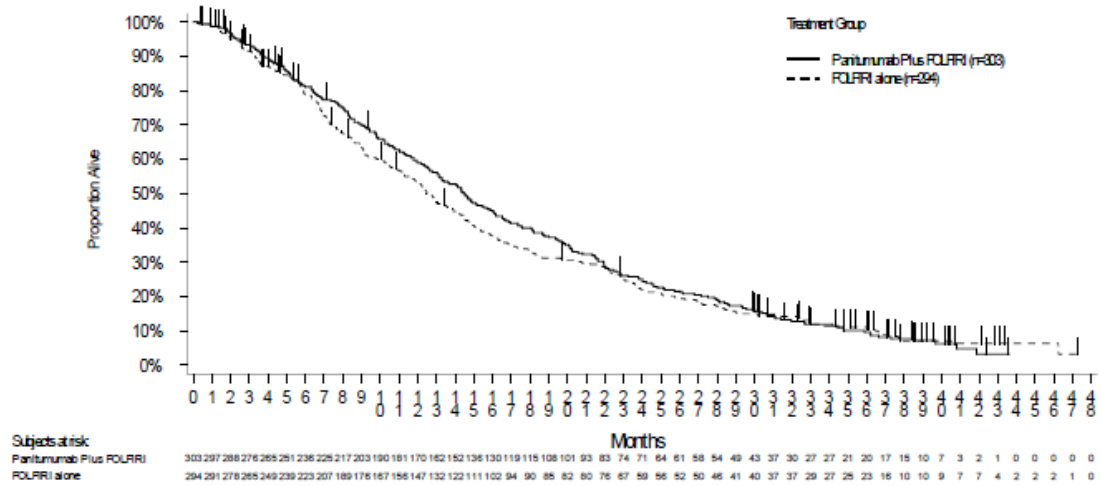


Figure 11: Forest Plot of Treatment Hazard Ratios (95% Confidence Interval) for PFS Within Subpopulations (Central Assessment, Wild-type *KRAS* Efficacy Analysis Set, Study 20050181)

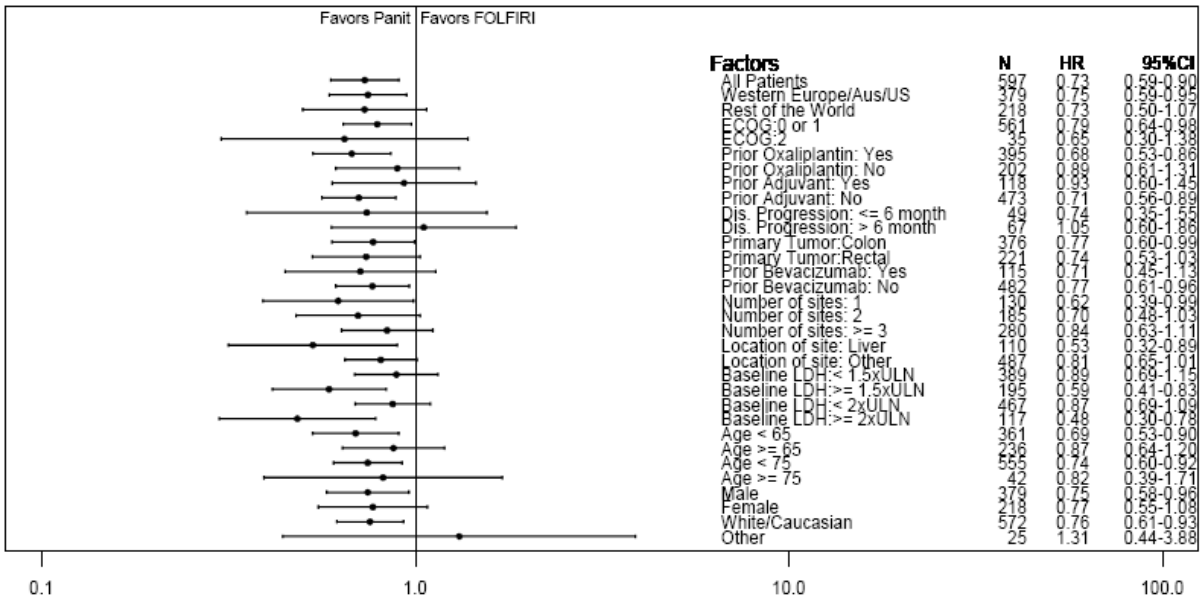
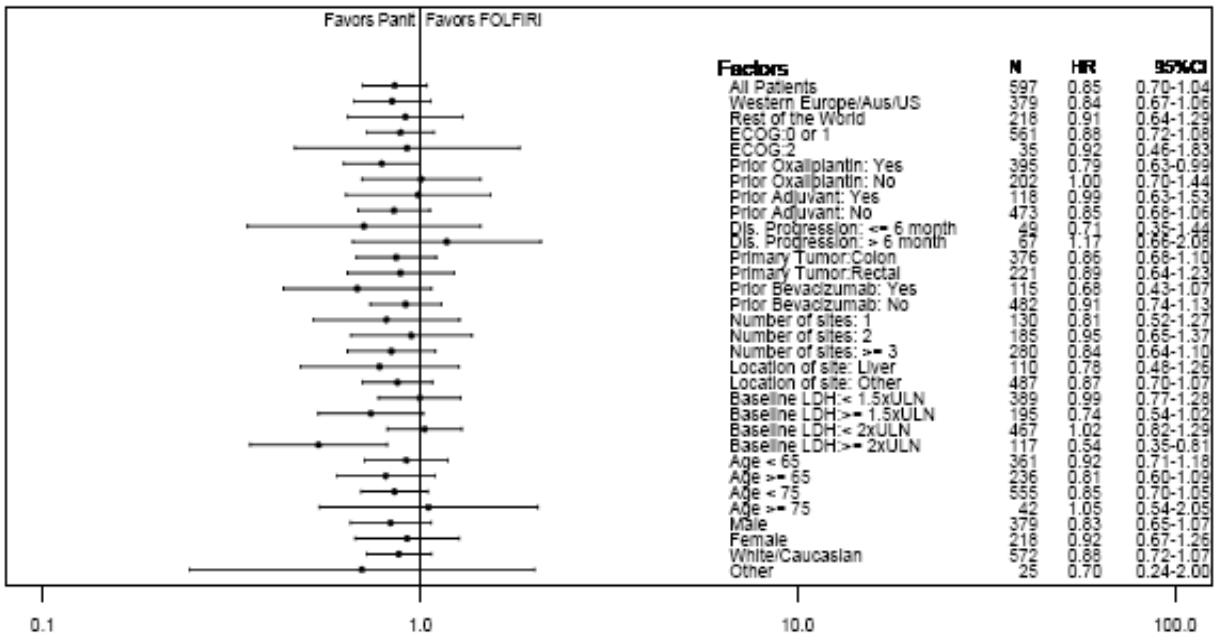


Figure 12: Forest Plot of Treatment Hazard Ratios (95% Confidence Interval) for OS Within Subpopulations (Wild-type *KRAS* Efficacy Analysis Set, Study 20050181)



The number of patients receiving subsequent anti-EGFR therapy of chemotherapy in the primary and final analysis is shown in the following Table 11.

Table 11: Subsequent therapy (Wild-type *KRAS* Efficacy Analysis Set, Study 20050181)

	Primary Analysis		Final Analysis	
Number of Subjects	Pmab + FOLFIRI n=303	FOLFIRI Alone n=294	Pmab + FOLFIRI n=303	FOLFIRI Alone n=294
Subjects receiving subsequent anti-EGFR therapy (n, %)	31 (10.2)	90 (30.6)	38 (12.5)	101 (34.4)
Median months from randomization to subsequent anti-EGFR therapy (Q1, Q3)	11.8 (6.0, 15.6)	7.6 (5.2, 11.1)	12.4 (7.4, 20.0)	7.9 (5.3, 13.7)
Subjects receiving subsequent chemotherapy (n, %)	142 (46.9)	142 (48.3)	160 (52.8)	148 (50.3)
Median months from randomization to subsequent chemotherapy (Q1, Q3)	9.9 (6.0, 13.6)	7.6 (4.8, 11.3)	10.9 (6.7, 15.5)	7.8 (5.1, 12.0)

A summary of the main efficacy results in the ***MK group*** is shown in Table 12 and Figures 13 and 14.

Table 12: Summary of efficacy endpoints (Central Assessment, Mutant KRAS group, Study 20050181)

	Panitumumab Plus FOLFIRI		FOLFIRI Alone
Progression-free survival (months)			
N	238		248
Subjects who progressed/died - n(%)	162 (68)		161 (65)
Median time (95% CI)	5.0 (3.8, 5.6)		4.9 (3.6, 5.6)
Log-rank test stratified by ECOG score, prior bevacizumab exposure and prior oxaliplatin exposure			
Normal score		-1.46	
P-value		0.1448	
Hazard ratio (95% CI) stratified by ECOG score, prior bevacizumab exposure and prior oxaliplatin exposure		0.846 (0.677, 1.059)	
Overall survival (months)			
N	238		248
Subjects who died - n(%)	181 (76)		193 (78)
Median (95% CI)	11.8 (10.4, 13.3)		11.1 (10.3, 12.4)
Log-rank test stratified by ECOG score, prior bevacizumab exposure and prior oxaliplatin exposure			
Normal score		-0.60	
P-value		0.5503	
Hazard ratio (95% CI) stratified by ECOG score, prior bevacizumab exposure and prior oxaliplatin exposure		0.939 (0.764, 1.154)	

	Panitumumab Plus FOLFIRI	FOLFIRI Alone
Objective tumour response		
N	232	237
Subject responding -n(%)	31 (13)	33 (14)
Rate (95% CI) - %	13.36 (9.26, 18.43)	13.92 (9.78, 19.00)
Difference in rates (95% CI)	-0.56 (-7.12, 6.02)	
Odds ratio (95% CI) stratified by ECOG score, prior bevacizumab exposure and prior oxaliplatin exposure	1.00 (0.56,1.76)	

Figure 13: Kaplan-Meier Plot of PFS Time (Central Assessment, Mutant *KRAS* Efficacy Analysis Set, Study 20050181)

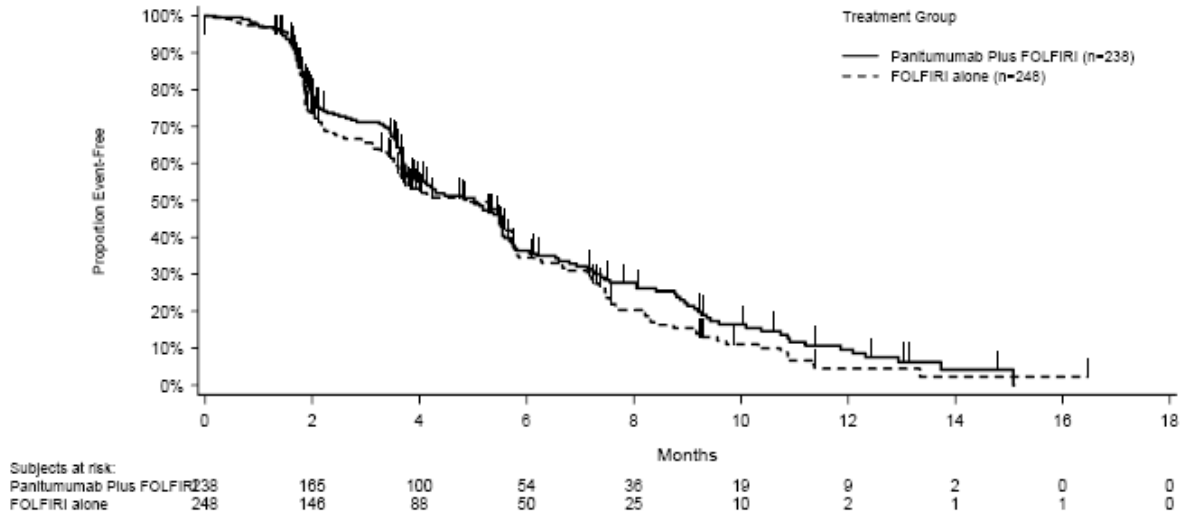
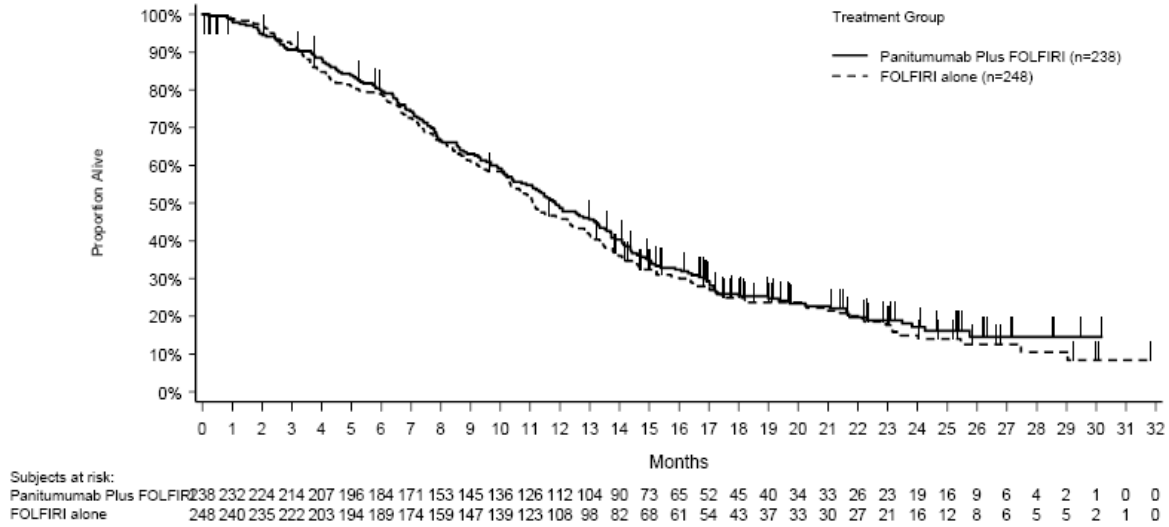


Figure 14: Kaplan-Meier Plot of OS Time (Mutant *KRAS* Efficacy Analysis Set, Study 20050181)



With regard to Patient Reported Outcomes (PROs), quality of life was not significantly affected by treatment with panitumumab and numerically, the results were in favour of FOLFIRI alone (data not shown). In the WT group, this result is supported by a higher proportion of patients with a deterioration of their performance according to their ECOG score in the P+FI arm (47%) than in the FI arm (37%).

Ancillary analyses

The MAH submitted a large number of ancillary analyses (data not shown).

Analysis performed across trials (pooled analyses and meta-analysis)

A pooled analysis of the two pivotal trials (20050203, 20050181) described above and of three phase II single arm studies (20060314, 20060277 and 20050184) is presented under supportive studies below.

Predictive and prognostic values of EGFR and KRAS biomarkers

To be eligible for studies 20050203 and 20050181, patients were required to have a paraffin-embedded tumour tissue from the primary tumour or metastasis available for central biomarker testing; however, patient eligibility criteria were unselected for EGFR expression. To evaluate the potential effect of EGFR staining parameters on efficacy endpoints, multivariate models were used to explore the predictive value of the various EGFR staining parameters for PFS, OS, and objective response rate among patients with wild-type KRAS tumour status. These parameters included levels of EGFR membrane and cytoplasmic staining intensity (0, 1+, 2+, 3+), and extent of EGFR membrane and cytoplasmic staining (percentage of cells).

Among patients who were evaluable for EGFR, no EGFR parameter was identified as having predictive value on efficacy endpoints of PFS, OS, or objective response rate in either study (data not shown).

Analyses to explore the predictive effect of KRAS mutation status on efficacy outcomes were performed. The results for the primary analysis of the quantitative interaction test in Study 20050203 indicated a significant interaction between treatment and KRAS status for PFS ($p = 0.0083$), which was confirmed in sensitivity analyses. The predictive value of KRAS status was significant for OS, as well, but no predictive value was found for response rate (data not shown).

The clinical utility of KRAS was not statistically demonstrated in Study 20050181. No significant interaction was observed between treatment and KRAS status for PFS (data not shown).

Clinical studies in special populations

No studies in special populations were submitted.

Supportive studies

Three phase II single arm studies (20060314, 20060277 and 20050184) are supportive of the efficacy of panitumumab in patients with wild-type KRAS mCRC (see Table 13). Study 20060314 was designed to provide data on the safety and efficacy of panitumumab in combination with FOLFIRI in patients not previously treated for mCRC (first-line). Study 20060277 was designed to evaluate the safety and efficacy of panitumumab plus FOLFIRI in patients who had received one prior regimen (including bevacizumab) for mCRC. Study 20050184, which combined panitumumab plus irinotecan-containing regimens as second-line therapy, was performed to determine if pre-emptive skin therapy could

mitigate the dermatological toxicity known to be associated with anti-EGFR therapy. As in the phase III studies, these studies have enrolled patients unselected for KRAS status.

