27 June 2013
EMA/413562/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vectibix

International non-proprietary name: PANITUMUMAB

Procedure No. EMEA/H/C/000741/II/0050

Note

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

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List of abbreviations

BRAF	virus-induced Rapidly Accelerated Fibrosarcoma (v-raf) B1 homologue
BSC	best supportive care
CI	confidence interval
CTCAE	common terminology criteria for adverse events
DHPC	direct healthcare professional communication
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EOI	events of interest
ESP	European Society of Pathologists
FOLFIRI	folinic acid (leucovorin), 5-fluorouracil, irinotecan
FOLFOX	folinic acid (leucovorin), 5-fluorouracil, oxaliplatin
GTP	guanosine triphosphate
HPLC	high performance liquid chromatography
HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene
IUO	investigational use only
KRAS	Kirsten rat sarcoma 2 viral oncogene homologue
mCRC	metastatic colorectal cancer
NRAS	neuroblastoma RAS viral (v-ras) oncogene homolog
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PEB	Physician Education Booklet
PFS	progression free survival
QA	quality assurance
RAS	rat sarcoma
TTP	time to progression
VEGF	vascular endothelial growth factor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 7 May 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Vectibix	panitumumab	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6.a	Change(s) to therapeutic indication(s) Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for a restriction of the indication for the treatment of colorectal cancer to patients with wild-type RAS tumours. Consequently, the MAH proposed the update of sections 4.1 and 5.1 of the SmPC. In addition, the MAH proposed to update the safety information regarding use of Vectibix in patients with mutant RAS tumours in sections 4.2, 4.3, 4.4 and 4.5 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0.

The variation proposed amendments to the SmPC, Annex II, 127a, Labelling and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/146/2009 on the granting of a class waiver.

However, the Agency considered that the requirements of article 8 of Regulation (EC) No 1901/2006 were not applicable, as this application was not for a new indication, a new pharmaceutical form or a new route of administration.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Robert James Hemmings

Submission date:	07 May 2013
Start of procedure:	28 May 2013
PRAC Rapporteur's RMP AR circulated on:	03 June 2013
PRAC Rapporteur's updated RMP AR circulated on:	07 June 2013
PRAC RMP Advice and Assessment Overview adopted on:	10 June 2013
Rapporteur's variation assessment report circulated on:	10 June 2013
CHMP opinion:	27 June 2013

2. Scientific discussion

2.1. 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 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 3 December 2007. Based on available data at the time of the application, panitumumab was granted a conditional marketing authorisation. Vectibix is indicated for the treatment of patients with wild-type *KRAS* metastatic colorectal cancer (mCRC):

- 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).
- as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

The recommended dose of Vectibix is 6 mg/kg of bodyweight given once every two weeks.

With this variation application, the MAH proposed to further restrict the metastatic colorectal cancer (mCRC) indication for Vectibix to patients with wild-type RAS (not only KRAS) tumour status. This proposal stemmed from the Annex II condition on the development of new biomarkers with potential to improve the benefit/risk balance of panitumumab. Towards fulfilling this condition, the MAH submitted prospective-retrospective analyses of RAS and BRAF in Study 20050203 (first-line combination with FOLFOX) with the latest Renewal application of the conditional Marketing Authorisation (EMEA/H/C/000741/R/0043, EC Decision date: 14 January 2013). Additional confirmatory data from studies 20020408 (last-line monotherapy study) and 20070509 (first-line combination with FOLFOX6 vs bevacizumab plus FOLFOX6) have become available and the MAH concluded that additional RAS mutations are negative predictive biomarkers of the benefit-risk of panitumumab in combination with oxaliplatin-based chemotherapy and proposed to restrict the indication of panitumumab to wild-type RAS rather than KRAS mCRC. The relevant contra-indication, posology recommendation and warnings against use of Vectibix with oxaliplatin-based chemotherapy in patients with mutant RAS tumours were proposed to be updated in accordance.

2.2. Clinical aspects

2.2.1. Introduction

The RAS gene family has three broadly expressed members: KRAS, neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS), and the v-Ha-ras Harvey rat sarcoma viral oncogene (HRAS). The three different isoforms share sequence identity at all regions regulating activation state and effector functions, and high sequence similarity in most of the remaining gene. The region of variability between the isoforms, containing only 23 to 24 amino acids, is involved in membrane binding. Each member of the RAS gene family functions as an oncogene when mutated by driving constitutive ligand-independent mitogen activated protein kinase signalling.

Whereas the KRAS exon 2 mutations that alter codons 12 and 13 are the most frequently occurring RAS mutations in CRC (approximately 40%), a number of mutations beyond KRAS exon 2 activate RAS family oncogenes. Somatic KRAS mutations within exon 3 and 4 and NRAS mutations within exons 2, 3, and 4 have also been documented in CRC and collectively occur in approximately 9% to 19% of wild-type KRAS exon 2 CRC cases. Thus, KRAS and NRAS mutations (in exons 2, 3, and 4) beyond KRAS exon 2 (codons 12 and 13) may be predictive biomarkers for panitumumab treatment. HRAS CRC mutations are infrequently reported (< 1%), and are thus not considered to be relevant in this population. In the proposed Product Information, KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4) are collectively referred to as RAS.

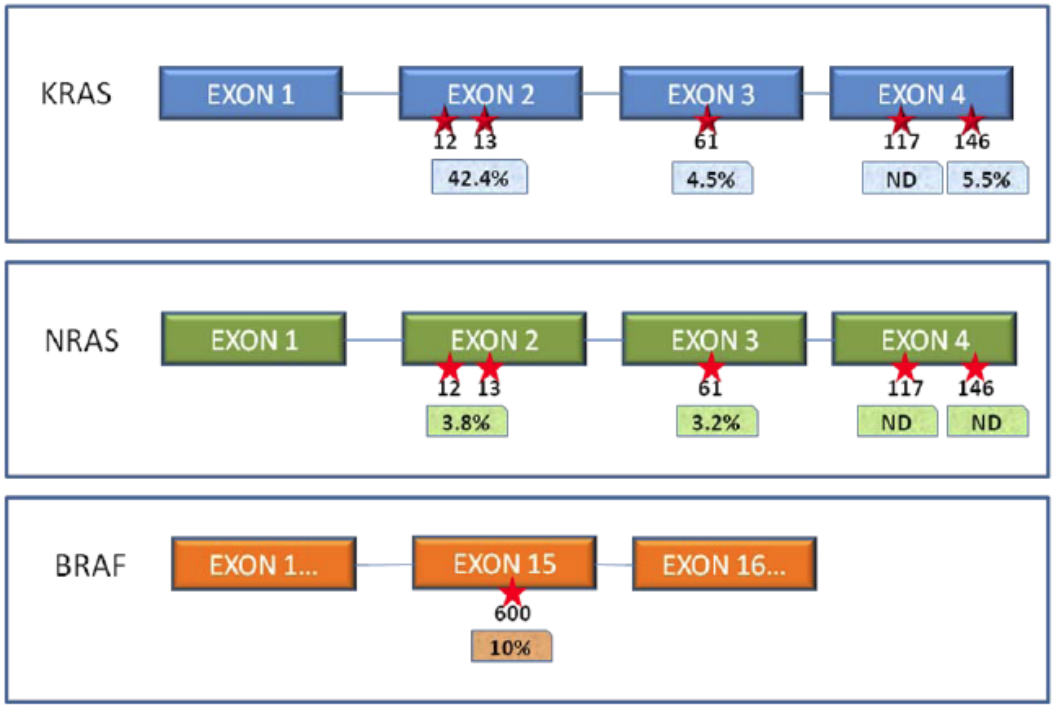
BRAF is an oncogene that functions downstream of the RAS proteins and is known to be mutated in approximately 10% to 15% of wild-type KRAS tumours. Somatic exon 15 BRAF mutations have been correlated with a poor prognosis; however, it is unclear whether these mutations are also predictive for the efficacy of anti-EGFR antibodies.

GCP

The Clinical trials (20020408, 20050203, 20070509) were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community (20020408, 20050203, 20070509) were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Figure 1: KRAS, NRAS and BRAF gene structure and common mutations in CRC



Source: Vaughn et al, 2011

Source: Vaughn CP, Zobell SD, Furtado LV, Baker CL, Samowitz WS (2011). Frequency of KRAS, BRAF, and NRAS mutations in colorectal cancer. Genes Chromosomes Cancer; 50(5): 307-12

2.3. Clinical efficacy aspects

2.3.1. Methods – analysis of data submitted

The MAH had taken a stepwise approach to determining the clinical phenotype of the above-mentioned biomarkers by first broadly interrogating mCRC tumour samples banked from the phase 3, randomised, controlled study of panitumumab monotherapy (study 20020408) for mutations within genes that encode key components of the EGFR signalling pathway. In 2009 and 2010, a multi-gene sequencing project had been performed using the banked tumour specimens from study 20020408.

Based on hypothesis-generating data from the monotherapy 20020408 study, the effect of RAS and BRAF mutation status on the efficacy and safety of panitumumab was further evaluated in a predefined retrospective subset analysis of study 20050203, the phase 3, randomised study of panitumumab in combination with FOLFOX chemotherapy. Tumour samples from patients who had wild-type KRAS exon 2 mCRC were further tested for mutations in KRAS exon 3 (codon 61) and exon 4 (codons 117/146); NRAS exon 2 (codons12/13), exon 3 (codon 61), and exon 4 (codon 117/146); and BRAF exon 15 (codon 600) using both Sanger sequencing and SURVEYOR/WAVE laboratory-developed tests. In addition, as somatic mutations have been identified in KRAS and NRAS at exon 3 (codon 59) (COSMIC database, February 2013), and KRAS codon 59 mutations have been specifically identified in CRC, a post-hoc, exploratory analysis of RAS mutations including codon 59 was performed after this mutation was discovered in 7 patients in Study 20050203.

Individuals involved in the testing were blinded to treatment allocation and outcome. DNA extractions were performed using the Qiagen DNA Mini Extraction Kit according to the manufacturer's instructions. For the Sanger sequencing analysis, PCR amplicons were bidirectionally sequenced using the ABI BigDye Terminator v3.1 kit and the ABI 3730XL Automated Sequencer. For the SURVEYOR/WAVE

analysis, double-stranded PCR amplicons were melted and cooled to form duplexed DNA fragments. When mutant DNA was present, the duplexed DNA was a mixture of WT:WT, MT:MT, and WT:MT. The mixture was treated with SURVEYOR Nuclease and the resulting DNA fragments were analysed on an HPLC system to detect DNA fragment size. Mutant:wild-type heteroduplexes result in variant size fragments. This assay was run in tandem with the Sanger sequencing and was used to confirm the presence of low levels of mutant DNA. Results presented below were the ones obtained by the Sanger sequencing analysis.

The primary endpoints of the updated efficacy analysis by RAS status were PFS and OS. Secondary endpoints included 60-day PFS, ORR, complete resection of metastases in subjects with liver only disease at baseline. The primary efficacy analyses for PFS and OS in this updated analysis used the primary PFS and OS data cut-off dates for Study 20050203, respectively (30 September 2008 for PFS and 28 August 2009 for OS). Objective response rate and complete resection were analysed using the primary PFS data cut-off date. The data cut-offs were event-driven as pre-specified in the primary Statistical Analysis Plan. These data were used to make definitive conclusions regarding treatment outcomes.

Pre-specified efficacy analyses by RAS status using the final data cut-off date (02 August 2010) were further provided for PFS and OS for descriptive purposes. An exploratory, updated analysis of OS by RAS status (as of 24 January 2013) was also provided.

2.3.2. Results

20020408 (last line monotherapy study)

Preliminary data supporting the predictive value of KRAS mutations beyond exon 2 and of NRAS mutations for response to panitumumab came from the monotherapy study 20020408.

Although few subjects with wild-type KRAS exon 2 status were identified who had other RAS mutations (n = 22), the results of this retrospective analysis were consistent with the hypothesis that all activating RAS mutations are negatively predictive of outcomes with panitumumab therapy. In study 20020408, 11 of 72 subjects (15%) with wild-type RAS tumours receiving panitumumab had an objective response compared to only 1 of 95 subjects (1%) with mutant RAS tumour status. Moreover, panitumumab treatment was associated with improved PFS compared to BSC in subjects with wild-type RAS tumours, but not in subjects with tumours harbouring a RAS mutation (see table below). An analysis of BRAF mutations indicated that BRAF status was prognostic for outcomes regardless of panitumumab treatment.

Table 1: Analysis by RAS Status; study 20020408 (monotherapy)

	Exploratory Analysis						Original Primary Analysis			
	Wild-type *RAS*		Mutant *RAS*		Wild-type *KRAS* Exon 2 Mutant *RAS*		Wild-type *KRAS* Exon 2		Mutant *KRAS* Exon 2	
	Pmab + BSC (n = 72)	BSC Alone (n = 61)	Pmab + BSC (n = 95)	BSC Alone (n = 111)	Pmab + BSC (n = 11)	BSC Alone (n = 11)	Pmab + BSC (n = 124)	BSC Alone (n = 119)	Pmab + BSC (n = 84)	BSC Alone (n = 100)
Median PFS[a] (95% CI)	12.3 (8.9, 22.9)	6.9 (6.0, 7.4)	7.4 (7.3, 7.7)	7.3 (6.4, 7.9)	7.1 (6.1, 8.0)	7.6 (3.9, 8.1)	12.3 (8.3, 16.1)	7.3 (7.0, 7.7)	7.4 (7.3, 7.9)	7.3 (6.3, 7.9)
PFS Hazard Ratio[b] (95% CI)	0.38 (0.27, 0.56)		0.98 (0.73, 1.31)		0.81 (0.29, 2.26)		0.45 (0.34, 0.59)		1.00 (0.73, 1.36)	
Median OS[c] (95% CI)	8.1 (6.3, 9.4)	7.5 (5.6, 9.2)	5.2 (4.4, 6.1)	4.4 (3.9, 5.9)	6.2 (2.3, 6.8)	5.2 (3.9, 13.7)	8.1 (6.3, 9.4)	7.6 (6.2, 8.8)	4.9 (4.2, 6.1)	4.4 (3.7, 6.5)
OS Hazard Ratio[b] (95% CI)	1.03 (0.71, 1.48)		1.06 (0.79, 1.42)		0.96 (0.37, 2.51)		0.99 (0.75, 1.30)		1.02 (0.75, 1.39)	

OS = overall survival; PFS = progression-free survival; Pmab = panitumumab; BSC = best supportive care
[a] Weeks
[b] Panitumumab plus BSC vs BSC alone
[c] Months
Source: Patterson et al, 2013; Study 20020408 KRAS Addendum CSR Table7-4 to Table 7-7; 20020408 RAS Analysis Table 14-04.001.003 and Table 14-04.004.003

20050203 (first line study, combination with FOLFOX)

The primary body of evidence regarding the predictive value of RAS (KRAS and NRAS) mutations for response to panitumumab were derived from the first-line combination with FOLFOX study 20050203.

In this study, the overall RAS ascertainment rate was high (90%; 1060 of 1183 randomised subjects including the previous results by KRAS exon 2 status), minimising the potential for systematic ascertainment bias. In the original primary analysis of Study 20050203, 656 patients (325 panitumumab plus FOLFOX, 331 FOLFOX alone) had wild-type KRAS exon 2 tumours. Tumour samples from 641 of these patients (98%) were acceptable to be tested for mutations in KRAS exon 3 and 4 and NRAS exon 2, 3, and 4. Few samples (≤ 3%) failed testing; reasons included no polymerase chain reaction (PCR) product or poor sequencing quality.