A descriptive summary of results across the 5 studies was presented by the MAH. A total of 2733 patients were enrolled in the first-line setting (n = 1337) or second-line setting (n = 1396). 91% to 95% of patients across studies were evaluable for KRAS status. Similar percentages of patients across studies and treatment arms had wild-type KRAS tumours (49% to 56%) or mutant KRAS tumours (39% to 42%).

Across all 5 studies, approximately two-thirds of patients had colon cancer and approximately one-third had rectal cancer (which reflects the distribution of CRC in the general population), and most were men (54-66%) and white (76-98%). Patient age ranged from 21 to 86 years with little variation between studies; median age ranged from 59.0 to 65.5 years.

A summary of ORR, PFS and OS results in patients with WT tumours is presented in Table 13.

Table 13: Kaplan-Meier Estimates for ORR (local assessment), PFS and OS (where available, Wild-Type KRAS Efficacy Analysis Set)

	First Line			Second Line			
	20050203		20060314	20050181		20050184	20060277
	Panitumumab Plus FOLFOX (N=325)	FOLFOX Alone (N=331)	Panitumumab Plus FOLFIRI (N=85)	Panitumumab Plus FOLFIRI (N=302)	FOLFIRI Alone (N=293)	Panitumumab Plus FOLFIRI or Irinotecan (N=49)	Panitumumab Plus FOLFIRI (N=64)
Subjects responding -n(%)	194 (60)	162 (49)	48 (56)	107 (35)	38 (13)	11 (22)	15 (23)
Rate (95% CI)[a] - %	59.69 (54.14,65.07)	48.94 (43.44,54.47)	56.47 (45.28,67.20)	35.43 (30.04,41.11)	12.97 (9.34,17.36)	22.45 (11.77,36.62)	23.44 (13.75,35.69)
Difference in rates (95% CI)[b]		10.75 (2.91,18.41)	N/A		22.46 (15.47,29.17)	N/A	N/A

	First Line			Second Line			
	20050203 Central Assessment		20060314 Investigator Assessment	20050181 Central Assessment		20050184 Central Assessment	20060277 Investigator Assessment
	Panitumumab Plus FOLFOX (N = 325)	FOLFOX Alone (N = 331)	Panitumumab Plus FOLFIRI (N = 86)	Panitumumab Plus FOLFIRI (N = 303)	FOLFIRI Alone (N = 294)	Panitumumab Plus FOLFIRI or Irinotecan (N = 49)	Panitumumab Plus FOLFIRI (N = 64)
Kaplan-Meier quartiles - months[c]							
Q1 (95% CI)[b]	5.6 (5.2, 6.0)	5.3 (4.1, 5.5)	5.8 (5.3, 7.3)	3.5 (2.5, 3.7)	1.9 (1.8, 2.5)	2.1 (1.9, 4.6)	2.3 (1.8, 3.7)
Median (95% CI)[b]	9.6 (9.2, 11.1)	8.0 (7.5, 9.3)	8.9 (7.6, 14.3)	5.9 (5.5, 6.7)	3.9 (3.7, 5.3)	6.0 (4.3, 6.8)	5.9 (4.5, 7.7)
Q3 (95% CI)[b]	14.9 (13.9, 16.6)	13.0 (11.1, 15.2)	14.8 (13.2, NE)	9.3 (8.3, 10.3)	8.6 (7.3, 9.7)	10.8 (6.4, 12.0)	8.8 (7.7, 10.5)

	First Line		Second Line			
	20050203		20050181		20050184	20060277
	Panitumumab Plus FOLFOX (N = 325)	FOLFOX Alone (N = 331)	Panitumumab Plus FOLFIRI (N = 303)	FOLFIRI Alone (N = 294)	Panitumumab Plus FOLFIRI or Irinotecan (N = 49)	Panitumumab Plus FOLFIRI (N = 64)
Kaplan-Meier quartiles – months[b]						
Q1 (95% CI)[a]	10.8 (9.4, 14.0)	10.6 (9.1, 12.3)	8.0 (6.4, 9.0)	6.8 (5.9, 7.3)	8.2 (4.5, 10.9)	6.5 (5.4, 8.4)
Median (95% CI)[a]	23.9 (20.3, 28.3)	19.7 (17.6, 22.6)	14.5 (13.0, 16.0)	12.5 (11.2, 14.2)	13.7 (10.0, NE)	11.4 (9.0, 17.4)
Q3 (95% CI)[a]	NE (NE, NE)	NE (32.8, NE)	25.2 (21.5, 29.9)	23.7 (19.6, 26.0)	NE (15.7, NE)	NE (17.2, NE)

3.5.3. Discussion on clinical efficacy

The two phase III studies (20050203, 20050181) were randomised and controlled, the sample size was acceptably large and the statistical methods employed were deemed appropriate. Given the well-known skin-related toxicities of panitumumab, the open-label design of the two pivotal studies is considered acceptable. The study protocols of both studies were amended twice but for both studies the study integrity was preserved since the changes were motivated by data external to the trials, and they were implemented after full enrolment and before any efficacy analysis and determination of KRAS status was performed.

In both studies, there was a high rate of treatments ended due to 'subject request'. This potentially covers various motives in reality, including adverse events and disease progression, but patients withdrawing due to own request were not reclassified according to information in the narratives, so that the analysis of treatment discontinuations cannot be considered accurate and reliable.

In study 20050203, there were slightly more patients with protocol deviations considered important as per protocol, i.e. thought to potentially impact the patient's safety or statistical analysis conclusions, in the P+FX arm (44%) than in the FX alone group (39%). The most common were "other treatment compliance", e.g. chemotherapy not per protocol (14%) or dosing in spite of neutropenia (33%), and "off-schedule study procedures" (13%). The rate of important protocol deviations is considered high with notable differences between countries/regions although the rate of the most severe protocol violations seems acceptable (<10%).

Similarly, in study 20050181, protocol deviations regarding patient eligibility, e.g. absence or more than one prior chemotherapy (3%), absence of radiographically documented progressive disease (6%) or randomisation within 30 days of the last dose of chemotherapy (15%), as well as non compliance to chemotherapy or off-schedule scans, raised concerns about the GCP compliance of the study and led to the GCP inspection mentioned before.

In patients with WT tumours

Both phase III studies demonstrated a statistically significant but modest increase in PFS as reflected by a small absolute difference in median survival (1.4 - 1.8 months) and hazard ratios around 0.80 in the most mature analyses.

In the primary analysis of the first line study (20050203), the addition of panitumumab to FOLFOX resulted in a modest increase in PFS (the primary endpoint) with an absolute difference in median survival of 1.6 months and an HR of 0.80 (0.66, 0.97), which was statistically significant ($p = 0.023$). The investigator assessment of PFS was in good agreement with the independent assessment with no signs of relevant bias and might give a better estimate of efficacy than the central assessment due to informative censoring in the latter analysis; it showed an even smaller benefit of only 1.2 months (primary analysis, data not shown).

In the primary analysis of the second line study (20050181), with the addition of panitumumab to FOLFIRI, a modest increase in PFS was shown as reflected by an absolute difference in median survival of 2.0 months and an HR of 0.73 (0.59, 0.90), which was statistically significant ($p = 0.004$). However, in the latest PFS analysis, the difference appeared smaller and much less significant (absolute difference in median survival of 1.8 months; HR = 0.82 (0.69, 0.97); $p = 0.023$), to the point that it becomes borderline to the $p<0.01$ threshold required in the primary analysis to preserve an overall 5% type I error. Therefore, the evidence of longer PFS cannot be considered as robust. The PFS analysis according to investigator assessment showed an absolute difference in median survival of 0.6 months at the primary analysis and 1.7 months in a later analysis; results showed good concordance between investigator and central assessment (data not shown).

In both studies and in sensitivity analyses, PFS results were robust to the type of population and analysis chosen.

In terms of OS, although both studies showed a trend favourable to the addition of panitumumab, it is questionable whether the survival difference observed is not due to chance and is clinically meaningful. In the FOLFOX study (20050203) a favourable trend (albeit not statistically significant) was shown on OS with Kaplan-Meier curves starting to separate after 1 year. The absolute difference in median survival of about 4 months is difficult to understand on the basis of the PFS results. In the second line FOLFIRI study (20050181), the same absolute difference in median survival of 2.0 months was observed in the primary analysis for both PFS and OS, the co-primary endpoint of the study in 2nd line treatment. Actually, Kaplan-Meier curves were separated only between 6 and 20 months and the difference did not reach significance (HR = 0.85; 0.70, 1.04 – p = 0.12). The MAH argued that the difference in OS was small due to more patients in the FOLFIRI arm receiving anti-EGFR therapies after disease progression (31% vs. 10%), but sensitivity analyses were not able to support this argument (see Table 11).

The objective tumour response to panitumumab was initially marginal in first-line treatment (55% vs. 48%) but increased slightly in the final analysis (57% vs. 48%); it was highly significant in second-line treatment (35% vs. 10%). The clinical relevance of response rate in this disease setting has not been established for this type of agent.

In the first-line study with FOLFOX, the findings lack internal consistency insofar as PFS and OS results in the WT subgroup are entirely driven by the ROW population, i.e. Central-Eastern Europe, Latin America, and South Africa. The difference between Kaplan-Meier curves in the Western-Europe/Canada/Australia region is marginal for PFS and nonexistent for OS, with even a higher mortality with panitumumab up to 15 months. This might partly be explained by an incidence of post-progression anti-EGFR therapy that was 3 times higher in the FOLFOX alone arm (27%) compared with the panitumumab plus FOLFOX arm (9%) while it was low and similar between arms (6%) for patients enrolled in the ROW region.

Similarly, there was no evidence of benefit (neither PFS, nor OS) in patients older than 75 years (HR for both PFS and OS greater than 1 in favour of FOLFOX alone) with a higher number of deaths (67%) in the panitumumab + FOLFOX arm than in the FOLFOX arm (57%) in the primary analysis. Even in the large subgroup of patients ≥ 65 years, the HR point estimate for the PFS was 1.0 with no difference in ORR (46% in both treatment arms). Likewise, adding panitumumab to FOLFOX appeared harmful in the small subgroup of patients with ECOG score of 2, where significantly shortened PFS (median 4.8 vs. 7.6 months; HR = 2.30; p = 0.03) and OS (median 7.0 vs. 11.7 months; HR = 1.83; p = 0.09) were observed togeher with increased toxicity.

In the subgroup analyses of the second line study with FOLFIRI, the positive effect of panitumumab on PFS and OS appeared more pronounced in patients with worse prognosis as reflected by prior oxaliplatin treatment and high baseline LDH levels. In addition, the effect on ORR and PFS did not seem to diminish with older age as it did in the FOLFOX study, although the HR point estimate for OS was 1.05 in the few patients older than 75 years. However, even in the largest group of patients aged < 65 years, an apparent benefit in PFS (HR=0.69) did not translate into clear OS benefit (HR = 0.92). Also, in contrast with the other study, the positive effects of panitumumab appeared more pronounced in the Western Europe/Australia/US region than in the ROW region (i.e. Central-Eastern Europe), but the results were still broadly comparable.

At the time of the conditional approval of Vectibix, the CHMP stated that the clinical efficacy was small on the basis of a small increase in PFS. Moreover, measures of overall Quality of Life did not indicate that panitumumab had a clear positive impact on Quality of Life. Therefore, additional data on Quality of Life using a validated scale were requested as Specific Obligations (SOB 06, 10). The various

analyses of QoL data did not show any benefit of adding panitumumab but rather a numerical trend in favour of chemotherapy alone (data not shown).

In patients with MK tumours

With the combination of panitumumab with FOLFOX, a deleterious impact was observed on time to progression, PFS (absolute difference in median survival of 1.5 months; HR of 1.29 (1.04, 1.62); p = 0.023), and OS (absolute difference in median survival of about 4 months; HR = 1.24 (0.98, 1.57; p = 0.069). Of note in the interim analysis, this difference was highly significant (p = 0.003). In contrast to the curves in the WT group, the Kaplan-Meier curves of OS separated from the start of the trial and this finding was consistent in both geographic regions. The absence of objective tumour response to panitumumab was expected but a clear negative effect on time to progression, PFS and OS when it was combined with oxaliplatin-based chemotherapy remains an unexplained finding. This is considered a major concern since the proportion of patients with KRAS mutations potentially treated with panitumumab is unknown and very difficult to estimate. The reasons for such wrong treatments are multiple and include non evaluable test results, unreliable test methods, or mutations not detectable by the test used.

In contrast, the combination of panitumumab with FOLFIRI does not appear harmful, and thus, this negative effect seems to be specific to the combination with oxaliplatin chemotherapy.

Predictive value of biomarkers in overall population

Overall, KRAS status was not consistently shown to be prognostic for PFS or OS in both studies. However, analyses to explore the predictive effect of KRAS mutation status on efficacy outcomes in FOLFOX study 20050203 indicated a significant interaction between treatment and KRAS status for PFS and OS but not for response rate. This result is consistent with overall results for PFS in this study, which significantly favoured the panitumumab plus chemotherapy arm in patients with wild-type KRAS tumours, but showed a negative effect in the panitumumab plus chemotherapy arm of patients with mutant KRAS tumours that also reached statistical significance.

The clinical utility of KRAS was not statistically demonstrated in Study 20050181. No significant interaction was observed between treatment and KRAS status for PFS. The lack of significance was expected, since the interaction test had low power for the observed magnitude of variability in PFS treatment effects between the KRAS subgroups. Pre-conditions for an OS interaction test were not met, although descriptive analysis results were similar to those for PFS. A planned descriptive interaction test for objective response achieved nominal significance, where a large treatment effect was essentially confined to the wild-type KRAS subgroup.

Both studies confirmed that a positive objective response to panitumumab was mainly confined to wild-type KRAS tumours while no objective response was seen in tumours with mutations. However, while a positive effect was observed on disease progression in patients with WT tumours, inconsistent effects were seen in patients with MK tumours: either neutral (on the positive side) with FOLFIRI or clearly negative with FOLFOX. It should also be remembered that the positive effect of panitumumab in patients with WT tumours was abrogated when it was combined with chemotherapy and bevacizumab. Moreover and given that KRAS determination is critical for the indication of panitumumab, the small benefit in wild-type KRAS tumours observed in phase III trials where KRAS status was centrally diagnosed cannot be generalised to a broad clinical setting, where the reliability of KRAS diagnosis has not yet been established. Taken together, these results still do not provide a full understanding of the predictive value of KRAS testing.

Among patients who were evaluable for EGFR, no EGFR parameter was identified as having predictive value on efficacy endpoints of PFS, OS, or objective response rate in either study. Based on these

results, the MAH argued that the wording "EGFR expressing" should be removed from the current monotherapy indication.

Many technical reasons have been advocated for the lack of association between EGFR detection by immunochemistry and response to EGFR-targeted treatment. More recently, tumours with an increased EGFR gene copy number as assessed by FISH or CISH have been shown to be dependent on the EGFR pathway for their survival and growth. There is some evidence that normal diploid EGFR gene copy number may predict tumour resistance to EGFR-targeted treatment. Therefore, the absence of predictive value on efficacy endpoints is highly dependent on the method used and is only relevant to IHC staining. Furthermore, even if the analyses from the combination studies indicate that EGFR expression is not predictive of efficacy it is not obvious that this would necessarily be the case with panitumumab as later line monotherapy.

Finally, the small effect of anti-EGFR therapies on wild-type KRAS tumours is not surprising since it is now known that a number of other mutations in the EGFR signalling pathway may confer resistance to these therapies. Other biomarkers such as BRAF, PIK3CA/PTEN, or NRAS but also EGFR gene copy number, EGFR ligands (epiregulin and amphiregulin), single nucleotide polymorphisms in codon 497 of EGFR, or levels of EGFR downstream signalling phosphoproteins (e.g. pMEK1, pP70S6K) may increase the predictive power for response to treatment and are awaiting validation in clinical trials.

3.5.4. Conclusions on the clinical efficacy

The two pivotal studies do not show robust evidence of benefit for the addition of panitumumab to oxaliplatin- or irinotecan-based chemotherapies in the treatment of wild-type KRAS tumours. Furthermore, the harmful effect of the combination with oxaliplatin in patients with mutant KRAS tumours is a major concern.