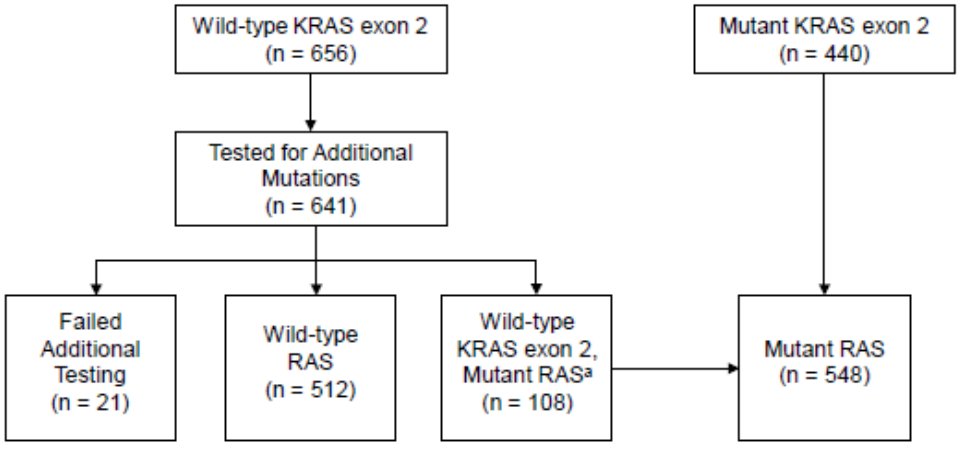
Of the 656 patients with wild-type KRAS exon 2 tumours, new mutations were identified for tumours in 108 patients (16%). The percentage of patients with newly identified mutations was similar between the panitumumab plus FOLFOX arm (51/325 patients, 16%) and the FOLFOX alone arm (57/331 patients, 17%). Mutations were identified in:

- KRAS exons 3 and 4 for 60 patients (9%)
- NRAS exons 2 and 3 for 48 patients (7%)
- with no patients testing positive for mutations in NRAS exon 4.

These results are consistent with recently published rates of mCRC mutations in KRAS exon 3 (5%), KRAS exon 4 (6%), NRAS exon 2 (4%), and NRAS exon 3 (3%), supporting the validity of the data.

Overall, 512 patients with evaluable samples had wild-type RAS tumour status (259 panitumumab plus FOLFOX, 253 FOLFOX alone) and 548 had mutant RAS tumour status (272 panitumumab plus FOLFOX, 276 FOLFOX alone). These patients comprised the main analysis sets for the predefined retrospective efficacy analysis (the Wild-type RAS Efficacy Analysis Set and the Mutant RAS Efficacy Analysis Set). Subjects with newly identified RAS mutations (i.e., those previously identified as having wild-type KRAS exon 2 status) were included in the Wild-type KRAS Exon 2 Mutant RAS Efficacy Analysis Set.

Figure 2: Patient disposition in RAS Efficacy Analysis Sets; study 20050203



[a]Patients with newly identified KRAS or NRAS mutations

[a] Subjects with wild-type *KRAS* exon 2 mCRC in the original primary analysis of Study 20050203 who had newly identified *KRAS* or *NRAS* mutations in the predefined retrospective subset analysis

Demographics and baseline disease characteristics in the predefined retrospective subset analysis were similar to those observed in the primary analysis by KRAS exon 2 status (data not shown).

Results in terms of OS and PFS are presented in the following Tables 2-4 and Figure 3.

Table 2: PFS and OS by RAS status; primary analyses (PFS: 30 September 2008 cut-off, OS: 28 August 2009 cut-off); study 20050203

Efficacy Analysis Set	Panitumumab Plus FOLFOX	FOLFOX Alone
Wild-type *KRAS* Exon 2 (Primary Study Analysis)	N = 325	N = 331
PFS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	0.80 (0.66, 0.97) (p = 0.023)	
Median PFS (95% CI), (months)	9.6 (9.2, 11.1)	8.0 (7.5, 9.3)
OS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	0.83 (0.67, 1.02) (p = 0.072)	
Median OS (95%,CI), (months)	23.9 (20.3, 28.3)	19.7 (17.6, 22.6)
Mutant *KRAS* Exon 2 (Primary Study Analysis)	N = 221	N = 219
PFS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.29 (1.04, 1.62) (p = 0.023)	
Median PFS (95% CI), (months)	7.3 (6.3, 8.0)	8.8 (7.7, 9.4)
OS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.24 (0.98, 1.57) (p = 0.068)	
Median OS (95% CI), (months)	15.5 (13.1, 17.6)	19.3 (16.5, 21.8)
Wild-type *RAS*	N = 259	N = 253
PFS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	0.72 (0.58, 0.90) (p = 0.004)	
Median PFS (95% CI), (months)	10.1 (9.3, 12.0)	7.9 (7.2, 9.3)
OS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	0.78 (0.62, 0.99) (p = 0.043)	
Median OS (95% CI), (months)	26.0 (21.7, 30.4)	20.2 (17.7, 23.1)
Mutant *RAS*	N = 272	N = 276
PFS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.31 (1.07, 1.60) (p = 0.008)	
Median PFS (95% CI), (months)	7.3 (6.3, 7.9)	8.7 (7.6, 9.4)
OS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.25 (1.02,1.55) (p = 0.034)	
Median OS (95% CI), (months)	15.6 (13.4, 17.9)	19.2 (16.7, 21.8)
Wild-type *KRAS* Exon 2 Mutant *RAS*	N = 51	N = 57
PFS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.28 (0.79, 2.07) (p = 0.326)	
Median PFS (95% CI), (months)	7.3 (5.3, 9.2)	8.0 (6.4, 11.3)
OS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.29 (0.79, 2.10) (p = 0.305)	
Median OS (95% CI), (months)	17.1 (10.8, 19.4)	18.3 (13.0, 23.2)

Blinded central review of scans using modified-RECIST criteria; a=stratification by Region and ECOG score

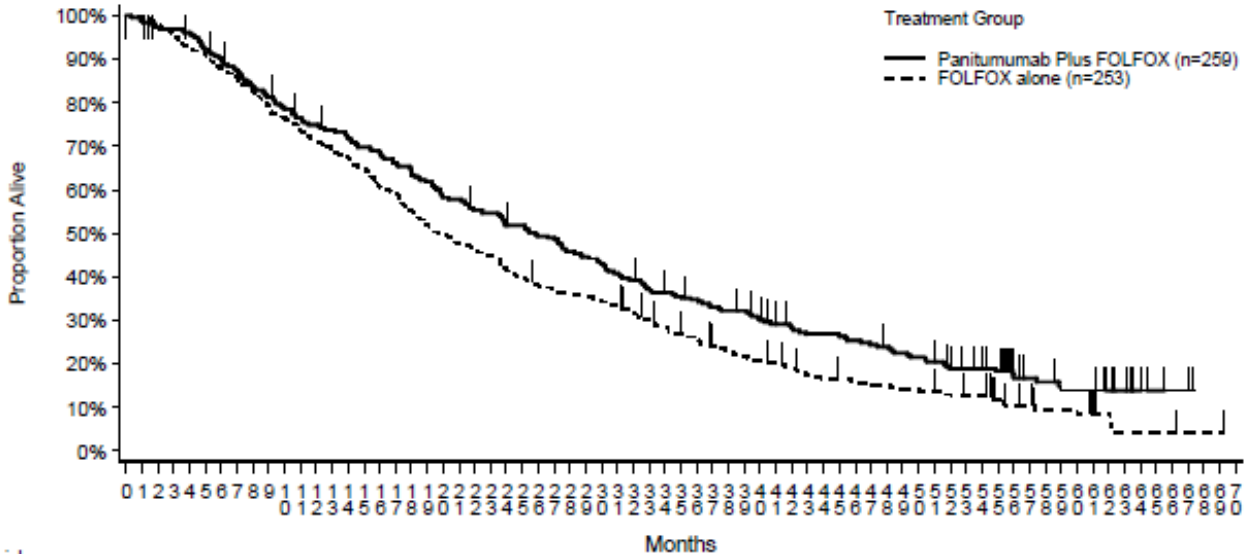
Table 3: PFS and OS by RAS status; final analyses (02 August 2010 cut-off); study 20050203

Efficacy Analysis Set	Panitumumab Plus FOLFOX	FOLFOX Alone
Wild-type *KRAS* Exon 2	N = 325	N = 331
PFS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	0.80 (0.67, 0.95) (p = 0.009)	
Median PFS (95% CI), (months)	10.0 (9.3, 11.4)	8.6 (7.5, 9.5)
OS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	0.88 (0.73, 1.06) (p = 0.171)	
Median OS (95%,CI), (months)	23.9 (20.3, 27.7)	19.7 (17.6, 22.7)
Mutant *KRAS* Exon 2	N = 221	N = 219
PFS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.27 (1.04, 1.55) (p = 0.019)	
Median PFS (95% CI), (months)	7.4 (6.9, 8.1)	9.2 (8.1, 9.9)
OS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.17 (0.95, 1.45) (p = 0.144)	
Median OS (95% CI), (months)	15.5 (13.1, 17.6)	19.2 (16.5, 21.7)
Wild-type *RAS*	N = 259	N = 253
PFS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	0.73 (0.60, 0.88) (p = 0.001)	
Median PFS (95% CI), (months)	10.8 (9.4, 12.9)	8.6 (7.3, 9.6)
OS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	0.82 (0.67, 1.02) (p = 0.072)	
Median OS (95% CI), (months)	25.8 (21.7, 29.7)	20.2 (17.6, 23.6)
Mutant *RAS*	N = 272	N = 276
PFS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.31 (1.10, 1.57) (p = 0.003)	
Median PFS (95% CI), (months)	7.4 (6.8, 8.0)	9.0 (8.0, 9.7)
OS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.23 (1.02,1.49) (p = 0.034)	
Median OS (95% CI), (months)	15.6 (13.4, 17.9)	18.9 (16.7, 21.7)
Wild-type *KRAS* Exon 2 Mutant RAS	N = 51	N = 57
PFS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.37 (0.90, 2.10) (p = 0.147)	
Median PFS (95% CI), (months)	7.4 (5.5, 9.4)	8.1 (7.2, 12.6)
OS Hazard Ratio (95% CI)[a] (stratified log-rank p-value)	1.44 (0.91, 2.26) (p = 0.116)	
Median OS (95%,CI), (months)	17.1 (10.8, 20.2)	18.3 (13.0, 27.2)

Table 4: OS by RAS mutation; exploratory analysis (24 January 2013 cut-off); study 20050203

	Predefined Retrospective Subset Analysis						*KRAS* Exon 2 Analysis			
	Wild-type *RAS* Efficacy Analysis Set		Mutant *RAS* Efficacy Analysis Set		Wild-type *KRAS* Exon 2 Mutant *RAS* Efficacy Analysis Set		Wild-type *KRAS* Exon 2		Mutant *KRAS* Exon 2	
	Pmab + FOLFOX (n = 259)	FOLFOX Alone (n = 253)	Pmab + FOLFOX (n = 272)	FOLFOX Alone (n = 276)	Pmab + FOLFOX (n = 51)	FOLFOX Alone (n = 57)	Pmab + FOLFOX (n = 325)	FOLFOX Alone (n = 331)	Pmab + FOLFOX (n = 221)	FOLFOX Alone (n = 219)
Subjects with Events – n(%)	204 (79)	218 (86)	239 (88)	241 (87)	46 (90)	46 (81)	256 (79)	279 (84)	193 (87)	195 (89)
Median OS[a] (95% CI)	25.8 (21.7, 29.7)	20.2 (17.6, 23.6)	15.5 (13.4, 17.9)	18.7 (16.5, 21.5)	17.1 (10.8, 19.4)	17.8 (13.0, 23.2)	23.8 (20.0, 27.7)	19.4 (17.4, 22.6)	15.5 (13.1, 17.6)	19.2 (16.2, 21.5)
OS Hazard Ratio[b] (95% CI)	0.77 (0.64, 0.94)		1.21 (1.01, 1.45)		1.39 (0.91, 2.13)		0.83 (0.70, 0.98)		1.16 (0.94, 1.41)	

Figure 3: Kaplan-Meier plot of OS; exploratory analysis, wild-type RAS efficacy analysis set; study 20050203



In terms of subgroups analyses, the treatment effect of panitumumab on PFS in the Wild-type RAS Efficacy Analysis Set was generally consistent across subpopulations defined by baseline covariates, with the exception of subjects who had an Eastern Cooperative Oncology Group (ECOG) status of 2 or who were ≥ 75 years of age. In these subgroups, the hazard ratios favoured the FOLFOX alone arm. For OS, the treatment effect of panitumumab was consistent across subpopulations with the exception of subjects who had an ECOG status of 2 (data not shown).

An analysis using an alternative definition of PFS that excluded deaths occurring > 60 days after the last evaluable tumour assessment or randomization date (whichever was later) was consistent with the main results (data not shown).

A best objective complete or partial response by central radiological assessment was achieved by 149 subjects (59%; 95% CI: 52%, 65%) in the panitumumab plus FOLFOX arm and 114 subjects (46%; 95% CI: 40%, 53%) in the FOLFOX alone arm. The adjusted odds ratio for objective response was 1.63 (95% CI: 1.13, 2.38), favouring the panitumumab plus FOLFOX arm, and the p-value was 0.009. In patients with mutant RAS tumours, the ORR in the panitumumab plus FOLFOX arm was 40% (95% CI: 34%, 46%) and in the FOLFOX alone arm it was 43% (95% CI: 37%, 49%) with an adjusted odds ratio of 0.87 (95% CI: 0.61, 1.25). In subjects with wild-type KRAS exon 2 mutant RAS tumours, fewer subjects had an objective response in the panitumumab plus FOLFOX arm (40%; 95% CI: 26%,

55%) than in the FOLFOX alone arm (54%; 95% CI: 40%, 67%), with an adjusted odds ratio of 0.59 (95% CI: 0.24, 1.38), favouring the FOLFOX alone arm.

Among the 90 subjects with metastasis to only the liver at baseline, complete resection (primary analysis) was performed in 15/49 (31%: 95% CI: 18%, 45%) subjects in the panitumumab plus FOLFOX arm and 7/41 (17%; 95% CI: 7%, 32%) subjects in the FOLFOX alone arm; the adjusted odds ratio was 2.31 (95% CI: 0.74, 7.66), and the p-value was 0.179. Among the 16 subjects with wild-type KRAS exon 2 mutant RAS tumours who had metastasis only to the liver at baseline, the complete resection rate was 13% in the panitumumab plus FOLFOX arm and 25% in the FOLFOX alone arm (adjusted odds ratio 0.55 [95% CI: 0.01, 10.49]).

Results of quantitative interaction tests comparing the magnitude of the relative treatment effect on PFS between the wild-type and different mutation efficacy analysis sets are presented in the following Tables 5 and 6.

Table 5: Quantitative Interaction Test; Wild-type and Mutant RAS Efficacy Analysis Sets; study 20050203

	Wild-type *RAS* (n = 512)	Mutant *RAS* (n = 548)	Interaction Test p-value
Primary Data Cutoff (30 September 2008)	0.72 (0.58, 0.90)	1.31 (1.07, 1.60)	< 0.0001
Planned Final Data Cutoff (02 August 2010)	0.73 (0.60, 0.88)	1.31 (1.10, 1.57)	< 0.0001

Table 6: Quantitative Interaction Test; Wild-type and Wild-type KRAS Exon 2 Mutant RAS Efficacy Analysis Sets; study 20050203

	Wild-type *RAS* (n = 512)	Wild-type *KRAS* Exon 2 Mutant *RAS* (n = 108)	Interaction Test p-value
Primary Data Cutoff (30 September 2008)	0.72 (0.58, 0.90)	1.28 (0.79, 2.07)	0.0361
Planned Final Data Cutoff (02 August 2010)	0.73 (0.60, 0.88)	1.37 (0.90, 2.10)	0.0079

Similarly, quantitative interaction test comparing the magnitude of the relative treatment effect on OS between the Wild-type and Mutant RAS Efficacy Analysis Sets indicated that the hazard ratios differed in these datasets for the primary (p = 0.004), final (p = 0.006), and exploratory updated (p = 0.001) data cut-off dates. In a post-hoc quantitative interaction test comparing the magnitude of the relative treatment effect on OS between the Wild-type RAS and the Wild-type KRAS Exon 2 Mutant RAS Efficacy Analysis Sets, the p-value from the primary analysis was 0.071. The p-values were 0.030 and 0.013 for the final and exploratory updated data cut-off dates, respectively.