3.6. Clinical safety

Patient exposure

The main safety analysis was conducted on the patients with mCRC:

- who received oxaliplatin-based chemotherapy with/without panitumumab in Study 20050203
- and those who received irinotecan-based chemotherapy with/without panitumumab in Studies 20050181, 20050184, 20060277, and 20060314.

The analyses sets (according to treatment received) are shown below.

	Panitumumab (N = 1536)	No Panitumumab (N = 1178)	All Subjects (N = 2714)
Oxaliplatin Safety Analysis Set[a]	585 (38)	584 (50)	1169 (43)
Irinotecan Safety Analysis Set[a]	951 (62)	594 (50)	1545 (57)
Oxaliplatin Wild-type KRAS Safety Analysis Set[a]	322 (21)	327 (28)	649 (24)
Irinotecan Wild-type KRAS Safety Analysis Set[a]	501 (33)	294 (25)	795 (29)

Exposure to panitumumab and oxaliplatin or irinotecan chemotherapy in the phase III trials is presented in Table 14.

Extent of exposure to panitumumab: Compared with patients in the Irinotecan group, patients in the Oxaliplatin group had a higher cumulative dose of panitumumab delivered, longer duration of treatment, and more infusions per patient.

Extent of exposure to chemotherapy: There were no notable differences between the panitumumab and no-panitumumab groups for oxaliplatin but the median treatment duration and cumulative dose of irinotecan were lower in the no-panitumumab treatment arm compared to the panitumumab treatment arm.

Doses withheld, delayed or changed: In study 2005203, 7% of the planned panitumumab infusions were withheld, and 40% of patients had at least 1 panitumumab infusion withheld. The most common reason was an adverse event (36%).

As for the studies with FOLFIRI, 6% of the planned panitumumab infusions were withheld in study 20050181 (8% in the All-Panitumumab group), and 33% of patients (Study 20050181) had at least 1 panitumumab infusion withheld (45% in the All-Panitumumab group). The most common reason was an adverse event.

The percentages of chemotherapy doses withheld, delayed or changed were usually higher when combined with panitumumab, e.g. 20% vs. 16% of irinotecan doses delayed or 12% vs. 9% of doses of oxaliplatin withheld.

Table 14 Summary of exposure to panitumumab and chemotherapy

Study 20050203			
All subjects	Panitumumab		No-panitumumab
	Panitumumab (N = 585)	Oxaliplatin (N = 585)	Oxaliplatin (N = 584)
Duration of Treatment (weeks)			
n	585	583	584
Mean (SD)	32.4 (25.9)	27.7 (17.9)	27.9 (16.6)
Median (range)	26.0 (2, 135)	25.9 (2, 124)	25.9 (2, 111)
Number of infusions per subject			
n	585	583	584
Mean (SD)	13.1 (10.6)	11.5 (7.1)	11.8 (6.7)
Median (range)	10.0 (1, 60)	11.0 (1, 47)	11.0 (1, 49)
Cumulative dose delivered (adjusted for weight or BSA)			
n	585	583	583
Mean (SD)	74.2 (58.8)	861.7 (485.6)	881.2 (448.5)
Median (range)	59.8 (0, 354)	847.9 (81, 3197)	855.6 (77, 2893)
Average dose delivered [a]			
n	585	583	583
Mean (SD)	5.8 (0.6)	77.1 (8.4)	77.0 (8.7)
Median (range)	6.0 (0, 7)	79.8 (52, 89)	80.3 (46, 94)
Relative dose intensity [b](%)			
n	585	583	583
Mean (SD)	80.2 (15.8)	77.8 (14.7)	78.6 (14.9)
Median (range)	82.2 (4, 109)	78.5 (26, 108)	79.7 (35, 110)
Study 20050181			
All subjects	Panitumumab		No-panitumumab
	Panitumumab (N = 587)	Irinotecan (N = 587)	Irinotecan (N = 594)
Duration of Treatment (weeks)			
n	587	587	594
Mean (SD)	25.6 (20.5)	26.0 (20.4)	21.6 (15.8)
Median (range)	21.1 (2, 115)	22.7 (2, 116)	18.0 (2, 105)
Number of infusions per subject			
n	587	587	594
Mean (SD)	10.8 (8.5)	11.4 (8.8)	9.8 (7.2)
Median (range)	9.0 (1, 52)	9.0 (1, 52)	8.0 (1, 50)
Cumulative dose delivered (adjusted for weight or BSA)			
n	587	583	594
Mean (SD)	62.7 (49.4)	1915.2 (1489.2)	1654.3 (1224.6)
Median (range)	49.1 (6, 313)	1589.3 (136, 9309)	1434.2 (134, 8784)
Average dose delivered [a]			
n	587	583	594
Mean (SD)	5.9 (0.4)	170.4 (14.6)	170.2 (14.4)
Median (range)	6.0 (4, 7)	176.6 (83, 192)	176.5 (107, 201)
Relative dose intensity [b](%)			
n	587	583	594
Mean (SD)	84.9 (14.5)	84.4 (13.5)	86.2 (12.9)
Median (range)	87.2 (24, 108)	86.6 (40, 106)	90.0 (45, 112)

[a] Average dose delivered is weight or BSA adjusted cumulative dose divided by number of cycles delivered.
[b] Relative dose intensity is the ratio of the actual weight or BSA adjusted cumulative dose of drug to the protocol specified.

Adverse events

Combination with oxaliplatin-based chemotherapy

Nearly all patients in both treatment arms of Study 20050203 experienced adverse events (AEs) (Table 15). Compared with FOLFOX alone, the addition of panitumumab to FOLFOX resulted in increased patient incidence of grade ≥ 3 AEs (88% vs. 76%), grade ≥ 4 AEs (32% vs. 25%), serious adverse events (SAEs) (45% vs. 34%), AEs causing permanent discontinuation of any study drug (chemotherapy and/or panitumumab) (23% and 14%) and fatal adverse events (7% vs. 5%).

The summary of high-level adverse events (grade ≥ 3, serious, leading to discontinuation) was generally similar between the wild-type KRAS and the mutant KRAS Safety Analysis Set, with the exception of a greater difference between treatment arms in serious adverse events in the MK group (47% vs. 30%) compared with the WT group (42% vs. 36%). In addition, the incidence of fatal adverse events in the P+FX arm was higher than in the FX arm among patients in the MK group (8% vs. 3%) compared to the WT group (5% vs. 6%).

Table 15 Summary of Adverse Events (Oxaliplatin Safety Analysis Set)

	Wild-type KRAS		Mutant KRAS	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)
Subjects with any adverse event - n(%)	322 (100)	323 (99)	215 (99)	217 (100)
Worst grade of 3[a]	181 (56)	161 (49)	127 (59)	115 (53)
Worst grade of 4[a]	90 (28)	66 (20)	46 (21)	45 (21)
Worst grade of 5[a]	16 (5)	20 (6)	17 (8)	7 (3)
Any Serious	135 (42)	118 (36)	103 (47)	65 (30)
Leading to permanent discontinuation of any study drug	81 (25)	49 (15)	47 (22)	29 (13)
Not serious	63 (20)	33 (10)	38 (18)	20 (9)
Serious	25 (8)	19 (6)	16 (7)	10 (5)

[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

The majority of most frequent adverse events have been previously recognized for panitumumab as listed in the current SmPC:

- diarrhoea, nausea, vomiting, constipation, abdominal pain,
- rash, dermatitis acneiform, pruritis, dry skin, paronychia,
- stomatitis, mucosal inflammation,
- pyrexia, fatigue,
- hypomagnesaemia, hypokalaemia.

Most of the events occurring at a > 5% higher incidence in the panitumumab arm were consistent with the known safety profile of panitumumab:

- diarrhoea,
- rash, dermatitis acneiform, pruritus, dry skin, nail disorder, paronychia, erythema, skin fissure, acne, alopecia,
- mucosal inflammation, stomatitis,
- dehydration, hypokalaemia, hypomagnesaemia,
- conjunctivitis,
- dyspnoea, epistaxis.

Adverse events with a ≥ 5% difference between the treatment arms that were not previously reported in the monotherapy setting include *Palmar-Plantar Erythrodysesthesia (PPE) syndrome, anorexia, and decreased weight.*

- *PPE* has been recently added as common in the SmPC based on these results as reported in a previous PSUR.
- *Anorexia* was reported with a higher patient incidence in the panitumumab arm compared to the no-panitumumab arm (35% compared to 23%). Only 2% of the events of anorexia in the panitumumab arm were serious compared to < 1% in the no-panitumumab arm, and in both arms, < 1% of patients discontinued due to anorexia.
- *Decreased weight* was reported with a patient incidence of 17% in the panitumumab arm compared to 7% in the no-panitumumab arm. It was reported as serious in < 1% of the patients in the panitumumab arm compared to 0% in the no-panitumumab arm. The worst grade reported was grade 3. In both arms, the event of decreased weight led to discontinuation in < 1% of patients.

The MAH proposed to add these last 2 AEs in section 4.8 of the SmPC.

Hypokalaemia appeared to be more pronounced in patients receiving panitumumab than in those receiving chemotherapy alone. It was reported with a higher patient incidence in the panitumumab arm compared to the no-panitumumab arm (20% versus 13%). Very few events of hypokalaemia were serious (1% in the panitumumab arm and 0% in the no-panitumumab arm) but one in the panitumumab arm was fatal. No patient in either arm discontinued treatment due to hypokalaemia.

A comparison of the patient incidence rates of *neutropenia and thrombocytopenia, paraesthesia, nausea and vomiting*, which all occurred more frequently in the FX alone arm, did not suggest any impact of add-on panitumumab on haematological and neurological toxicities as well as emesis induced by chemotherapy.

Combination with irinotecan-based chemotherapy

Nearly all patients in both treatment arms of Study 20050181 experienced adverse events (Table 16).

Compared with FOLFIRI alone, the addition of panitumumab to FOLFIRI resulted in increased patient incidence of grade ≥ 3 AEs (75% vs. 56%), grade ≥ 4 AEs (24% vs. 21%), serious adverse events (SAEs) (40% vs. 29%), AEs causing permanent discontinuation of any study drug (chemotherapy and/or panitumumab) (21% and 11%) and fatal adverse events (6% vs. 5%).

The summary of high-level adverse events (grade ≥ 3, serious, leading to discontinuation) was generally similar between the wild-type KRAS and the mutant KRAS Safety Analysis Set.

Table 16 Summary of Adverse Events (Irinotecan Safety Analysis Set)

	Wild-type KRAS			Mutant KRAS		
	All Panit. (N = 501)	Panit. in 181 (N = 302)	No Panit. 181 (N = 294)	All Panit. (N = 379)	Panit. in 181 (N = 237)	No Panit. 181 (N = 246)
Subjects with any adverse event - n(%)	500 (100)	301 (100)	289 (98)	377 (99)	235 (99)	237 (96)
Worst grade of 3[a]	275 (55)	161 (53)	102 (35)	181 (48)	113 (48)	89 (36)
Worst grade of 4[a]	92 (18)	58 (19)	50 (17)	66 (17)	38 (16)	34 (14)
Worst grade of 5[a]	27 (5)	12 (4)	18 (6)	28 (7)	17 (7)	13 (5)
Any Serious	214 (43)	124 (41)	91 (31)	152 (40)	88 (37)	74 (30)
Leading to permanent discontinuation of any study drug	121 (24)	64 (21)	37 (13)	85 (22)	46 (19)	25 (10)
Not serious	81 (16)	40 (13)	26 (9)	58 (15)	33 (14)	8 (3)
Serious	47 (9)	28 (9)	14 (5)	35 (9)	16 (7)	17 (7)
Missing	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

Amongst the most frequent adverse events in the panitumumab arm (Study 20050181), only *anorexia* was not listed in the current SmPC. Importantly, events of *neutropenia and vomiting* were equally frequent in both treatment arms. As with oxaliplatin, newly identified risks for panitumumab included *PPE, anorexia, and decreased weight.*

Grade 3/4 Adverse Events

Combination with oxaliplatin-based chemotherapy

Overall, the patient incidence of grade 3/4 adverse events was higher in the panitumumab arm compared to the no-panitumumab arm (**87% versus 76%**). Grade 3/4 AEs that were more common (at least 5% difference) in panitumumab-treated patients were:

- diarrhoea (18% vs. 9%)
- rash and dermatitis acneiform (respectively 15% and 9% vs. 0%)
- hypokalaemia (9% vs. 4%)
- fatigue (10% vs. 3% in the WT group)
- hypomagnesaemia (6% vs. 0%)
- dehydration (6% vs. 0% in the MK group).

In contrast, the patient incidence of neutropenia, the most frequent grade 3/4 AE, was higher in the no-panitumumab arm of the MK group (46% vs. 35%).

Combination with irinotecan-based chemotherapy

Overall, the patient incidence of grade 3/4 adverse events was higher in the panitumumab arm compared to the no-panitumumab arm of the phase III trial (**74% versus 55%**). Grade 3/4 AEs that were more common in panitumumab-treated patients were:

- rash and dermatitis acneiform (respectively 17% and 8% vs. 0%)
- diarrhoea (14% vs. 9%)
- hypokalaemia (5% vs. <1%)
- mucosal inflammation (7% vs. 2% in the MK group).

The patient incidence of neutropenia, the most frequent grade 3/4 AE, was similar in both treatment arms (19% in the panitumumab and 21% in the no-panitumumab arm).

Adverse events of special interest

These include: Cardiac toxicity, Diarrhoea, Hypomagnesaemia, Hypocalcaemia, Impaired or delayed wound healing, Infusion related reactions, Integument toxicities, Pulmonary toxicity, Stomatitis/oral mucositis, Vascular toxicity.

Grade ≥ 3 AEs of interest are summarised in Tables 17 & 18. Grade ≥ 3 events of skin toxicity, stomatitis, diarrhoea, and hypomagnesaemia occurred more frequently in panitumumab-treated patients in both chemotherapy groups whereas pulmonary and cardiac toxicities occurred with similar patient incidence in the two treatment arms. Grade ≥ 3 thromboembolic events occurred more frequently in panitumumab-treated patients when combined to oxaliplatin.

Skin toxicities specific to anti-EGFR inhibitors are an important contributor to the overall increase in severe toxicities of the combination of panitumumab with chemotherapy. The occurrence of severe (grade 3/4) rash and acneiform dermatitis increased with treatment duration: in study 20050203, it

raised from 5% and 4%, respectively, in patients with less than 3 months of treatment to 23% and 12%, respectively, in those with more than 9 months of treatment. They prompted chemotherapy discontinuation in up to 3% of the cases and dose delays/adjustment in up to 16% of the patients.

The occurrence of diarrhoea is greatly increased on combined therapy (up to 68%) in comparison with panitumumab monotherapy (21% in the pivotal trial). Most importantly, it is also substantially augmented, including the occurrence of the most severe cases (from 9% up to 14-18%) and serious cases (from 3-4% up to 10%; one fatal case in study 20050181), as compared to chemotherapy alone.

Grade ≥ 3 infusion reactions occurred at a similar patient incidence in the two treatment arms regardless of the definition used in both analysis sets. Of note however, more patients received prophylactic medications when panitumumab was added to chemotherapy. In total, there were three cases of life-threatening reaction in the two phase III trials: two anaphylactic reactions and one angioedema, which prompted discontinuation of therapy.