With regard to BRAF, Of the 656 subjects with wild-type KRAS exon 2 tumours, a BRAF exon 15 mutation was identified in 53 subjects (8%). The PFS and OS hazard ratios favoured panitumumab in the subgroup with tumours that were wild-type KRAS exon 2 and wild-type BRAF (regardless of other RAS mutations) (PFS: 0.76 [95% CI: 0.62, 0.94]; OS: 0.80 [95% CI: 0.64, 1.00]), and showed improvement with panitumumab therapy in the subgroup with tumours that were wild-type KRAS exon 2 and mutant BRAF (PFS: 0.58 [95% CI: 0.29, 1.15]; OS: 0.90 [95% CI: 0.46, 1.76]). In addition, the PFS and OS hazard ratios favoured panitumumab among subjects with wild-type RAS and BRAF tumours (PFS: 0.68 [95% CI: 0.54, 0.87]; OS: 0.74 [95% CI: 0.57, 0.96]) and among subjects with wild-type RAS mutant BRAF tumours (PFS: 0.58 [95% CI: 0.29, 1.15]; OS: 0.90 [95% CI: 0.46, 1.76]). The OS hazard ratios (wild-type vs mutant) from a Cox proportional hazards model that explored the prognostic value of the genotypes in the wild-type KRAS exon 2 dataset suggested a

prognostic effect favouring wild-type status for the BRAF subgroup regardless of treatment: FOLFOX alone: 0.45 [95% CI: 0.29, 0.70]; panitumumab plus FOLFOX: 0.38 [95% CI: 0.23, 0.63]; all subjects: 0.41 [95% CI: 0.30, 0.58].

20070509 (first line study, combination with FOLFOX6, comparison with bevacizumab)

Supportive preliminary data evaluating additional RAS mutations in the first-line setting were also available from study 20070509, a phase 2 MAH-sponsored study that estimated the treatment effect (i.e., with no formal hypothesis testing) of panitumumab plus FOLFOX6 versus bevacizumab plus FOLFOX6 in previously untreated subjects with mCRC. This study was originally conducted in subjects with wild-type KRAS exon 2 tumours, and a prospective analysis was conducted to detect further mutations in KRAS exon 3 (codon 59/61) and exon 4 (codons 117/146); NRAS exon 2 (codons 12/13), exon 3 (codon 59/61), and exon 4 (codon 117/146); and BRAF exon 15 (codon 600) using the same laboratory-developed tests as those used for the RAS/BRAF analysis in study 20050203. The initial ascertainment rate for the updated analysis was 75%. Results are presented in the following Table 7.

Table 7: PFS and OS by RAS status; study 20070509

	Predefined Retrospective Analysis				Original Primary Analysis	
	Wild-type *RAS*		Wild-type *KRAS* Exon 2 Mutant *RAS*		Wild-type *KRAS* exon 2	
	Pmab + FOLFOX6 (n = 80)	Bev + FOLFOX6 (n = 80)	Pmab + FOLFOX6 (n = 24)	Bev + FOLFOX6 (n = 23)	Pmab + FOLFOX6 (n = 142)	Bev + FOLFOX6 (n = 143)
Median PFS[a] (95% CI)	13.1 (10.7, 15.1)	9.5 (7.9, 12.7)	7.8 (6.5, 9.8)	8.9 (7.3, 12.0)	10.9 (9.4, 13.0)	10.1 (9.0, 12.6)
PFS Hazard Ratio[b] (95% CI)	0.63 (0.43, 0.94)		1.31 (0.66, 2.59)		0.87 (0.65, 1.17)	
Median OS[a] (95% CI)	NR (28.8, NR)	29.0 (24.3, NR)	NR (13.0, NR)	21.6 (13.9, 25.4)	NR (28.8, NR)	25.4 (22.9, 29.5)
OS Hazard Ratio[b] (95% CI)	0.55 (0.30, 1.01)		0.72 (0.28, 1.83)		0.72 (0.47, 1.11)	

Pmab = panitumumab; Bev = bevacizumab, PFS = progression-free survival; OS = overall survival; NR = not reached

[a] Months

[b] Panitumumab plus FOLFOX6 vs bevacizumab plus FOLFOX6

2.3.3. Discussion

Based on preliminary hypothesis-generating data from monotherapy study 20020408, study 20050203 was selected for additional analyses as it was a large, well-controlled study with sample availability for the required biomarkers. In addition, this study had previously demonstrated a negative treatment effect of panitumumab in patients with mutant KRAS exon 2 tumour status, thus providing the appropriate backdrop to evaluate the clinical phenotype of additional, potential activating RAS mutations.

The study was originally unselected for KRAS status, but the protocol and Statistical Analysis Plan were modified to prospectively evaluate the results by KRAS status. KRAS testing in the original primary analysis was performed by an independent central laboratory blinded to treatment and outcomes using an investigational use only (IUO) KRAS mutation test kit that detected the 7 most common mutations occurring in exon 2 (codons 12 and 13) of the KRAS gene. KRAS assay results were obtained for more than 90% of all randomised subjects.

The current predefined retrospective subset analysis of additional RAS mutations was pre-specified in a supplemental Statistical Analysis Plan. Although this biomarker analysis was retrospective and exploratory in nature, it was conducted under the rigorous statistical standards employed for a prospective analysis to enable robust conclusions on the predictive value of RAS and BRAF mutation status. The 20050203 study was an adequate, well-conducted, and well-controlled trial with one of the largest sample sizes in a mCRC study. Consistent effort was put forth to ensure that all possible samples were collected and tested (and re-tested if the first test failed), with the goal of reaching a 90% ascertainment rate. The detailed supplemental Statistical Analysis Plan was finalised before the RAS and BRAF test results became available. Sanger sequencing is the most commonly used approach for mutation testing, and is widely regarded as the gold standard. Results from the SURVEYOR/WAVE system were identical to the Sanger sequencing results.

In the previously reported primary analysis of Study 20050203, a statistically significant improvement in PFS and a non-significant trend for improvement in OS were observed following treatment with panitumumab in combination with FOLFOX compared with FOLFOX alone among subjects with wild-type KRAS exon 2 (codons 12 and 13) mCRC. However, in the last updated analysis (2013), an increase in median OS of 4.4 months was reported, which was statistically significant. In contrast, PFS and OS outcomes favoured the FOLFOX alone arm in subjects with mutant KRAS exon 2 tumours.

In this supplemental, prospective-retrospective, exploratory biomarker analysis, additional RAS mutations (ie, KRAS exons 3, 4 and NRAS exons 2, 3, 4) and mutations in BRAF exon 15 were assessed to determine their ability to predict outcomes following administration of panitumumab. Tumours from subjects with wild-type KRAS exon 2 status were tested for mutations in KRAS exons 3 and 4, NRAS exons 2, 3, and 4, and BRAF exon 15, and key efficacy and safety analyses were repeated for the newly identified datasets based on RAS (including KRAS exon 2) and RAS/BRAF mutation status. The RAS ascertainment rate was 90% overall (1060 of 1183 randomized subjects), minimizing the potential for significant ascertainment bias. The RAS/BRAF ascertainment rate was 89% (1047 of 1183 randomized subjects).

The efficacy results from the supplemental biomarker analysis suggest that additional activating mutations in RAS beyond KRAS exon 2 were negatively predictive for panitumumab in combination with FOLFOX compared with FOLFOX alone. Improvements in PFS and OS outcomes were observed for wild-type RAS tumours compared with wild-type KRAS tumours. In the OS update analysis, median OS was increased by 5.6 months (highly significant difference); with more OS events and greater follow up time, the results from this post-hoc OS update analysis may be a more reliable estimate of OS. Compared with FOLFOX alone, panitumumab in combination with FOLFOX demonstrated improvement in both PFS and OS among subjects with wild-type RAS tumours. Conversely, differences between treatment arms that favoured the FOLFOX alone arm (relative to the panitumumab plus FOLFOX arm) were observed for PFS and OS among subjects with mutant RAS tumours.

The results for subjects with wild-type RAS tumours were improved from what was previously reported for subjects with wild-type KRAS exon 2 tumours, and the results for subjects with mutant RAS tumours were consistent with what was previously reported for subjects with mutant KRAS exon 2 tumours. In addition, PFS and OS were numerically inferior among subjects with newly identified RAS mutations (i.e., wild-type KRAS exon 2 mutant RAS) who received panitumumab plus FOLFOX compared with those who received FOLFOX alone.

In the last OS update analysis (24 January 2013 data cut-off), 204 subjects (79%) in the panitumumab plus FOLFOX arm and 218 subjects (86%) in the FOLFOX alone arm of the Wild-type RAS Efficacy Analysis Set had died. The median OS was 25.8 months (95% CI: 21.7, 29.7) in the panitumumab plus FOLFOX arm and 20.2 months (95% CI: 17.6, 23.6) in the FOLFOX alone arm, an absolute difference of 5.6 months. The hazard ratio from a stratified Cox proportional hazards ratio

was 0.77 (95% CI: 0.64, 0.94), favouring the panitumumab plus FOLFOX arm. The stratified log-rank p-value was 0.009.

In terms of subgroups analyses for PFS and OS, the findings are consistent with the original primary analysis of Study 20050203 in subjects with wild-type KRAS exon 2 status. Section 4.4 of the panitumumab Summary of Product Characteristics (SmPC) currently states that for patients with ECOG 2 performance status, assessment of benefit-risk is recommended prior to initiation of panitumumab in combination with chemotherapy, as a positive benefit-risk balance has not been documented in patients with ECOG 2 performance status.

The ORR and liver resection rates were higher in the panitumumab plus FOLFOX arm compared with the FOLFOX alone arm among subjects with wild-type RAS tumours in the primary analysis. In contrast, no difference in ORR was observed between the panitumumab plus FOLFOX arm and FOLFOX alone arm in subjects with mutant RAS tumours. In subjects with wild-type KRAS exon 2 mutant RAS tumours, fewer subjects had an objective response in the panitumumab plus FOLFOX arm than in the FOLFOX alone arm.

Quantitative interaction test comparing the magnitude of the relative treatment effect on PFS between the Wild-type and Mutant RAS (or Wild-type KRAS Exon 2 Mutant RAS) Efficacy Analysis Sets supported the negative predictive value of additional activating RAS mutations beyond KRAS exon 2 for outcomes with panitumumab treatment. Similarly, a trend towards increasing strength of the interaction with greater OS event ascertainment was noted further lending support to the negative predictive value of additional activating RAS mutations beyond KRAS exon 2 for outcomes with panitumumab treatment.

The results from the RAS/BRAF efficacy analysis sets suggest that while BRAF mutation status is prognostic of outcome regardless of treatment, it is not predictive of the effect of panitumumab therapy in this analysis. The OS hazard ratios (wild-type vs mutant) from a Cox proportional hazards model that explored the prognostic value of the genotypes in the wild-type KRAS exon 2 dataset suggested a prognostic effect favouring wild-type status for the BRAF subgroup regardless of treatment.

Finally, in supportive study 20070509 and as was observed in study 20050203, both PFS and OS favoured the panitumumab arm relative to the control arm for subjects with wild-type RAS tumours; however, PFS favoured the control arm for subjects with newly detected RAS (i.e. non-exon 2 KRAS and NRAS) mutations. OS appeared to favour the panitumumab arm in subjects with newly detected RAS mutations, although these data were based on a small number of events.

Based on these data, the MAH's initial position was that the predictive value of additional activating mutations in RAS for outcomes with panitumumab treatment has been demonstrated but that the level of evidence for panitumumab in the monotherapy setting does not have sufficient statistical rigor yet. Controlled data are not yet available by RAS status for panitumumab in the second-line setting in combination with FOLFIRI.

The CHMP questioned the rationale for proposing a change to the indication of panitumumab restricted to its combination to FOLFOX. Although the number of additional mutations identified in the monotherapy trial is very small, the data clearly show similar trends to those observed in study 20050203. More importantly, given the common function of NRAS and KRAS isoforms, it is not biologically plausible that the impact of mutations in the NRAS gene on the therapeutic effect of panitumumab only manifests when panitumumab is administered as first-line therapy in combination with FOLFOX. Therefore, the MAH agreed to propose a restriction of the indication of Vectibix to wild-type RAS tumours regardless of the line of therapy.

2.4. Clinical safety

2.4.1. Methods – analysis of data submitted

Subjects who received at least 1 dose of panitumumab or chemotherapy in study 20050203 were included in safety analyses. The safety results discussed below are based on the final analysis data cut-off date (02 August 2010). Key safety analyses (adverse event summary and tabulation of adverse events of interest) were repeated using the later exploratory OS update data cut-off date (24 January 2013) but no changes to the adverse event profile of panitumumab plus FOLFOX were observed in the OS update analysis compared with the previous analysis.

2.4.2. Results

The subject incidence rate of adverse events by severity in the panitumumab plus FOLFOX vs. FOLFOX alone arms of the study for RAS was similar to KRAS.

Table 8: Incidence rate of adverse events by severity and RAS status; study 20050203

	Wild Type *RAS*		Wild Type *KRAS*	
Adverse Event by Severity	Pmab + FOLFOX (N=256)	FOLFOX (N=250)	Pmab+ FOLFOX (N=322)	FOLFOX (N=327)
Serious adverse events	43%	37%	42%	36%
Grade 3/4 adverse events (CTCAE v3)	85%	70%	84%	70%
Fatal adverse events (Grade 5)	5%	6%	5%	6%
Adverse events leading to treatment discontinuation	26%	16%	25%	15%

	Mutant *RAS*		Mutant *KRAS*	
Adverse Event by Severity	Pmab + FOLFOX (N=268)	FOLFOX (N=275)	Pmab + FOLFOX (N=217)	FOLFOX (N=218)
Serious adverse events	45%	31%	47%	30%
Grade 3/4 adverse events (CTCAE v3)	81%	73%	80%	74%
Fatal adverse events (Grade 5)	7%	4%	8%	3%
Adverse events leading to treatment discontinuation	23%	15%	23%	15%,

The subject incidence rates of the most frequent adverse events with a greater than 5% difference by preferred term in the panitumumab plus FOLFOX vs. FOLFOX alone for RAS were similar to KRAS.

Table 9: Incidence rate of adverse events with a greater than 5% difference in the panitumumab plus FOLFOX vs. FOLFOX alone by RAS status; study 20050203

	Wild Type *RAS*		Wild Type *KRAS*	
Preferred Term	Pmab + FOLFOX (N=256)	FOLFOX (N=250)	Pmab + FOLFOX (N=322)	FOLFOX (N=327)
Rash	55%	8%	56%	7%
Dermatitis acneiform	34%	0%	33%	0%
Hypomagnesemia	30%	7%	30%	8%
Paronychia	23%	0%	21%	0%

	Mutant *RAS*		Mutant *KRAS*	
Preferred Term	Pmab + FOLFOX (N=268)	FOLFOX (N=275)	Pmab + FOLFOX (N=217)	FOLFOX (N=218)
Rash	51%	5%	48%	5%
Dermatitis acneiform	32%	1%	32%	1%
Hypomagnesemia	30%	7%	31%	6%
Diarrhea	58%	49%	60%	47%

Finally, the subject incidence rates of events of interest (EOI) that are subject to heightened pharmacovigilance were similar for RAS and KRAS.