Table 17 Patient incidence of Grade ≥ 3 AEs of interest (Oxaliplatin Safety Analysis Set)

	Wild-type KRAS		**Mutant KRAS**		**All Patients**	
	FOLFOX+P (N=322)	FOLFOX (N=327)	FOLFOX+P (N=217)	FOLFOX (N=218)	FOLFOX+P (N=585)	FOLFOX (N = 584)
Patients with any adverse event of interest - n(%)	214 (66)	81 (25)	136 (63)	58 (27)	375 (64)	152 (26)
Hypomagnesemia	21 (7)	1 (0)	14 (6)	1 (0)	38 (6)	2 (0)
Hypocalcemia	3 (1)	1 (0)	2 (1)	0 (0)	6 (1)	1 (0)
Diarrhea	59 (18)	29 (9)	43 (20)	22 (10)	108 (18)	56 (10)
Cardiac Toxicity - Pre-specified	14 (4)	10 (3)	11 (5)	9 (4)	26 (4)	20 (3)
Cardiac Arrythmias - SMQ	9 (3)	6 (2)	9 (4)	8 (4)	20 (3)	14 (2)
Ischaemic Heart Disease - SMQ	1 (0)	3 (1)	4 (2)	0 (0)	5 (1)	3 (1)
Pulmonary Toxicity	11 (3)	14 (4)	7 (3)	2 (1)	19 (3)	19 (3)
Vascular Toxicity - Pre-specified	37 (11)	24 (7)	20 (9)	14 (6)	62 (11)	44 (8)
Vasculitis - SMQ	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Embolic and Thrombotic - SMQ[a]	39 (12)	24 (7)	22 (10)	15 (7)	65 (11)	43 (7)
Impaired or Delayed Wound Healing	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)
Interstitial Lung Disease - SMQ	2 (1)	2 (1)	0 (0)	0 (0)	2 (0)	2 (0)
Stomatitis or Oral Mucositis	28 (9)	2 (1)	13 (6)	6 (3)	42 (7)	9 (2)
Integument and Eye Toxicities - Pre-specified	130 (40)	9 (3)	72 (33)	3 (1)	212 (36)	13 (2)
Skin Toxicity	119 (37)	7 (2)	68 (31)	3 (1)	197 (34)	10 (2)
Nail Toxicity	17 (5)	0 (0)	5 (2)	0 (0)	23 (4)	0 (0)
Hair Toxicity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Eye Toxicity	8 (2)	2 (1)	4 (2)	0 (0)	13 (2)	3 (1)
Cheilitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe Cutaneous Adverse Reactions - SMQ	2 (1)	0 (0)	2 (1)	0 (0)	4 (1)	0 (0)
Infusion Reaction	12 (4)	8 (2)	6 (3)	10 (5)	20 (3)	20 (3)
USPI	8 (2)	5 (2)	4 (2)	7 (3)	14 (2)	14 (2)
CTCAE	9 (3)	4 (1)	4 (2)	5 (2)	15 (3)	10 (2)
Reported AE	8 (2)	6 (2)	4 (2)	10 (5)	14 (2)	18 (3)

[a] Includes: Embolic and thrombotic events, arterial; Embolic and thrombotic events, venous; Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous.

Table 18 Patient incidence of Grade ≥ 3 AEs of interest (Irinotecan Safety Analysis Set)

	Wild-type KRAS			Mutant KRAS			All Patients		
	overall	Study 20050181		overall	Study 20050181		overall	Study 20050181	
	FOLFIRI + panitum		FOLFIRI	FOLFIRI + panitum		FOLFIRI	FOLFIRI + panitum		FOLFIRI
	N=501	N=302	N=294	N=379	N=237	N=246	N=951	N=587	N=594
Patients with any adverse event of interest - n(%)	287 (57)	164 (54)	75 (26)	203 (54)	126 (53)	58 (24)	530 (56)	318 (54)	141 (24)
Hypomagnesaemia	21 (4)	9 (3)	1 (0)	15 (4)	12 (5)	0 (0)	41 (4)	25 (4)	1 (0)
Hypocalcemia	10 (2)	3 (1)	0 (0)	7 (2)	5 (2)	1 (0)	18 (2)	9 (2)	1 (0)
Diarrhoea	83 (17)	42 (14)	27 (9)	58 (15)	32 (14)	26 (11)	156 (16)	83 (14)	56 (9)
Cardiac Toxicity - Pre-specified	16 (3)	5 (2)	7 (2)	10 (3)	5 (2)	3 (1)	28 (3)	12 (2)	12 (2)
Cardiac Arrythmias - SMQ	11 (2)	4 (1)	7 (2)	5 (1)	1 (0)	1 (0)	19 (2)	8 (1)	9 (2)
Ischaemic Heart Disease - SMQ	1 (0)	1 (0)	1 (0)	3 (1)	3 (1)	2 (1)	4 (0)	4 (1)	3 (1)
Pulmonary Toxicity	15 (3)	12 (4)	12 (4)	13 (3)	8 (3)	6 (2)	30 (3)	22 (4)	18 (3)
Vascular Toxicity - Pre-specified	51 (10)	22 (7)	21 (7)	34 (9)	16 (7)	15 (6)	94 (10)	45 (8)	36 (6)
Vasculitis - SMQ	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Embolic and Thrombotic - SMQ[a]	52 (10)	22 (7)	22 (7)	35 (9)	14 (6)	14 (6)	97 (10)	44 (7)	36 (6)
Impaired or Delayed Wound Healing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Interstitial Lung Disease - SMQ	2 (0)	2 (1)	1 (0)	0 (0)	0 (0)	0 (0)	2 (0)	2 (0)	1 (0)
Stomatitis or Oral Mucositis	37 (7)	23 (8)	8 (3)	31 (8)	22 (9)	9 (4)	70 (7)	46 (8)	19 (3)
Integument and Eye Toxicities - Pre-specified	180 (36)	115 (38)	9 (3)	122 (32)	80 (34)	3 (1)	325 (34)	211 (36)	13 (2)
Skin Toxicity	170 (34)	111 (37)	7 (2)	111 (29)	75 (32)	2 (1)	302 (32)	201 (34)	10 (2)
Nail Toxicity	25 (5)	13 (4)	1 (0)	20 (5)	10 (4)	0 (0)	49 (5)	24 (4)	1 (0)
Hair Toxicity	1 (0)	0 (0)	1 (0)	3 (1)	0 (0)	0 (0)	4 (0)	0 (0)	1 (0)
Eye Toxicity	16 (3)	12 (4)	0 (0)	2 (1)	1 (0)	1 (0)	21 (2)	15 (3)	1 (0)
Cheilitis	3 (1)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0)	3 (1)	0 (0)
Severe Cutaneous Adverse Reactions - SMQ	6 (1)	1 (0)	0 (0)	6 (2)	3 (1)	0 (0)	13 (1)	4 (1)	0 (0)
Infusion Reaction	7 (1)	4 (1)	2 (1)	1 (0)	1 (0)	1 (0)	8 (1)	5 (1)	4 (1)
USPI	1 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	1 (0)
CTCAE	5 (1)	3 (1)	1 (0)	1 (0)	1 (0)	1 (0)	6 (1)	4 (1)	3 (1)
Reported AE	3 (1)	2 (1)	1 (0)	0 (0)	0 (0)	0 (0)	3 (0)	2 (0)	1 (0)

Serious adverse event/deaths/other significant events

In the ***Oxaliplatin Safety Analysis Set***, the patient incidence of SAEs was higher in the panitumumab-treated arm compared with the no-panitumumab arm (45% versus 34%) with a greater difference seen in the mutant KRAS group (47% vs. 30%) compared to the wild-type KRAS group (42% vs. 36%). No single event appeared to account for this difference. Diarrhoea was the only SAE with a ≥5% greater incidence in the panitumumab arm (10%) compared to the no-panitumumab arm (3%); dehydration was also more frequent (3% vs. <1%, respectively).

In the ***Irinotecan Safety Analysis Set*** of study 20050181, the same absolute difference was observed with 40% and 29% of patients in the panitumumab and no-panitumumab arms reporting SAEs. Unlike with oxaliplatin, incidences were similar in the WT and MK groups. The most common serious adverse event was diarrhoea (6% vs. 4% in the panitumumab and no-panitumumab arms, respectively).

In the phase III trials, all deaths that occurred during treatment or within the safety follow-up period (generally 30 days after the last dose of any study treatment), including those that occurred in the setting of disease progression, were recorded as fatal adverse events (see Table 19).

Table 19 On-treatment fatal events in phase III trials

Patients with any fatal AE n (%)	**WT**		**MK**		**All patients**	
	PAN +	PAN -	PAN +	PAN -	PAN +	PAN -
Study 20050203 (Oxaliplatin)	16 (5)	20 (6)	17 (8)	7 (3)	39 (7)	28 (5)
Study 20050181 (Irinotecan)	12 (4)	18 (6)	17 (7)	13 (5)	34 (6)	32 (5)

In both trials, there was a small excess of deaths in the no-panitumumab arms of the WT groups as opposed to increased on-treatment mortality in the panitumumab arms of the MK groups. With the oxaliplatin combination, this difference was significant (HR = 2.58; 95%CI = 1.01, 6.23). In the All-panitumumab group combined with irinotecan (N=951 patients), the patient incidence of fatal events was similar (7%).

The patient incidence of fatal AEs decreased with longer treatment duration; the excess of fatal events with panitumumab was mainly observed with treatments less than 3 months while no difference between treatment arms was seen with treatments lasting more than 6 months.

Most fatal events were disease progression or a direct consequence of progression of the underlying malignancy. There were few deaths from other causes that occurred in more than a single patient in the panitumumab arm of study 20050203; however, it is acknowledged that cause of death in terminal cancer patients is very much open to interpretation. No obvious pattern of deaths emerged in the mutant KRAS group; rather, deaths were due to a variety of causes, including mCRC. Notwithstanding, these data alone cannot account for the clear difference in survival favouring the no-panitumumab arm that was shown in the MK group of study 20050203.

Laboratory findings

Severe (grade ≥ 3) decreases in serum magnesium, calcium and potassium were observed in small percentages (3-7%) of patients on chemotherapy alone but in 2-3 times more patients with panitumumab (e.g. 11% of grade ≥ 3 decreases in magnesium). These figures are substantially higher than those of the corresponding AEs but the trends are consistent.

As expected, the patient incidence of anti-panitumumab antibodies in the combination chemotherapy setting was rare and similar to the incidence observed in the monotherapy setting, with 1.8% of patients developing binding antibodies and 0.2% neutralising antibodies.

Safety in special populations

Elderly

The rate of grade ≥ 3 AEs was similar between younger and older patients in the panitumumab arms in both the Oxaliplatin and Irinotecan Safety Analysis Sets. However, serious adverse events and grade 4/5 events occurred with a greater frequency in older patients. As an example, serious AEs were reported by 52% of the patients ≥ 65 years vs. 40% of the patients < 65 years with the combination of panitumumab and oxaliplatin whereas in the oxaliplatin arm the percentages were 35% vs. 33%, respectively.

Likewise, for the grade ≥ 3 AEs of interest, the differences between patients older and younger than 65 years were modest in the no-panitumumab arms, except for diarrhoea in the trial with irinotecan (13% vs. 7%, respectively). In contrast, the differences between patients older and younger than 65

years in the panitumumab arms were substantial for diarrhoea (21-23% vs. 14-15%), thromboembolic events (13-14% vs. 8-9%), stomatitis/oral mucositis (10% vs. 5-6%), hypomagnesaemia with irinotecan (6% vs. 3%), and to a lesser extent, cardiac arrhythmias and pulmonary toxicity with oxaliplatin.

Region

In the Irinotecan Safety Analysis Set (study 20050181), Grade ≥ 3 AEs, in both panitumumab and no-panitumumab arms, were reported with a higher patient incidence among patients in the Western Europe/Australia/US region compared with the ROW region (by 15%-19%). Likewise, the patient incidence of serious adverse events was 22%-25% higher in Western Europe/Australia/US region than in the ROW region (essentially Central and Eastern Europe). The MAH argued that this was due to 'regional and cultural differences' although it is unclear why a similar finding was not observed in the other study, even in the countries where both studies were conducted.

Discontinuation due to adverse events

In both phase III trials, panitumumab increased the rate of discontinuation of chemotherapy and more than 20% patients stopped panitumumab and/or chemotherapy as shown below.

Table 20: Discontinuations due to adverse events in studies 20050203 and 20050181

% subjects with adverse events causing discontinuation from	Study 20050203		Study 20050181	
	Panitumumab	No Panitumumab	Panitumumab	No Panitumumab
Panitumumab	18%	-	19%	-
All chemotherapy	17%	14%	15%	11%
Either*	23%	14%	21%	11%
Serious	8%	5%	8%	5%

The most common events leading to FOLFOX discontinuation were (for the panitumumab, no-panitumumab arms): paraesthesia (2%, 1%), fatigue (1%, < 1%), diarrhoea (1%, < 1%), and hypersensitivity (1%, < 1%). The most common events leading to panitumumab discontinuation were rash (4%) and dermatitis acneiform (2%).

The most common events causing FOLFIRI discontinuation in study 20050181 were (for the panitumumab, no-panitumumab arms): diarrhoea (2%, < 1%), fatigue (2%, 1%), rash (2%, 0%), and asthenia (1%, 0%). In the All-Panitumumab group, the most common events leading to panitumumab discontinuation were rash (4%), diarrhoea (2%), and dermatitis acneiform (1%).

Post marketing experience

As of 30 September 2010, panitumumab has been approved for use in 37 countries. Cumulatively, since the inception of the panitumumab development program, an estimated 54,126 patients have been exposed to the product.

During the latest reporting period (01 April 2010 to 30 September 2010), the MAH received a total of 427 (296 in the previous PSUR period) medically confirmed case reports describing 1095 (769 in the previous PSUR period) adverse events. The majority of reports were from clinical trials. One hundred and eighty-six reports (44%) contained unlisted serious reactions; 43 non-serious reports contained unlisted reactions. The most frequently reported serious adverse reactions (preferred terms) were diarrhoea, vomiting, dehydration, nausea and pyrexia, which are listed events. The most frequently reported non-serious adverse reactions were rash and 'skin toxicity', which are listed events, and 'skin

reaction', which is an unlisted event. Many cases were confounded by underlying disease and concomitant chemotherapy.

A total of 14 new cases of venous thromboembolic events were received including eight reports of pulmonary embolism, six of deep vein thrombosis and one of thrombophlebitis. Since pulmonary embolism is a known adverse reaction associated with panitumumab, it is probable that, although many cases are confounded, deep venous thromboembolism may also be causally associated with the drug.

Moreover, one serious case of keratitis and three serious cases of ulcerative keratitis have been cumulatively identified in patients treated with panitumumab. All four cases were reported in the spontaneous setting. Three of the cases were reported in patients who were administered panitumumab in the monotherapy setting and one case was reported in a patient who received Vectibix in combination with chemotherapy. Taken together, a review of the cases of ulcerative keratitis and keratitis, biologic plausibility (integument and eye toxicity with the administration of EGFR inhibitors), and possible class effect (both ulcerative keratitis and keratitis are listed events in package inserts for other EGFR inhibitors), provide evidence to suggest a casual drug event association for panitumumab and these events.

Of note in the FOLFIRI trial are 5 cases of ileus/subileus in the P+FOLFIRI arm (2 fatal) vs. only one case in the FOLFIRI alone arm. Moreover, there have been spontaneous reports of subileus in patients treated with the (off-label) combination of panitumumab + irinotecan outside of clinical trials. However, an aggregate review of the composite terms for gastrointestinal obstruction/perforation identified no imbalance between subjects who received panitumumab plus FOLFIRI and FOLFIRI alone (26 subjects [4%]; 29 subjects [5%], respectively.) No imbalance of ileus or subileus was observed when comparing subjects treated with panitumumab plus FOLFIRI versus FOLFIRI alone (4 [1%] vs. 6 [1%] and 3 [1%] vs. 4 [1%], respectively).

3.6.1. Discussion on clinical safety

The addition of panitumumab did not aggravate the haematological and neurological toxicities of the cytotoxic chemotherapies. Neither did it increase the incidence of infusion-related reactions in comparison with these treatments alone (< 1% with irinotecan, comparable to panitumumab monotherapy, and 2% with oxaliplatin).

However, the addition of panitumumab did substantially increase the overall incidence of the high-level AEs reported; for example, the patient incidence of grade ≥ 3 AEs was augmented from 76% to 88% with oxaliplatin and from 56% to 75% with irinotecan. This unfavourable effect of panitumumab was particularly pronounced in patients with mutant KRAS receiving oxaliplatin-based chemotherapy.

The occurrence of *diarrhoea* with panitumumab was much higher on combined therapy (up to 68% of the patients) than on monotherapy (21% in the pivotal trial). Most importantly, it was also substantially augmented when compared with chemotherapy alone, including the occurrence of the most severe cases (from 9% up to 14-18%) and serious cases (from 3-4% up to 10%; one fatal case in study 20050181). This was associated with an increased proportion of patients presenting with hypokalaemia and dehydration.

Skin toxicities specific to EGFR inhibitors are an important contributor to the overall increase in severe toxicities of the combination of panitumumab with chemotherapy; grade ≥3 skin toxicities were observed in 34% of the patients treated with panitumumab vs. 2% on chemotherapy alone. This includes in particular severe (grade 3/4) rash and acneiform dermatitis, the occurrence of which rose with treatment duration. Palmar-plantar erythrodysesthesia syndrome was a new adverse reaction that had not been described on monotherapy.

Hypomagnesaemia, another specific effect of anti-EGFR therapies, and sometimes associated with hypocalcaemia, also contributed to the excess toxicity of the combination of panitumumab with chemotherapy, as reflected by severe (grade ≥3) decreases in magnesium levels in 11% of the patients.

Even general toxicities including fatigue/asthenia, anorexia and decreased weight were reported more frequently by patients receiving panitumumab than chemotherapy alone. Anorexia and decreased weight were new adverse reactions.

Importantly, all these effects of panitumumab, and especially diarrhoea and rash, had an impact on compliance with chemotherapy and its intensity in a significant number of cases with permanent discontinuation or dose delays and adjustments. Overall, 15-17% of the patients stopped chemotherapy and 18-19% stopped panitumumab treatment due to an adverse event.