Table 10: Incidence rate of events of interest by RAS status; study 20050203

	Wild Type *RAS*		Wild Type *KRAS*	
Event of Interest (EOI)	Pmab + FOLFOX (N=256)	FOLFOX (N=250)	Pmab + FOLFOX (N=322)	FOLFOX (N=327)
Integument Toxicities	97%	44 %	97%	43 %
Hematologic Toxicities	71%	74%	70%	75%
Neurologic Toxicities	65%	72%	65%	72 %
Diarrhea	65%	52%	62%	52%
Stomatitis/Oral Mucositis	49%	30%	49%	29%
Hypomagnesemia	32%	7%	30%	8%
Vascular toxicity	29%	29%	29%	27%
Infusion reactions	23%	0%	24%	0%
Pulmonary toxicity	21%	32%	20%	30%
Cardiac toxicity	14%	14%	14%	13%
Hypocalcemia	6%	3%	6%	2%

Event of Interest (EOI)	Mutant *RAS*		Mutant *KRAS*	
	Pmab + FOLFOX (N=268)	FOLFOX (N=275)	Pmab + FOLFOX (N=217)	FOLFOX (N=218)
Integument Toxicities	96%	44%	96%	43%
Hematologic Toxicities	67%	75%	67%	75%
Neurologic Toxicities	60%	75%	59%	74%
Diarrhea	58%	49%	60%	47%
Stomatitis/Oral Mucositis	44%	26%	43%	26%
Hypomagnesemia	31%	7%	33%	6%
Vascular toxicity	28%	24%	26%	24%
Infusion reactions	21%	0%	20%	0%
Pulmonary toxicity	20%	19%	21%	18%
Cardiac toxicity	16%	12%	15%	13%
Hypocalcemia	5%	2%	5%	2%

2.4.3. Discussion

A comparison of the safety data in subjects administered panitumumab plus FOLFOX over FOLFOX alone shows that the adverse event profile is similar for subjects with wild-type RAS vs. wild-type KRAS and mutant RAS vs. mutant KRAS. In these groups of subjects, there were no appreciable differences in the proportion of adverse events, including serious events, severe events by CTCAE grade, events leading to study discontinuation, and adverse events of interest. There were no new safety signals observed in subjects with wild-type RAS mCRC tumours administered panitumumab plus FOLFOX chemotherapy.

2.5. Risk management plan

2.5.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

The RMP could be acceptable provided an updated RMP and satisfactory responses to the list of outstanding issues below is submitted:

'Patients with pulmonary impairment' has been deleted from the list of important missing information; this should be reinstated unless otherwise justified.

The summary table of ongoing and planned studies in the PhV development plan (Table 51, section III.5.1) should be updated to include details of the additional pharmacovigilance activities relating to biomarkers (as described in Table 49).

The summary of the RMP requires revision following the conclusion of the procedure in order to comply with the updated template for Part VI of the RMP, as follows:

VI.2.1 Overview of disease epidemiology

(Maximum 150 words per indication)

Abbreviated lay language version of RMP Part II Module I

VI.2.2 Summary of treatment benefits

The summary of treatment benefits should be in lay language and non-promotional.

The text should not exceed a maximum of 200 words (up to 300 if multiple indications).

VI.2.3 Unknowns relating to treatment benefits

(1 short paragraph per indication of 50 words maximum)

A short summary of the applicability of efficacy to all patients in the target population can be provided in lay language.

Based on the PRAC recommendation, the MAH submitted an updated RMP (version 11) which addressed the PRAC outstanding issues prior to CHMP Opinion.

The following content of the Risk Management Plan was finally agreed with the CHMP:

Safety concerns

The MAH identified the following safety concerns.

Table 11: Summary of safety concerns

Important identified risks	Skin Disorders Eye Disorders Stomatitis and oral mucositis Pulmonary toxicities Hypomagnesemia, hypocalcemia, and hypokalemia Diarrhea Dehydration Infusion reactions and other hypersensitivity reactions Lack of response in patients with mCRC with mutant *RAS* tumors Negative effects in combination with oxaliplatin-containing chemotherapy in patients with mCRC with mutant *RAS* tumors Worse outcomes in patients with poor performance status (ECOG 2) receiving panitumumab in combination with chemotherapy in mCRC Pulmonary embolism
Important potential risks	Vascular toxicity Immunogenicity Delayed wound healing
Important missing information	Pregnant women Lactating women Pediatric patients Patients with renal impairment Patients with hepatic impairment Patients with pulmonary impairment Patients with cardiovascular disease Patients of different race or ethnic origins Biomarkers for response to panitumumab therapy

Pharmacovigilance plans

Table 12: Ongoing and planned studies in the PhV development plan

Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
Study 20101120 Category 1	Medical records review study, specifically assessing the impact of the *KRAS* test results on patterns of panitumumab use	Lack of response, and negative effects in combination with oxaliplatin-containing chemotherapy, in patients with mCRC with mutant *RAS* tumors	Study ongoing, first interim report submitted to CHMP on 27 March 2013. (this interim report included results from the first 25 of 150 complete charts extracted for round 1)	Interim reports 1Q2013 and 4Q2013. Final report 4Q2014
Study 20101121 Category 1	Physician survey to assess knowledge of the importance of *KRAS* testing over time	Lack of response, and negative effects in combination with oxaliplatin-containing chemotherapy, in patients with mCRC with mutant *RAS* tumors	Study ongoing, first interim report submitted to CHMP on 27 March 2013.	Interim reports 1Q2013 and 4Q2013. Final report 4Q2014
Study 20050252 Category 3	Pediatric dose-finding study and Phase 2 study if the drug is found to be well-tolerated in children and/or adolescents	Pediatric patients	Enrolling	1Q2014

Category 1 are imposed studies considered key to the benefit risk of the product.
Category 2 studies are specific obligations.
Category 3 studies are required additional PhV activities (to address specific safety concerns or to measure effectiveness of risk minimisation measures).

No Category 1, 2, or 3 studies have completed.

Table 13: Activities to assess the effectiveness of risk minimisation measures

Component Measured	Activity	Rationale
Effectiveness of the risk minimization measures for a lack of response and negative effects in combination with oxaliplatin-containing chemotherapy in patients with mCRC who have mutant *RAS* tumors.	1. Physician survey (Protocol 20101121) to assess knowledge of the importance of *KRAS* testing over time; reporting of results in PSUR and in study report. 2. Medical records review study (Protocol 20101120), specifically assessing the impact of the *KRAS* test	The objectives of these studies are: • to evaluate oncologists' awareness and understanding of the importance of tumor *KRAS* testing for patients receiving panitumumab • to describe the frequency of *KRAS* testing and impact of the *KRAS* test results on patterns of panitumumab use in patients with mCRC

	results on patterns of panitumumab use; reporting of results in PSUR and in study report.	• to explore which *KRAS* tests are used. The results of these studies will be used to resolve the uncertainties about *KRAS* testing by: • collecting information about the range of diagnostic tests conducted in clinical practice and their performance • collecting data on and evaluating the compliance of physicians with the recommended use of Vectibix in confirmed cases of wild-type tumours.

The PRAC, having considered the updated data submitted, was of the opinion that the proposed post-authorisation PhV development plan remains sufficient to identify and characterise the risks of the product.

The PRAC also considered that the studies in the post-authorisation development plan remain sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 14: Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Identified Risks		
Skin Disorder	Text in SmPC 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. Statement that life threatening and fatal infectious complications including events of necrotizing fasciitis and/or sepsis have been observed in patients treated with Vectibix. 4.8 Undesirable Effects *Tabulated Summary of Adverse Reactions* Under skin and subcutaneous tissue disorders, dermatitis acneiform, rash, erythema, pruritus, dry skin, skin fissures, acne, and alopecia listed as very common; palmar-plantar erythrodysaesthesia syndrome, skin ulcer, scab, hypertrichosis, onychoclasis, and nail disorder listed as common; angioedema, hirsutism, ingrowing nail, and onycholysis listed as uncommon *Description of Selected Adverse Reactions*	A DHPC was distributed in the EU in 2012 to inform healthcare professionals of life-threatening and fatal infectious complications of severe skin reactions associated with panitumumab treatment, including necrotising fasciitis.