Fatal adverse events occurred with a higher incidence in patients with mutant KRAS receiving panitumumab and oxaliplatin relative to those receiving oxaliplatin alone; no particular pattern with regard to the type of fatal events was apparent. The number of potential toxic (on-treatment) deaths seemed marginal when considering that a number of the fatal events were likely related to the underlying disease. These data alone cannot account for the clear difference in survival favouring the no-panitumumab arm that was shown in the MK group treated with oxaliplatin-based chemotherapy.

Whereas cardiac toxicity of cetuximab has been identified, there has not been a clear signal for panitumumab until now but a marginal increase in cardiac toxicity cannot be ruled out.

Panitumumab seemed to augment the incidence of thromboembolism, including severe cases (from 7% to 11% with oxaliplatin).

Elderly patients are in general more susceptible to chemotherapy toxicities, as can be observed to some extent in the control groups, but serious adverse events were more common in patients aged ≥ 65 years than in younger patients when panitumumab was added to chemotherapy. Some toxicities of panitumumab appear particularly more frequent in patients older than 65 years; these mainly included diarrhoea, thromboembolic events, stomatitis/oral mucositis, and hypomagnesaemia.

3.6.2. Conclusions on the clinical safety

The toxicity of the combined therapy was worse than the toxicity of the chemotherapy alone, especially in patients older than 65 years, and had some impact on the compliance to chemotherapy. Although panitumumab is indicated for patients with wild-type KRAS only, the lack of an explanation for the harmful effects of panitumumab in combination with oxaliplatin in patients with mutant KRAS raised concerns about the safety of administering panitumumab in combination with oxaliplatin-based chemotherapy to patients with mCRC.

3.7. Benefit-Risk Balance

Benefits

- Beneficial effects

In both phase III studies a statistically significant but modest increase in progression-free survival was observed in patients with wild-type KRAS tumours. There was a small absolute difference in median survival (1.4 - 1.8 months) and hazard ratios around 0.80 in the most mature analyses. In the first-line setting with FOLFOX, a 10%-13% difference in the estimated event-free rates was only observed

around the 1-year endpoint while in the second-line setting with FOLFIRI, a 7%-15% difference was observed over the first 40 weeks only.

None of the studies showed a statistically significant effect on overall survival favourable to the addition of panitumumab in patients with wild-type KRAS tumours.

- Uncertainty in the knowledge about the beneficial effects

None of the studies showed a statistically significant effect of panitumumab on overall survival in patients with wild-type KRAS tumours. The objective tumour response to panitumumab was marginal in first-line treatment (55% vs. 48%), although slightly improved in the final analysis (57% vs. 48%), and only significant in second-line treatment (35% vs. 10%). The clinical relevance of response rate in this disease setting has not been established for this type of agent.

In the first-line setting (study 20050203):

- The findings lack internal consistency insofar as the differences in PFS and OS in patients with wild-type KRAS tumours are entirely driven by the ROW population, i.e. Central-Eastern Europe/Latin America/South Africa.
- There is also no evidence of benefit on PFS in patients older than 75 years or even in the large subpopulation of patients older than 65 years. Furthermore, in the very small group of elderly patients ≥ 75 years old there was a higher number of deaths, likely due to increased susceptibility to the toxicity of the combined regimen as reflected in the safety data. Any extrapolation of benefit to this population, which currently represents 40% of the patients with mCRC at diagnosis, is therefore impossible.
- Adding panitumumab to FOLFOX appears harmful in patients with an ECOG score of 2, where significantly shortened PFS and OS as well as increased toxicity were observed.

In the second-line setting (study 20050181):

- The highly statistical results shown in the primary PFS analysis ($p < 0.004$) are not considered robust in a more mature analysis, where they become borderline to the threshold level ($p< 0.01$) requested in the statistical analysis plan.
- A certain level of inconsistency was noted in the results. Importantly, no OS benefit was reported in the small group of patients older than 75 years (HR > 1). Even in the largest group of patients aged < 65 years, an apparent benefit in PFS (HR=0.69) did not translate into OS benefit (HR = 0.92); the overall mortality rates were similar (66% vs. 65%), especially because of more deaths due to disease progression in the long-term follow-up (63% vs. 57% with FOLFIRI alone) (data from FU2 029.1).

Patient reported outcomes can be important especially given the high toxicity of the combined regimens. The various analyses of QoL data do not show any benefit of adding panitumumab but rather a numerical trend in favour of chemotherapy alone. This result is supported by a higher proportion of WT patients with a deterioration of their ECOG score in the FOLFIRI trial. These observations add uncertainties about any possible benefits of panitumumab in the claimed indications,

Finally, the uncertainties about the effects of anti-EGFR therapies on wild-type KRAS tumours are expected since it is now known that a number of other mutations in the signalling pathway may confer resistance to these therapies. Other biomarkers such as BRAF, PIK3CA/PTEN, or NRAS but also EGFR gene copy number, EGFR ligands (epiregulin and amphiregulin), single nucleotide polymorphisms in codon 497 of EGFR, or levels of EGFR downstream signalling phosphoproteins (e.g. pMEK1, pP70S6K) may increase predictive power for response to treatment and are awaiting validation in clinical trials.

Risks

- Unfavourable effects

In patients with mutant KRAS tumours, a clear negative impact of panitumumab was observed on time to progression, PFS and OS when it was combined with oxaliplatin-based chemotherapy in the first-line setting. These results were robust and found in both geographic regions. In contrast, the combination of panitumumab with FOLFIRI did not appear harmful in these patients, and thus, this negative effect seemed to be specific to oxaliplatin-based chemotherapy. The MAH hypothesised that this was due to a negative interaction between anti-EGFR antibodies and oxaliplatin in patients with mutant KRAS mCRC.

The addition of panitumumab did substantially increase the overall incidence of the high-grade AEs reported (i.e. grade ≥3, serious, or leading to treatment discontinuation). The patient incidence of grade ≥ 3 AEs was augmented from 76% to 88% with oxaliplatin and from 56% to 75% with irinotecan. This was due mainly to an increase in incidence/severity of diarrhoea, a well-known ADR of oxaliplatin and irinotecan, as well as to the added contribution of the toxicities specific to EGFR inhibitors.

- The occurrence of *diarrhoea* with panitumumab was higher than on chemotherapy alone, especially the most severe cases (with patient incidence increasing from 9% up to 14-18%) and serious cases (from 3-4% up to 10%; one fatal case). This was associated with an increased proportion of patients presenting with hypokalaemia and dehydration.
- Grade ≥3 *skin toxicities* were observed in 34% of the patients treated with panitumumab vs. 2% on chemotherapy alone. This included in particular severe (grade 3/4) rash and acneiform dermatitis, the occurrence of which rose with treatment duration.
- *Hypomagnesaemia*, sometimes associated with hypocalcaemia, also contributed to the excess toxicity of the combination of panitumumab with chemotherapy, as reflected by severe (grade ≥3) decreases in magnesium levels in 11% of the patients.
- Panitumumab also seemed to increase the incidence of *thromboembolism*, including severe cases (from 7% to 11% with oxaliplatin).
- Even general toxicities including fatigue/asthenia, anorexia and decreased weight were reported more frequently by patients receiving panitumumab than chemotherapy alone. A new ADR of Palmar-Plantar Erythrodysesthesia (PPE) syndrome was identified.

Importantly, all these effects of panitumumab, and especially diarrhoea and rash, had an impact on compliance with chemotherapy and its intensity in a significant number of cases with permanent discontinuation or dose delays and adjustments.

Elderly patients were in general more susceptible to chemotherapy toxicities, as could be observed to some extent in the control groups, but serious adverse events were more common in patients aged ≥ 65 years than in younger patients when panitumumab was added to chemotherapy. Some toxicities of panitumumab appeared particularly more frequent in patients older than 65 years; these mainly included diarrhoea, thromboembolic events, stomatitis/oral mucositis, and hypomagnesaemia.

- Uncertainty in the knowledge about the unfavourable effects

In study 20050181, the reporting rates of severe and serious AEs were about 20% lower in the ROW region (essentially Central-Eastern Europe), which provided 39% of the total population, than in the Western Europe/US/Australia region. This finding was attributed by the MAH to 'regional and cultural differences' but is still largely unexplained.

Fatal adverse events occurred at a similar rate in the treatment arms of the wild-type KRAS groups of both studies. In the mutant KRAS groups, increases in fatal adverse events with panitumumab were seen to some extent in both studies: 8% vs. 3% in the control arm of study 20050203 and 7% vs. 5% in the control arm of study 20050181. Recent analyses of the timing and cause of deaths in study 20050203 did not identify obvious toxicities to explain the mortality that was not related to disease progression. There was no clear signal for worse cardiac toxicity but a marginal increase cannot be ruled out.

The MAH argued that toxicity of panitumumab is manageable. However, severe protracted diarrhoea and disfiguring or painful skin lesions may be severely disabling with patients eventually being homebound. The impact of these toxicities on the patient quality of life was reflected by the absence of improvement with the addition of panitumumab and rather a numerical trend favouring chemotherapy alone. Furthermore, a higher proportion of patients exhibited a deterioration of their ECOG score in the FOLFIRI trial.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

The difference in PFS was small and did not translate into significant improvement in OS or other clinical benefit.

The lack of evidence of QoL benefit over chemotherapy alone with a numerical trend in favour of chemotherapy alone and more frequent deterioration of ECOG performance status in the second-line setting is to be expected given the substantial increase in toxicity of the combination of panitumumab with chemotherapy as compared with chemotherapy alone. This is especially a concern in the older patients.

Given that KRAS determination is critical for the indication of panitumumab, it is questionable whether the small benefits achieved in clinical trials where KRAS status was centrally diagnosed can be generalised. Indeed, they are likely to be smaller in a broad clinical setting, where the reliability of KRAS diagnosis has not yet been established.

The negative impact of panitumumab on the survival of patients with KRAS mutant tumours when combined with oxaliplatin-based chemotherapy is considered a major concern since the proportion of patients with KRAS mutations potentially treated with panitumumab is unknown and very difficult to estimate. The reasons for such wrong treatments are multiple and include non evaluable test results, unreliable test methods, or mutations not detectable by the test used. Moreover, no clear reason has been found to explain this negative impact. No obvious toxic interaction has been found and it is not clear whether the negative effect is to be related to the mutant KRAS status only, or if there are other groups of patients at risk of negative effects, such as those with poor performance status. The MAH hypothesised that this is due to a negative interaction between anti-EGFR antibodies and oxaliplatin in patients with mutant KRAS mCRC.

- Benefit-risk balance

The modest increase in PFS observed in patients with wild-type KRAS tumours by the addition of panitumumab to the first and second line of chemotherapy for mCRC was not considered sufficient to outweigh the increased toxicity of the combinations.

4. Conclusion

On 17 March 2011 the CHMP considered this Type II variation not to be acceptable on the following grounds:

- The benefit in terms of progression free survival in the target population with wild-type KRAS tumours is modest. No effect could be observed in elderly patients and a detrimental effect was observed in patients with ECOG performance status of 2 in some of the subgroup analyses. No statistically significant difference was observed for overall survival. No benefit has been established in terms of other clinical endpoints such as Quality of Life
- The add-on toxicity of panitumumab is clinically significant with substantial increase in the rate of SAEs and grade ≥ 3 events. These concerns are heightened in elderly patients, as some toxicities of panitumumab appear particularly more frequent in these patients
- There is uncertainty about the current reliability of KRAS testing in clinical practice, which raises a concern since a detrimental effect on progression-free and overall survival has been reported in patients with mutant KRAS tumours for the combination of panitumumab with FOLFOX
- The modest increase in PFS observed in patients with wild-type KRAS tumours by the addition of panitumumab to the first and second line of chemotherapy for mCRC is not considered sufficient to outweigh the increased toxicity of the combinations

5. Re-examination of the CHMP opinion of 18 March 2011

Following the CHMP conclusion that the variation to the terms of the Marketing Authorisation of Vectibix to extend the indication to treatment of metastatic colorectal carcinoma in combination with chemotherapy was not approvable, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented in writing and at an oral explanation a number of arguments refuting the grounds for refusal.

Ground #1 (modest efficacy): The MAH acknowledged the CHMP concern regarding the lack of consistency of the observed benefit in subgroups and presented further subgroup efficacy analyses for both studies according to age and performance status. Moreover, the MAH argued that resectability of liver-only metastases after first line chemotherapy may provide an important survival benefit, so that analyses of resectability of liver-only metastases of patients receiving FOLFOX + panitumumab vs FOLFOX in the first line 20050203 study were submitted. Finally, with regard to Quality of Life captured through Patient Reported Outcomes (PRO), the MAH repeated that overall no statistically significant deterioration was observed and submitted additional analyses showing that this was also the case specifically with regard to skin toxicities and diarrhoea. PRO scores did not differ between patients with different grades of skin toxicities or diarrhoea (data not shown).

Table 21: Study 20050203 – Patient numbers and efficacy outcomes (primary endpoint) in key subgroups (Final Analysis)

	PFS Hazard Ratio (95% CI)
Overall (n = 656)	0.80 (0.67, 0.95)
ECOG 0/1 (n = 616)	0.76 (0.64, 0.91)
ECOG 2 (n = 40)	1.80 (0.88, 3.69)
Age < 65 years and ECOG 0/1 (n = 372)	0.65 (0.52, 0.82)
Age ≥ 65 years and ECOG 0/1 (n = 244)	0.95 (0.72, 1.25)
Age < 75 years and ECOG 0/1 (n = 564)	0.73 (0.61, 0.88)
Age ≥ 75 years and ECOG 0/1 (n = 52)	1.27 (0.66, 2.46)

Table 22: Study 20050203 - Efficacy outcomes by Age < 65 Years and ≥ 65 years in patients with ECOG 0/1 Status and Wild-type *KRAS* tumours (Final Analysis)

	Age < 65 years		Age ≥ 65 years	
	Panitumumab + FOLFOX n = 186[a]	FOLFOX Alone n = 186[a]	Panitumumab + FOLFOX n = 119[a]	FOLFOX Alone n = 125[a]
PFS Hazard Ratio (95% CI)	0.65 (0.52, 0.82)		0.95 (0.72, 1.25)	
Quantitative interaction test for PFS	p = 0.03			
Median PFS (mos)	12.0	9.0	9.3	8.0
OS Hazard Ratio (95% CI)	0.88 (0.68, 1.13)		0.75 (0.56, 1.02)	
Quantitative Interaction Test for OS	p = 0.61			
Median OS (mos)	27.2	22.7	20.2	17.4
Objective Response Rate[b]	65%	49%	51%	45%

[a] Wild-type *KRAS* Efficacy Analysis Set, [b] Wild-type *KRAS* Central Tumor Response Analysis Set: Age < 65 (n = 182 pmab plus FOLFOX, 183 FOLFOX alone); Age ≥ 65 (n = 115 pmab plus FOLFOX, 121 FOLFOX alone)

Table 23: Study 20050203 - Efficacy outcomes by Performance Status in patients with Wild-type KRAS tumours (Final Analysis)

	ECOG 0/1		ECOG 2	
	Panitumumab + FOLFOX n = 305[a]	FOLFOX Alone n = 311[a]	Panitumumab + FOLFOX n = 20[a]	FOLFOX Alone n = 20[a]
PFS Hazard Ratio (95% CI)	0.76 (0.64, 0.91)		1.80 (0.88, 3.69)	
Quantitative interaction test for PFS	p = 0.02			
Median PFS (mos)	10.8	8.7	4.8	7.5
OS Hazard Ratio (95% CI)	0.84 (0.69, 1.02)		1.59 (0.80, 3.16)	
Quantitative Interaction Test for OS	p = 0.09			
Median OS (mos)	25.8	20.6	7.0	11.7
Objective Response Rate[b]	60%	48%	20%	45%

[a] Wild-type *KRAS* Efficacy Analysis Set, [b] Wild-type *KRAS* Central Tumor Response Analysis Set: ECOG 0/1 (n = 297 pmab plus FOLFOX, 304 FOLFOX alone); ECOG 2 (n = 20 pmab plus FOLFOX, 20 FOLFOX alone)

Figure 15: Study 20050203: Kaplan-Meier Plot of PFS time in patients with ECOG 0/1 PS and < 65 Years of Age (Central Assessment, Wild-type KRAS Analysis Set, Final Analysis)

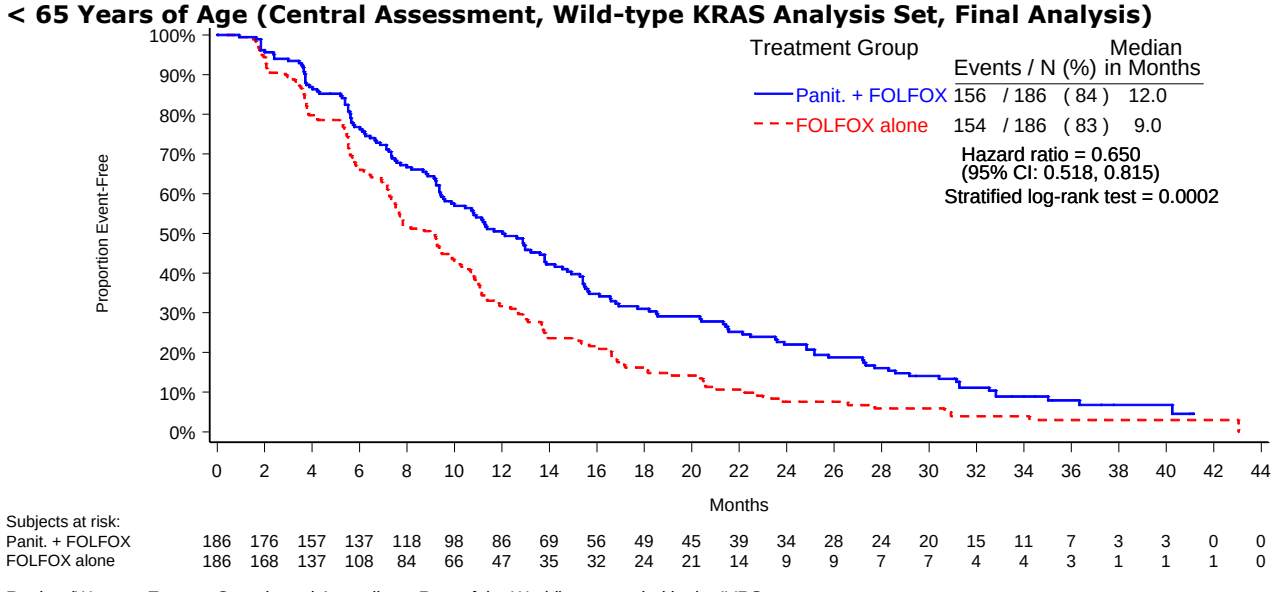


Figure 16: Study 20050203 - Kaplan-Meier plot of OS time in patients with ECOG 0/1 PS and < 65 Years of Age (Wild-type KRAS Analysis Set, Final Analysis)

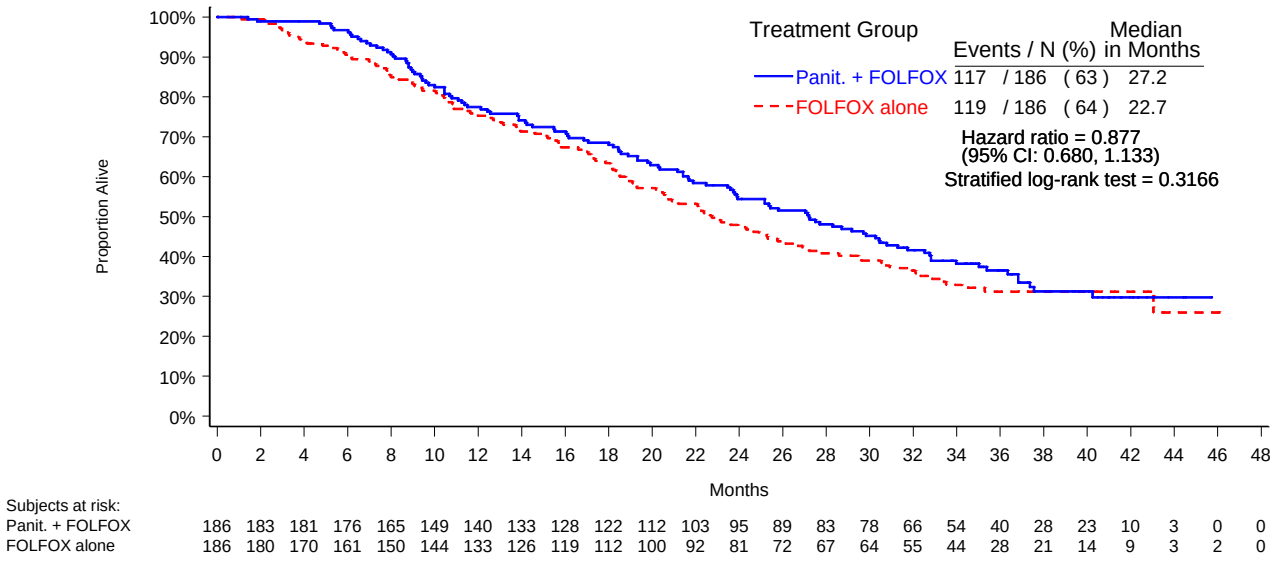


Table 24: Study 20050203 - complete resection rate (Wild-type *KRAS* Analysis Set - patients with liver-only metastases and ECOG PS of 0/1 at Baseline)

Final Analysis	Pmab + FOLFOX (N = 325)	FOLFOX (N = 331)
Patients with Liver-only Metastases at Baseline	59 (18%)	56 (17%)
Complete Resection Rate	17 (29%)	10 (18%)

Table 25: Study 20050181 – Number of patients and efficacy outcomes (co-primary Endpoints) in key subgroups (Final Analysis)

	PFS Hazard Ratio (95% CI)	OS Hazard Ratio (95% CI)
Overall (n = 597)	0.82 (0.69,0.97)	0.92 (0.78, 1.10)
ECOG 0/1 (n = 569)	0.81 (0.68,0.96)	0.91 (0.76, 1.09)
ECOG 2 (n = 28)	1.08 (0.48, 2.45)	1.14 (0.51, 2.52)
Age < 65 years (n = 361)	0.81 (0.65,1.02)	1.00 (0.80 to 1.26)
Age ≥ 65 years (n = 236)	0.79 (0.60,1.03)	0.84 (0.64 to 1.11)
Age < 75 years (n = 555)	0.82 (0.69,0.98)	0.90 (0.75 to 1.08)
Age ≥ 75 years (n = 42)	0.77 (0.39,1.51)	0.98 (0.51 to 1.91)

Table 26: Study 20050181 - Efficacy outcomes by Age < 65 Years and ≥ 65 Years in patients with Wild-type KRAS tumours (Final Analysis)

	Age < 65 years		Age ≥ 65 years	
	Panitumumab + FOLFIRI n = 179[a]	FOLFIRI Alone n = 182[a]	Panitumumab + FOLFIRI n = 124[a]	FOLFIRI Alone n = 112[a]
PFS Hazard Ratio (95% CI)	0.81 (0.65 to 1.02)		0.79 (0.60 to 1.03)	
Quantitative interaction test for PFS	p = 0.71			
Median PFS (mos)	7.4	5.1	6.1	4.2
OS Hazard Ratio (95% CI)	1.00 (0.80 to 1.26)		0.84 (0.64 to 1.11)	
Quantitative Interaction Test for OS	p = 0.53			
Median OS (mos)	14.7	13.9	14.3	11.8
Objective Response Rate[b]	38%	9%	34%	11%

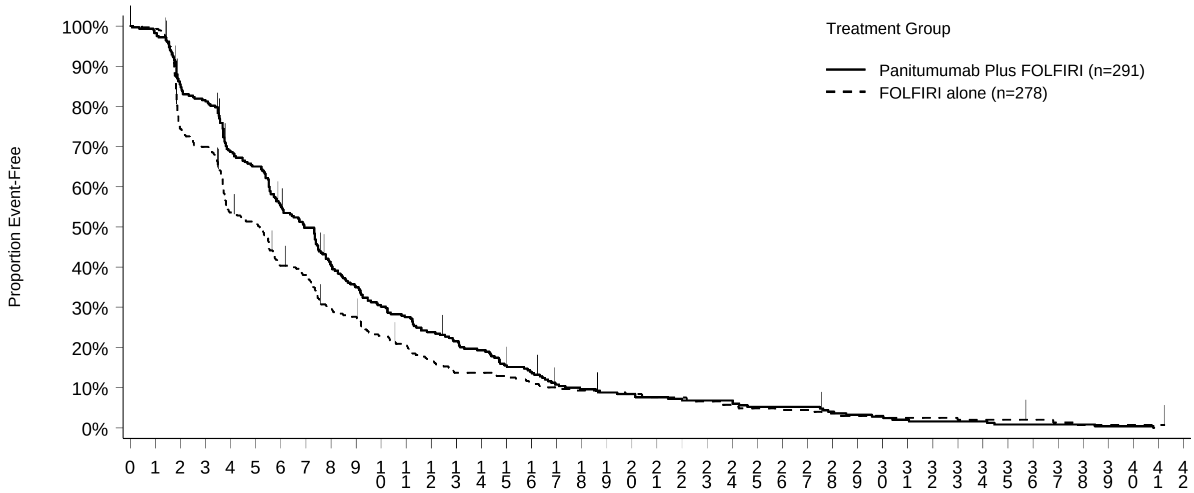
[a] Wild-type *KRAS* Efficacy Analysis Set, [c] Wild-type *KRAS* Central Tumor Response Analysis Set: Age < 65 (n = 176 pmab plus FOLFIRI, 180 FOLFIRI alone); age ≥ 65 (n = 121 pmab plus FOLFIRI, 106 FOLFIRI alone)

Table 27: Study 20050181 - Efficacy outcomes by Performance Status in patients with Wild-type KRAS (Final Analysis)

	ECOG 0/1		ECOG 2	
	Panitumumab + FOLFIRI n = 21[a]	FOLFIRI Alone n = 278[a]	Panitumumab + FOLFIRI n = 12[a]	FOLFIRI Alone n = 16[a]
PFS Hazard Ratio (95% CI)	0.81 (0.68, 0,96)		1.08 (0.48, 2.45)	
Quantitative interaction test for PFS	p = 0.88			
Median PFS (mos)	6.9	5.2	3.4	3.1
OS Hazard Ratio (95% CI)	0.91 (0.76, 1.09)		1.14 (0.51, 2.52)	
Quantitative Interaction Test for OS	p = 0.50			
Median OS (mos)	14.7	12.9	5.7	4.8
Objective Response Rate[b]	37%	29%	45%	69%

[a] Wild-type *KRAS* Efficacy Analysis Set, [b] Wild-type *KRAS* Central Tumor Response Analysis Set: ECOG 0/1 (n = 286 pmab plus FOLFIRI, 270 FOLFIRI alone); ECOG 2 (n = 11 pmab plus FOLFIRI, 16 FOLFIRI alone)

Figure 17: Study 20050181 - Kaplan-Meier plot of PFS time for patients with baseline ECOG PS of 0/1 (Central Assessment, Wild-type KRAS Analysis Set, Final Analysis)

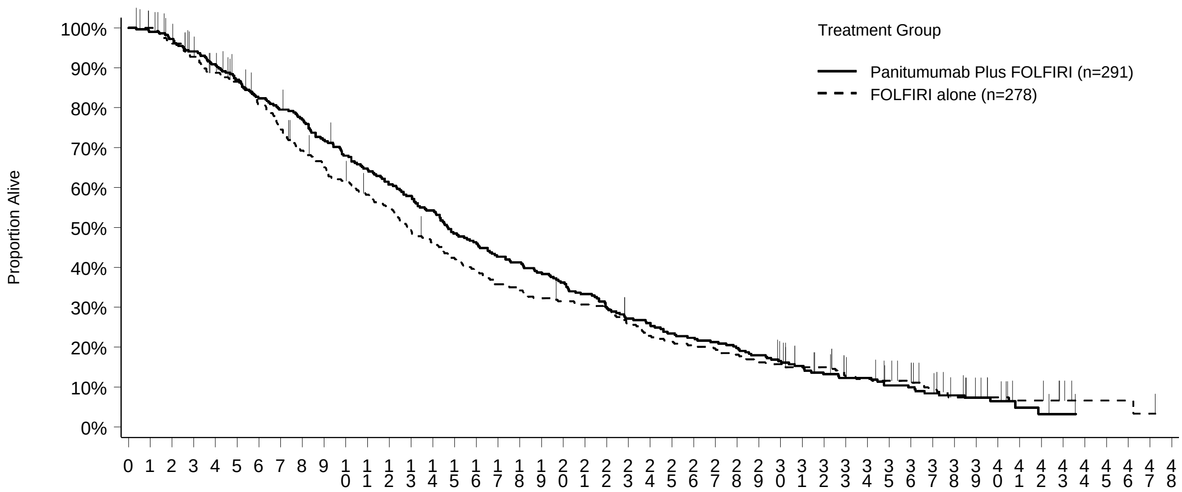


Subjects at risk:

Months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Panitumumab Plus FOLFIRI	291	278	240	228	190	180	152	136	109	94	81	74	64	57	51	41	36	27	24	22	21	19
FOLFIRI alone	278	274	202	190	143	135	106	99	76	71	58	51	42	34	34	32	28	24	22	20	19	17

Months	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Panitumumab Plus FOLFIRI	18	17	17	13	13	13	10	8	7	5	4	4	4	2	2	2	2	1	1	0	0
FOLFIRI alone	17	15	12	11	10	10	7	6	6	5	5	4	4	4	3	2	1	1	1	1	0

Figure 18: Study 20050181 - Kaplan-Meier plot of OS time for patients with baseline ECOG PS of 0/1 (Central Assessment, Wild-type KRAS Analysis Set, Final Analysis)



Subjects at risk:

Months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Panitumumab Plus FOLFIRI	291	286	278	267	258	245	230	222	214	200	188	179	168	160	150	134	128	118	114	107	100	92	83	74	71
FOLFIRI alone	278	277	266	254	240	231	216	201	183	171	162	151	142	128	119	109	100	92	88	83	80	78	75	66	58

Months	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Panitumumab Plus FOLFIRI	64	61	58	54	49	43	37	30	27	27	21	20	17	15	10	7	3	2	1	0	0	0	0	0
FOLFIRI alone	55	51	50	46	41	40	37	37	29	27	25	23	16	10	10	9	7	7	4	2	2	2	1	0

Ground #2 (add-on toxicity) The MAH argued that in both first and second line studies the toxicity of panitumumab was manageable and consistent with the addition of an EGFR inhibitor to chemotherapy and that it didn't lead to any higher discontinuation of treatment in any of the two studies. The MAH submitted further subgroup safety analyses in patients with ECOG 0/1 PS and age <65 years for the first line 20050203 study and in patients with ECOG 0/1 PS for the second line 20050181 study.

Table 28: Study 20050203 - Safety by ECOG Status and Age 65 Status (Wild-Type KRAS Safety Analysis Set: Final Analysis)

%	ECOG 0/1 Age < 65 Pmab vs No Pmab (N=185) vs (N=183)	ECOG 0/1 Age ≥ 65 Pmab vs No Pmab (N=118) vs (N= 124)	ECOG 2 Age < 65 Pmab vs No Pmab (N=9) vs (N=13)	ECOG 2 Age ≥ 65 Pmab vs No Pmab (N=10) vs (N=7)
Serious adverse event	34 vs 34	53 vs 38	78 vs 46	50 vs 29
Grade 3 Grade 4 Grade 5	61 vs 53 24 vs 16 3 vs 6	50 vs 46 34 vs 25 7 vs 6	44 vs 46 44 vs 15 11 vs 8	50 vs 29 20 vs 29 10 vs 0

Table 29: Study 20050203 - Summary of Adverse Events in patients with ECOG 0/1 PS and Age < 65 (Wild-type KRAS Safety Analysis Set, Final Analysis)

	Panitumumab Plus FOLFOX (N = 185)	FOLFOX Alone (N = 183)
Subjects with any adverse event - n(%)	185 (100)	181 (99)
Worst grade of 3[a]	113 (61)	97 (53)
Worst grade of 4[a]	44 (24)	30 (16)
Worst grade of 5[a]	6 (3)	11 (6)
Any Serious	62 (34)	63 (34)
Leading to permanent discontinuation of chemotherapy	29 (16)	26 (14)

Adverse events were coded using the MedDRA dictionary V12.0.
[a]Severity graded using the CTCAE v 3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications. Fatal adverse events are classified as grade 5.

Table 30: Study 20050203 - Patient Incidence of Grade 3 or Higher Adverse Events with ≥ 5% Difference Between Treatment Arms in Descending Order of Preferred Term for patients with Baseline ECOG PS: 0/1 and Age < 65 (Wild-type KRAS Safety Analysis Set)

Preferred Term	Panitumumab Plus FOLFOX (N = 185)	FOLFOX Alone (N = 183)	Total (N = 368)
Subjects with any adverse event - n(%)	163 (88)	138 (75)	301 (82)
Rash	36 (19)	1 (1)	37 (10)
Diarrhoea	29 (16)	13 (7)	42 (11)
Dermatitis acneiform	23 (12)	0 (0)	23 (6)
Fatigue	20 (11)	1 (1)	21 (6)
Hypokalaemia	18 (10)	8 (4)	26 (7)
Hypomagnesaemia	11 (6)	1 (1)	12 (3)

Table 31: Study 20050181 - Summary of Adverse Events in patients With ECOG 0/1 Status (Wild-type KRAS Safety Analysis Set, Final Analysis)

	Panitumumab Plus FOLFIRI (N = 291)	FOLFIRI Alone (N = 278)
Subjects with any adverse event - n(%)	290 (100)	273 (98)
Worst grade of 3	155 (53)	98 (35)
Worst grade of 4	57 (20)	46 (17)
Worst grade of 5	12 (4)	15 (5)
Any Serious	119 (41)	81 (29)
Leading to permanent discontinuation of chemotherapy	46 (16)	38 (14)

Table 32: Study 20050181 - Subject Incidence of Grade 3 or Higher Adverse Events with a ≥ 5% Difference Between Treatment Arms in Descending Order of Preferred Term in Study 20050181 (Wild-type KRAS Safety Analysis Set - patients with Baseline ECOG Performance Status of 0/1)

Preferred Term	Panitumumab plus FOLFIRI (N = 291)	FOLFIRI Alone (N = 278)	Total (N = 569)
Subjects with any adverse event - n(%)	224 (77)	159 (57)	383 (67)
Rash	45 (15)	0 (0)	45 (8)
Diarrhoea	40 (14)	25 (9)	65 (11)
Dermatitis acneiform	28 (10)	0 (0)	28 (5)
Hypokalaemia	19 (7)	3 (1)	22 (4)

With regard to the deterioration of PFS and OS for patients with mutant KRAS tumour status with panitumumab in combination with FOLFOX specifically, the MAH argued that most of the fatal adverse events were in the setting of disease progression and that no single cause appeared to account for the worse outcomes or increased incidence of fatal adverse events. They considered that a pharmacodynamic interaction between panitumumab and oxaliplatin that attenuates the treatment effect of oxaliplatin likely contributed to the negative outcomes and that for patients with mutant *KRAS* mCRC tumours or for whom *KRAS* mCRC tumour status is unknown, the combination of panitumumab with oxaliplatin-based chemotherapy should be contraindicated.

Integument-related toxicity is the most common reason for the increase in adverse and serious adverse events associated with panitumumab treatment. Interestingly, it has been reported that subjects who experience greater skin toxicity derive more clinical benefit from EGFR antibodies (Van Cutsem et al, 2011), as skin toxicity represents a pharmacodynamic consequence of EGFR inhibition. In the first line study 20050203, for patients with wild-type *KRAS* tumour status with maximum skin toxicity of grade 2 to 4 vs grade 1, median PFS (n = 305) was 10.8 months vs 6.0 months (hazard ratio = 0.63; 95% CI: 0.42-0.93; p = 0.019), and median OS (n = 308) was 28.3 months vs 11.5 months (hazard ratio = 0.47; 95 CI: 0.32-0.71; p = 0.0002. Similarly, in the second line study 20050181, for patients with wild-type *KRAS* status with skin toxicity of grade 2 to 4 vs grade 1, median PFS was 7.4 months vs 5.2 months (hazard ratio = 0.67; 95% CI: 0.49-0.90, p = 0.009); median OS was 16.5 months vs 10.3 months (hazard ratio = 0.46; 95 CI: 0.33-0.65; p < 0.0001).

Ground #3 (reliability and use of KRAS testing in clinical practice) The MAH repeated that only patients with wild-type *KRAS* tumour status confirmed using a validated test kit should be treated with panitumumab and that panitumumab should not be administered to patients with mutant *KRAS* tumours or patients who have not been evaluated for *KRAS* tumour status. Moreover, they argued that

- Awareness of the importance of KRAS testing prior to initiation of anti-EGFR agents is high. Current EU mCRC therapy guidelines (Van Cutsem et al, 2010) support the need for KRAS testing in patients with mCRC, and this recommendation is reflected in the currently approved SmPC.
- KRAS mutations occur early in tumourigenesis, and once acquired, are maintained throughout carcinogenesis; therefore test results can be relied on to always reflect the current state of disease, even if based on archived tumour tissue.
- The current KRAS testing methods are robust, sensitive, specific (false positive and false negative results in the order of 1%) and KRAS testing is one of the most accurate molecular diagnostic tools in oncology (compared to HER2 and EGFR testing) regardless of the method used.
- Wild-type KRAS tumour status is required for reimbursement for EGFR monoclonal antibody use in all EU member states. It is therefore highly unlikely that a significant number of patients with unknown or mutant KRAS tumour status would be treated with panitumumab.
- Risks from wrongly administering panitumumab to patients with mutant KRAS tumour status or patients that have not been tested for KRAS tumour status can be managed via proposed routine risk minimisation activities through the Product Information and additional risk minimisation activities proposed in the risk management plan.

Ground #4 (benefit-risk balance) The MAH argued that with regard to the combination with FOLFOX:

- Panitumumab represents an important therapeutic option for appropriately selected patients (ECOG status 0/1 and < 65 years of age).
- The increase in complete resection rate in subjects with metastases to the liver only at baseline represents an important clinical benefit. Given that complete resection of metastases is the only chance for long term survival, or possibly cure, for patients with mCRC, the use of panitumumab in combination with FOLFOX should be offered as a treatment option for patients with resectable disease.

Moreover, with regard to the combination with FOLFIRI the MAH argued that:

- the overall benefit-risk of panitumumab in combination with FOLFIRI has been established based on the results of Study 20050181. However, the benefit-risk profile of this combination is questionable in patients with ECOG 2 status.

Based on all the MAH arguments presented above and additional analyses (responses to Grounds #1-4), the MAH proposed to restrict the indication of panitumumab in combination with chemotherapy for the treatment of metastatic colorectal carcinoma as follows:

- *in combination with FOLFIRI for patients with ECOG 0/1 performance status*
- *in combination with FOLFOX for patients with ECOG 0/1 performance status and who are less than 65 years of age or for patients who are eligible for resection of liver metastases"*

Scientific Advisory Group-Oncology consultation

The CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the MAH's response. In addition, the experts were requested to respond to a number of questions related to the re-analyses presented by the MAH, and they considered the following:

First line of metastatic CRC in combination with FOLFOX

1. Study 20050203 shows the following effect of panitumumab+FOLFOX as compared to placebo+FOLFOX:

- A median PFS increase in wild-type KRAS patients of 1.4 months and hazard ratio of 0.80 (p=0.009)

- A not statistically significant difference in median survival of 4 months and hazard ratio of 0.88 (p=0.17)

- A significant increase in objective response rate: 57% vs. 48% (p=0.02)

- No demonstrated benefit in QoL outcomes, with numerical differences in favour of chemotherapy alone

In the light of these data, does the SAG consider that the effect of panitumumab added to FOLFOX in first line treatment of mCRC is clinically relevant as to outweigh the increased toxicity observed with the combination?

The SAG considered that the clinical efficacy of panitumumab in the first line treatment of wild-type KRAS, metastatic colorectal cancer in combination with FOLFOX was demonstrated.

This conclusion pertains specifically to the combination with FOLFOX at the applied dose and schedule and it cannot be extrapolated to other oxaliplatin regimens. One reason that could explain discrepancies with other schedules is that overlapping toxicity between panitumumab and non-FOLFOX oxaliplatin regimens tested in clinical trials (e.g. capecitabine-XELOX) led to interruptions/dose reductions of the chemotherapy with loss in efficacy.

The toxicity overall seems to be manageable.

It is at this moment uncertain which biological factors besides Kras mutational status affect activity of panitumumab in this combination.

The size of the effect in combination with FOLFOX appears to be smaller in comparison to the combination of panitumumab with FOLFIRI in second line treatment due to uncertain biological factors.

The ECOG performance score was a moderate predictor of activity in the first line setting whereas age did not have any predictive value.

Skin rash in the course of treatment appears to be a predictive marker of benefit from panitumumab, but this will need to be further substantiated. Towards this end, the MAH may present outcomes of patients in the chemotherapy alone arms of the two pivotal trials according to the appearance and the grade of skin rash. There is evidence from trials with other EGFR inhibitors to suggest that patients who develop rash although not receiving EGFR inhibitors fare better compared to patients who do not develop rash at all, a fact which would argue against skin rash being a predictor of specific anti-EGFR activity. However, based on the currently available data, skin rash in the course of panitumumab treatment may be used to guide clinical decision making.

2. Patients with ECOG performance status 2 show a significant increase in toxicity associated with significantly shorter PFS and OS compared with FOLFOX alone. Similarly, patients older than 75 years present increased mortality and no effect on PFS and OS (HR≥1).

2.1. How does the SAG interpret the lack of consistency of the results described above across the study population?

The SAG noted the low numbers of patients in various subgroups (ECOG PS 2, old age). They considered that subgroup analyses in the absence of both hypothesis testing and adequate statistical power should be interpreted with caution. Based on the existing data, relevant decisions on practical clinical use are better left to clinical judgement.

2.2. Does the SAG consider that restricting the indication to patients with ECOG 0-1 would resolve this concern?

Based on limited available data, there are concerns about the benefit/risk balance in certain patients with ECOG PS 2 in this treatment setting, but no overall recommendations can be made for PS2 patients (refer also to 2.1). It is conceivable, for example, that patients with ECOG PS 2 due to disease burden may be better able to benefit from panitumumab treatment compared to patients with similar performance status due to co-morbidities.

2.3 Considering data from study 20050203, does the SAG-O consider that older age is an independent predictor of poor response and increased toxicity in patients treated with panitumumab?

The SAG do not consider old age (of any cut-off) as an independent risk factor, but toxicity may be considerably increased in older patients in this treatment setting (refer also to 2.1). Based on available data, there is no biological rationale to suggest a restriction based on age, e.g. data to suggest different pharmacokinetics of panitumumab in older patients. Such pharmacological (pharmacokinetic-dynamic) data are lacking.

3. Does the SAG consider that, based on the data provided, a detrimental effect of the addition of panitumumab in patients with mutant KRAS tumours can be reasonably excluded? Is KRAS testing in clinical practice performed without exception by all treating physicians and is the quality of the available KRAS tests sufficiently reliable to ensure that patients with mutant KRAS tumours will not be treated with panitumumab?

The SAG considered that a detrimental effect of the addition of panitumumab in patients with mutant KRAS tumours cannot be excluded. Patients with mutant KRAS tumours should be excluded from treatment with panitumumab. The SAG also considered that clinically available KRAS testing is sufficiently reliable and that panitumumab should not be used in untested patients, but it should only be used in patients with wild-type KRAS tumours.

Second line of metastatic CRC in combination with FOLFIRI

4. Study 20050181 shows the following effect of panitumumab+FOLFIRI as compared to placebo+FOLFIRI:

- A median PFS increase in wild-type KRAS patients of 1.8 months and hazard ratio of 0.82 (p=0.002);

- A no effect in overall survival, with a median difference of 2 months and hazard ratio of 0.92 (p=0.37)]

- A significant increase in objective response rate: 36% vs. 10% (p=0.0001)

- No demonstrated benefit in QoL outcomes, with numerical differences in favour of chemotherapy alone

In the light of these data, does the SAG consider that the effect of panitumumab added to FOLFIRI in second line treatment of mCRC is clinically relevant as to outweigh the increased toxicity observed with the combination?

The SAG considered that the effect of panitumumab added to FOLFIRI in second line treatment of mCRC is clinically relevant as to outweigh the increased toxicity of the combination. As already noted in the answer to question 1, the effect appears in fact to be stronger with the FOLFIRI combination than with the FOLFOX combination at the applied dose and schedule. This conclusion pertains specifically to the combination with FOLFIRI at the applied dose and schedule and it should not be extrapolated to other irinotecan regimens.

General question

5. Does the SAG-O overall consider the results observed for panitumumab to be in line with what has been observed for cetuximab? If not, what could possibly be the reasons considering the same mechanism of action of the two drugs?

Caution should always be exercised in comparing results from different trials. Notwithstanding that, results from trials with cetuximab and panitumumab seem broadly comparable. On this point, it is of note that in the two more readily comparable last-line monotherapy trials the post-progression cross-over to subsequent anti-EGFR therapy was much higher in the panitumumab trial (76%) than it was in the cetuximab one (7%), which may have confounded Overall Survival results in the case of panitumumab. On the other hand, the two antibodies belong to different subclasses of IgG and they apparently differ in their molecular pharmacology (e.g. ADCC, avidity, FcR binding), so that different outcomes from the two antibodies clinically cannot be excluded. In this respect, differences in the rate of infusion reactions and in the treatment schedule between the two drugs are also of relevance.

In addition, the SAG-oncology wished to stress that panitumumab treatment should only be considered in patients who are anti-EGFR therapy naïve.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group-Oncology that unanimously expressed a positive opinion towards the positive benefit/risk of the requested indications (combination with FOLFOX-first line indication and the combination with FOLFIRI–second line indication).

The Committee noted that although the improvement in median PFS was modest, it is within the same magnitude as that seen with other biological agents added to chemotherapy in both first and second line treatment and that the addition of anti-EGFR antibodies to chemotherapy in these disease settings is established in clinical practice in the EU. Especially in second line treatment (combination with FOLFIRI) the observed effect may be of higher clinical relevance given the poorer health status and worse prognosis of patients in this setting.

The lack of support by statistically significant improvements of OS could indeed be attributed to subsequent anti-EGFR therapy which was higher in the control arms of both studies (25.4% vs 12.9% with panitumumab add-on in patients with wild-type KRAS tumours in the first line FOLFOX study [Table 6] and 34.4% vs 12.5%, respectively, in the same population in the second line FOLFIRI study [Table 11]). The fact that patients in the control arms of the panitumumab studies were likely to cross over and receive subsequent anti-EGFR therapy once out of the studies and that this cross-over was higher in these later panitumumab studies compared to earlier cetuximab ones, may be seen as an indicator that the addition of anti-EGFR antibodies to chemotherapy for mCRC has been increasing.

Although the clinical relevance of ORR may not have been established for this type of agent in first and second line treatment of mCRC, the observed improvement cannot be ignored and it can be of clinical relevance in the first line setting, as a response (tumour shrinkage) may render the tumour resectable and thus allow surgical resection of metastases in certain cases, which may significantly prolong survival of patients eligible for this resection.

With regard to the inferior (in some instances numerically worse) results observed in elderly patients and patients with poor ECOG Performance Status (ECOG PS 2), the CHMP considered that indeed the numbers of patients in the relevant subgroups of the two studies are small and that the relevant post-hoc subgroup analyses should be interpreted with caution. It was therefore not considered appropriate to restrict any potential indication based on age or performance status. It is already clinical reality and it is reinforced via adequate warnings and precautions in the Product Information that decisions to use panitumumab in combination with chemotherapy in mCRC are based on clinical judgement which takes into account individual patient characteristics, including performance status and age. Furthermore, skin rash in the course of panitumumab treatment may be used to guide clinical decision making, although no strict recommendations can be given at present. No additional analyses were presented by the MAH on the potential value of skin rash as a predictive marker of benefit from panitumumab, as proposed by the SAG-O, but the MAH confirmed during the Oral Explanation that no skin rash was observed in patients receiving chemotherapy only, other than the Palmar-Plantar Erythrodysaesthesia (or hand-foot) Syndrome, as expected during treatment with fluoropyrimidines.

In terms of Quality of Life, the CHMP noted that, although an improvement in this would have been desirable, QoL was by and large unaffected by the addition of panitumumab to chemotherapy, even so in patients experiencing the common skin rash and diarrhoea. Moreover, the Committee was reassured by clinical experts' affirmations that toxicity of panitumumab was indeed manageable and that there is experience in handling panitumumab toxicity in clinical practice. With regard to elderly patients, who tended to show increased toxicity, it was confirmed that it is usual clinical practice for this type of anti-cancer agents to exercise expert clinical judgement in deciding who should receive panitumumab add-on taking into account performance status and other clinical considerations (disease burden, comorbidities etc).

Panitumumab should only be used in patients with wild-type KRAS tumour status and it should not be used in patients with mutant KRAS tumour status or in patients who have not been tested. The Committee was reassured that the KRAS testing methods were widely available and used in clinical practice, that the methods are robust and adequately sensitive and specific, at least as much as other established diagnostic methods such as HER2 and EGFR testing. In considering the SAG-O outcome the CHMP decided to contraindicate the combination of Vectibix with FOLFOX in patients with mutant *KRAS* mCRC or patients whose KRAS tumour status is unnown. Moreover, the risk of administering panitumumab to mutant KRAS tumour patients can be adequately managed via the agreed risk management plan (please refer to Risk Management Plan below).

With regard to biomarkers other than KRAS, the CHMP agreed that the level of EGFR expression does not play a major role in CRC in contrast to non-small cell lung cancer (NSCLC) and squamous cell

cancer of the head and neck (SCCHN), in which mean expression levels of EGFR are much higher and there is much larger inter-tumour variability. The CHMP stressed the importance of attempts to identify such biomarkers that could potentially help better the target population of panitumumab.

In conclusion, the CHMP considered after reviewing the additional subgroup efficacy analyses provided by the MAH and considering the expert advice received from the SAG-Oncology, that there is sufficient reassurance that the toxicity observed for panitumumab in combination with FOLFOX as first line treatment of patients with mCRC and in combination with FOLFIRI as second line treatment is manageable and no longer constitutes a major issue. It was confirmed by the experts, for example, that careful monitoring of skin toxicity is an established practice, which can be used to guide clinical decision making. Overall, the efficacy was considered to be clinically relevant in the applied doses and schedules of the specific combinations and very consistent with the known effect of other drugs with similar mechanism of action used in the same clinical setting. However, these conclusions cannot be considered to apply in general to other chemotherapy combinations. The product information has been amended to adequately reflect these restrictions.

The CHMP also acknowledged that in line with the advice received from the expert group, subgroup-specific trial mortality results cannot provide a reliable basis for individualising patient care, due to the play of chance. Thus, the CHMP concluded that the results in poor performance status and older age subgroups should be interpreted more cautiously as they may lead to a significant number of patients being left untreated inappropriately. Sufficient reassurance was provided from the expert group that clinical decisions can be sufficiently informed by the available data to allow adequate patient selection and management of toxicity depending on the clinical characteristics of the patients. Overall, the apparent lack of consistency in light of the unfavourable results seen in elderly and poor health status subgroups was no longer considered a major concern.

The CHMP was also reassured that KRAS testing is widely available in clinical practice and that its operational characteristics are adequate and well defined. The product information was amended on this issue and, most prominently, a contraindication was added on the use of panitumumab in combination with oxaliplatin-containing chemotherapy in patients with mutant KRAS tumour status or for whom KRAS status is unknown. Moreover, the agreed risk management plan and the additional risk minimisation activities in the form of physician educational materials can adequately manage the risk of treating with panitumumab patients with mutant KRAS tumours or patients whose KRAS tumour status is unknown, so that this risk was sufficiently low as not to pose a major concern. Finally, the CHMP agreed on the wording of a Direct Healthcare Professional Communication (please refer to Attachment 13) to be circulated to prescribers prior to the start of use of Vectibix with the aim to raise awareness on the issue of KRAS testing and its role during treatment with panitumumab.

Taking all these considerations into account, the CHMP revised its initial opinion and concluded that the benefit-risk balance of panitumumab in combination with FOLFOX as first line treatment of patients with mCRC and in combination with FOLFIRI as second line treatment of patients with mCRC who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) for their disease was positive.

Risk Management Plan

The MAH submitted an updated risk management plan with this application for an extended indication, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety Concern	Pharmacovigilance Activities	Risk Minimization Activities
Identified Risks		
Integument and eye toxicity	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.2 Posology and Method of Administration Statement that modification of Vectibix may be necessary in cases of severe (≥ grade 3) dermatological reactions 4.4 Special Warnings and Precautions for Use (Dermatological Reactions) Description of dermatologic reactions and recommendations for dose modifications, preventive measures, and treatment 4.4 Special Warnings and Precautions for Use (Ocular toxicities) Description of rare, serious cases of keratitis and ulcerative keratitis in the post-marketing setting, recommendations for treatment discontinuation, and precautions for use in patients with a history of keratitis, ulcerative keratitis or severe dry eye, or contact lens use 4.8 Undesirable Effects <u>Tabulated Summary of Adverse Reactions</u> Under eye disorders, conjunctivitis listed as very common; blepharitis, growth of eyelashes, lacrimation increased, ocular hyperaemia, dry eye, eye pruritus, and eye irritation listed as common; eyelid irritation and keratitis listed as uncommon; ulcerative keratitis listed as rare Under skin and subcutaneous tissue disorders, dermatitis acneiform, rash, erythema, pruritus, dry skin, skin fissures, acne, and alopecia listed as very common; palmar-plantar erythrodysesthesia syndrome, skin ulcer, scab, hypertrichosis, onychoclasis, and nail disorder listed as common; angioedema, hirsutism, ingrowing nail, and onycholysis listed as uncommon <u>Description of Selected Adverse Reactions</u> Skin and Subcutaneous Skin Disorders: Description of skin rash and infectious complications in the clinical trial and postmarketing settings Ocular Toxicities: Description of keratitis, including nonserious events (in the clinical trial setting) and serious events (in the postmarketing setting)
Stomatitis and oral mucositis	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.8 Undesirable Effects Tabulated Summary of Adverse Reactions Stomatitis listed as very common
Pulmonary toxicity	Routine - Postmarketing surveillance - Clinical study safety monitoring Additional - Enhanced monitoring targeted questions (by questionnaire or by the	4.3 Contraindications Interstitial pneumonitis or pulmonary fibrosis 4.4 Special Warnings and Precautions for Use Description of interstitial lung disease and recommendations for treatment interruption of discontinuation 4.8 Undesirable Effects Tabulated Summary of Adverse Reactions Under respiratory, thoracic and mediastinal disorders,

	use of clinical queries	dyspnea and cough listed as very common; pulmonary embolism and epistaxis listed as common; bronchospasm and nasal dryness listed as uncommon
Hypomagnesemia, hypocalcemia, and hypokalemia	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.4 Special Warnings and Precautions for Use Description of electrolyte disturbances and recommendations for treatment 4.8 Undesirable Effects Tabulated Summary of Adverse Reactions Hypomagnesemia and hypokalemia listed as very common; hypocalcemia listed as common
Diarrhea	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.4 Special Warnings and Precautions for Use Description of diarrhea in patients receiving Vectibix in combination with IFL chemotherapy and in combination with bevacizumab and chemotherapy 4.5 Interaction with other medicinal products and other forms of interaction Description of severe diarrhea in patients receiving Vectibix in combination with IFL chemotherapy 4.8 Undesirable Effects Tabulated Summary of Adverse Reactions Diarrhea listed as very common Description of Selected Adverse Reactions Gastrointestinal Disorders: Description of diarrhea and reports of acute renal failure in patients who developed diarrhea and dehydration Other Special Populations Description of an increased number of serious adverse events of diarrhea with Vectibix plus FOLFOX or FOLFIRI relative to FOLFOX or FOLFIRI alone in elderly patients (≥ 65 years of age)
Dehydration	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.4 Special Warnings and Precautions for Use Description of dehydration in patients receiving Vectibix in combination with bevacizumab and chemotherapy 4.8 Undesirable Effects Tabulated Summary of Adverse Reactions Dehydration listed as common Description of Selected Adverse Reactions Gastrointestinal Disorders: Reports of acute renal failure in patients who developed diarrhea and dehydration Other Special Populations Description of an increased number of serious adverse events of dehydration with Vectibix plus FOLFIRI relative to FOLFIRI alone in elderly patients (≥ 65 years of age)
Infusion reactions and other hypersensitivity reactions	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.2 Posology and Method of Administration Statement that a reduction in the rate of infusion of Vectibix may be necessary in cases of infusion-related reactions 4.3 Contraindications History of severe or life-threatening hypersensitivity reactions to the active substance or to any of the excipients 4.4 Special Warnings and Precautions for Use Description of infusion-related reactions, including rare post-marketing reports with a fatal outcome, and recommendations for treatment discontinuation or

		reduction in infusion rate (for mild or moderate reactions) 4.8 Undesirable Effects Tabulated Summary of Adverse Reactions Infusion-related reaction listed as uncommon, hypersensitivity listed as common, anaphylactic reaction listed as rare Description of Selected Adverse Reactions Infusion related reactions: Description of infusion-related reactions in clinical trials, including a case of fatal angioedema in a patient with recurrent and metastatic squamous cell carcinoma of the head and neck, and hypersensitivity reactions occurring > 24 hours after infusion in the postmarketing setting
Lack of Response and Negative Effects in Combination with Oxaliplatin-Based Chemotherapy in Patients with Mutant KRAS Tumors	Routine: - Postmarketing surveillance - Clinical study safety monitoring Additional - Conduct a physician survey to assess knowledge of the important of KRAS testing over time (Protocol 20101120) - Conduct a medical records review study specifically assessing the impact of the KRAS test results on patterns of panitumumab use (Protocol 20101121)	4.1 Therapeutic Indications Vectibix is indicated for the treatment of patients with wild-type KRAS metastatic colorectal cancer 4.2 Posology and Method of Administration Statement that evidence of wild-type KRAS status is required before initiating treatment with Vectibix and that KRAS mutational status should be determined using a validated test method by an experienced laboratory. 4.3 Contraindications Patients with mutant KRAS mCRC or for whom KRAS mCRC status is unknown 4.4 Special Warnings and Precautions for Use (Vectibix in combination with oxaliplatin-based chemotherapy in patients with mutant KRAS mCRC or for whom KRAS tumor status is unknown) Description of shortened progression free survival and overall survival in patients with mutant KRAS tumors who received panitumumab and FOLFOX vs FOLFOX alone 4.5 Interaction with other medicinal products and other forms of interaction Description of shortened progression free survival and overall survival in patients with mutant KRAS tumors who received panitumumab and FOLFOX vs FOLFOX alone. Statement that Vectibix should not be administered to patients with mutant KRAS mCRC or for whom KRAS tumor status is unknown in combination with oxaliplatin-containing chemotherapy. 5.1 Pharmacodynamic Properties Description of shortened progression free survival and overall survival in patients with mutant KRAS tumors who received panitumumab and FOLFOX vs FOLFOX alone Additional: Provide annual updates to the CHMP with relevant publicly available information on the progress of the ESP quality assurance programme in KRAS mutation testing Provide in the annual update to the CHMP any further relevant non-publicly available information that the ESP group have shared with the MAH (provided that the ESP are in agreement that this data can be shared with CHMP Provide educational materials to inform healthcare

		practitioners of the importance of KRAS ascertainment before treatment with panitumumab
Worse outcomes in patients with poor performance status (ECOG 2) receiving panitumumab in combination with chemotherapy for mCRC	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.4 Special Warnings and Precautions for Use (Patients with ECOG 2 performance status treated with Vectibix in combination with chemotherapy) Statement that for patients with ECOG 2 performance status, assessment of benefit-risk is recommended prior to initiation of Vectibix in combination with chemotherapy for treatment of mCRC, and that a positive benefit-risk balance has not been documented in patients with ECOG 2 performance status 5.1 Pharmacodynamic Properties Description of shortened progression free survival and overall survival with panitumumab plus FOLFOX relative to FOLFOX alone in patients with an ECOG performance status of 2
Anorexia	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.8 Undesirable Effects Tabulated Summary of Adverse Reactions Anorexia listed as very common
Weight decreased	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.8 Undesirable Effects Tabulated Summary of Adverse Reactions Decreased weight listed as very common
Pulmonary embolism	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.4 Special Warnings and Precautions for Use Description of pulmonary embolism in patients receiving Vectibix in combination with bevacizumab and chemotherapy 4.8 Undesirable Effects Tabulated Summary of Adverse Reactions Pulmonary embolism listed as common Description of Selected Adverse Reactions Other Special Populations Description of an increased number of serious adverse events of pulmonary embolism with Vectibix plus FOLFIRI relative to FOLFIRI alone in elderly patients (≥ 65 years of age)
Potential Risks		
Vascular toxicity	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.8 Undesirable Effects Tabulated Summary of Adverse Reactions Deep vein thrombosis, hypotension, hypertension, flushing listed as common
Cardiac toxicity	Routine - Postmarketing surveillance - Clinical study safety monitoring	None
Immunogenicity	Routine - Postmarketing surveillance - Clinical study safety monitoring	5.1 Pharmacodynamic Properties Description of the incidence of anti-panitumumab antibody formation in clinical trials (monotherapy and in combination with chemotherapy)
Delayed wound healing	Routine - Postmarketing surveillance - Clinical study safety monitoring	None
Missing or limited patient populations with no or limited safety data		

Pregnancy	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.6 Fertility, pregnancy and lactation Statement that there are no adequate data on the use of Vectibix in pregnant women. In women of childbearing potential, appropriate contraceptive measures must be used during treatment with Vectibix, and for 6 months following the last dose. Women who become pregnant during Vectibix treatment are encouraged to enroll in Amgen's Pregnancy Surveillance programme. Contact details are provided in section 6 of the Package Leaflet – Information for the user.
Lactation	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.6 Fertility, pregnancy and lactation Statement that it is unknown whether panitumumab is excreted in human breast milk. Because human IgG is secreted into human milk, panitumumab might also be secreted. It is recommended that women do not breast feed during treatment with Vectibix and for 3 months after the last dose.
Pediatric patients	Routine - Postmarketing surveillance - Clinical study safety monitoring Additional - Pediatric study (20050252)	4.2 Posology and Method of Administration Statement that there is no experience in children and Vectibix should not be used in those patients less than 18 years of age. 4.8 Undesirable Effects Description of Selected Adverse Reactions Paediatric Population Statement that there is no experience in children and Vectibix should not be used in those patients less than 18 years of age.
Nonwhite patients	Routine - Postmarketing surveillance - Clinical study safety monitoring	None
Patients with renal, hepatic, cardiac, or pulmonary impairment	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.2 Posology and Method of Administration Statement that the safety and efficacy of Vectibix have not been studied in patients with renal or hepatic impairment 4.3 Contraindications Interstitial pneumonitis or pulmonary fibrosis 4.4 Special Warnings and Precautions for Use Statement that patients with a history of, or evidence of, interstitial pneumonitis or pulmonary fibrosis were excluded from clinical studies 4.8 Undesirable Effects Description of Selected Adverse Reactions Statement that the safety and efficacy of Vectibix have not been studied in patients with renal or hepatic impairment 5.2 Pharmacokinetic Properties Statement that no clinical studies have been conducted to examine the pharmacokinetics of Vectibix in patients with renal or hepatic impairment
Patients who receive panitumumab at a dose schedule that has not been evaluated extensively	Routine - Postmarketing surveillance - Clinical study safety monitoring	4.2 Posology and Method of Administration Statement that the recommended dose of Vectibix is 6 mg/kg of body weight given once every two weeks. 4.9 Overdose Statement that doses up to 9 mg/kg have been tested in clinical trials. There have been reports of overdose at doses up to approximately twice the recommended

		therapeutic dose (12 mg/kg). Adverse events observed included skin toxicity, diarrhea, dehydration and fatigue and were consistent with the safety profile at the recommended dose.
Patients with cancer type other than refractory mCRC	Routine - Postmarketing surveillance - Clinical study safety monitoring	None
Biomarkers	Routine - Postmarketing surveillance - Clinical study safety monitoring Additional - Investigation of potential biomarker development based on assessment of blood cells, tumor cells, and the proposed mechanism of action of panitumumab in Study 20050181 and 20050203	None

The CHMP, having considered the data submitted in the application is of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns and that the following risk minimisation activities were required for the safe and effective use of the medicinal product:

- The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe Vectibix are provided with educational materials informing them of the importance of KRAS ascertainment before treatment with panitumumab. The key elements of these educational materials will be the following:
  - Brief introduction to the Vectibix indication and the purpose of this tool
  - Brief introduction to KRAS and its role in the panitumumab mechanism of action
  - Information that in patients with mutant KRAS tumours panitumumab has shown a detrimental effect in combination with FOLFOX and no effect as monotherapy and in combination with FOLFIRI
  - Recommendation that Vectibix:
    - should only be used in patients whose tumours are wild-type KRAS
    - should not be used in patients whose tumours are mutant KRAS or patients whose tumours have not been tested for KRAS status
    - is contraindicated in combination with FOLFOX in patients with mutant KRAS tumours
  - Information on how the testing should be appropriately conducted

The Marketing Authorisation Holder shall agree the format and content of the above materials with the National Competent Authority of each Member State.

Recommendation following re-examination

Based on the CHMP review of data on safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the risk-benefit balance of Vectibix in the treatment of metastatic colorectal cancer:

- in first line in combination with FOLFOX

- in second line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan),

was favourable and that the application satisfied the criteria for authorisation and recommended the granting of the variation to the terms of the marketing authorisation.

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