	Skin and Subcutaneous Skin Disorders: Description of skin rash and infectious complications in the clinical trial and postmarketing settings	
Eye Disorder	Text in SmPC 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 *Tabulated Summary of Adverse Reactions* 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. *Description of Selected Adverse Reactions* *Ocular Toxicities:* Description of keratitis, including nonserious events (in the clinical trial setting) and serious events (in the postmarketing setting)	A DHPC was distributed in the EU in 2011 to inform healthcare professionals of the association of panitumumab with reports of keratitis and ulcerative keratitis.
Stomatitis and oral mucositis	4.4 Special Warnings and Precautions for Use (Dermatological Reactions) Description of dermatologic reactions (including stomatitis) and recommendations for dose modifications, preventive measures, and treatment. 4.8 Undesirable Effects *Tabulated Summary of Adverse Reactions* Stomatitis listed as very common	None
Pulmonary toxicity	Text in SmPC 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, dyspnea and cough listed as very common; pulmonary embolism and epistaxis listed as common; bronchospasm and nasal dryness listed as uncommon	None
Hypomagnesemia, hypocalcemia, and hypokalemia	Text in SmPC 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	None

	common; hypocalcemia listed as common	
Diarrhea	Text in SmPC 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)	None
Dehydration	Text in SmPC 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)	None
Infusion reactions and other hypersensitivity reactions	Text in SmPC 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	A DHPC was distributed in the EU in 2010 to inform healthcare professionals of the association of panitumumab with serious hypersensitivity reactions.

	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 in patients with mCRC with mutant *RAS* tumors	Text in SmPC 4.1 Therapeutic Indications Vectibix is indicated for the treatment of adult patients with wild-type *RAS* metastatic colorectal cancer 4.2 Posology and Method of Administration statement that evidence of wild-type *RAS* (*KRAS* and *NRAS*) status is required before initiating treatment with Vectibix and that mutational status should be determined using a validated test method by an experienced laboratory.	A DHPC and PEB explaining the importance of *KRAS* status determination prior to initial treatment with panitumumab were distributed to relevant healthcare professionals following the approval of the extension of the approved indication to include first-line treatment in combination with FOLFOX (distribution started in 2011). • Amgen is supporting the ESP QA programme to help ensure the validation of *KRAS* testing methods and accreditation of laboratories. Amgen has submitted a Type II variation to the EMA, which includes proposals to: • Update the SmPC to refine the indication for panitumumab from the treatment of adult patients with wild-type *KRAS* mCRC to the treatment of adult patients with wild-type *RAS* mCRC • Update the panitumumab PEB to include an explanation of the importance of determining *RAS* status prior to initial treatment with

		panitumumab. • Distribute a DHPC to relevant healthcare professionals to ensure that this new information reaches clinical practice in a timely manner Provide support for the ESP QA program with regard to testing for additional *RAS* mutations.
Negative effects in combination with oxaliplatin-containing chemotherapy in patients with mutant *RAS* tumors	Text in SmPC 4.1 Therapeutic Indications Vectibix is indicated for the treatment of adult patients with wild-type *RAS* metastatic colorectal cancer 4.2 Posology and Method of Administration statement that evidence of wild-type *RAS* (*KRAS* and *NRAS*) status is required before initiating treatment with Vectibix and that mutational status should be determined using a validated test method by an experienced laboratory. 4.3 Contraindications The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant *RAS* mCRC or for whom *RAS* mCRC status is unknown. 4.4 Special Warnings and Precautions for Use (Vectibix in combination with oxaliplatin-based chemotherapy in patients with mutant *RAS* mCRC or for whom *RAS* 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. Description of a predefined retrospective subset analysis of subjects with wild-type *KRAS* (exon 2) tumours from the phase 3 study identified additional *RAS* (*KRAS* [exons 3 and 4] or *NRAS* [exons 2, 3, 4]) mutations in 16% of subjects. A shortening of PFS and OS was observed in subjects with mutant *RAS* tumours who received panitumumab and FOLFOX versus 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 *RAS* tumors who received panitumumab and FOLFOX vs FOLFOX alone. Statement that Vectibix should not be administered to patients in combination with oxaliplatin-containing chemotherapy to patients with mutant *RAS* mCRC or for whom *RAS* mCRC status is unknown.	• A DHPC and PEB explaining the importance of *KRAS* status determination prior to initial treatment with panitumumab were distributed to relevant healthcare professionals following the approval of the extension of the approved indication to include first-line treatment in combination with FOLFOX. • Amgen is supporting the ESP QA programme to help ensure the validation of *KRAS* testing methods and accreditation of laboratories. Amgen has submitted a Type II variation to the EMA, which includes proposals to: • Update the SmPC to: o extend the contraindication for the use of panitumumab in combination with oxaliplatin-containing chemotherapy to include patients with mutant or unknown *RAS* status, with a corresponding warning in Section 4.4. o refine the indication for panitumumab from the treatment

	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	of adult patients with wild-type *KRAS* mCRC to the treatment of adult patients with wild-type *RAS* mCRC. • Update the panitumumab PEB to include an explanation of the importance of determining *RAS* status prior to initial treatment with. • Distribute a DHPC to relevant healthcare professionals to ensure that this new information reaches clinical practice in a timely manner • Provide support for the ESP QA program with regard to testing for additional *RAS* mutations.
Worse outcomes in patients with poor performance status (ECOG 2) receiving panitumumab in combination with chemotherapy for mCRC	Text in SmPC 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.	None
Pulmonary embolism	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).	None
Potential Risks		
Vascular toxicity	Text in SmPC 4.8 Undesirable Effects	None

	Tabulated Summary of Adverse Reactions Deep vein thrombosis, hypotension, hypertension, flushing listed as common; oedema peripheral listed as very common.	
Immunogenicity	Text in SmPC 5.1 Pharmacodynamic Properties Description of the incidence of anti-panitumumab antibody formation in clinical trials (monotherapy and in combination with chemotherapy)	None
Delayed wound healing	None	None
Missing or limited patient populations with no or limited safety data		
Pregnancy	Text in SmPC 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.	None
Lactation	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.	None
Pediatric patients	Text in SmPC 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.	None
Patients with renal, hepatic, or pulmonary impairment	Text in SmPC 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	None

	conducted to examine the pharmacokinetics of Vectibix in patients with renal or hepatic impairment	
Patients with cardiovascular disease	None	None
Patients of different race or ethnic origins	None	None
Biomarkers	None	None

The proposed changes to the educational materials are included in Annexes 10 and 11 to the RMP and are considered appropriate.

The proposal to circulate a DHPC is endorsed. The DHPC should be sent to medical oncologists, pathologists responsible for testing mCRC tumour samples for RAS status and chief pharmacists.

The PRAC, having considered the updated data submitted, was of the opinion that the proposed risk minimisation measures remains sufficient to minimise the risks of the product in the proposed indications

The CHMP endorsed the advice without changes and considered the RMP which was finally submitted to have addressed the PRAC outstanding issues and to be acceptable.

2.6. Direct Healthcare Professional Communication

The CHMP considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the restriction of the indication to patients with wild-type RAS tumour status, as inferior PFS and OS have been shown in patients with RAS mutations beyond KRAS exon 2 who received Vectibix in combination with FOLFOX chemotherapy versus FOLFOX alone.The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent upon receipt of the Commission Decision with the revised SmPC with the changes highlighted to medical oncologists, pathologists responsible for testing mCRC tumour samples for RAS status and chief pharmacists.

3. Benefit-Risk Balance

Following a CHMP request to update the Product Information in line with new biomarker data at the time of the latest Renewal of the Vectibix conditional Marketing Authorisation (EMEA/H/C/000741/R/0043, EC Decision date: 14 January 2013), the MAH submitted the full analysis of the updated results of Study 20050203 taking into account not only KRAS mutations but also NRAS and BRAF mutations. Additional preliminary results from a phase II study that also evaluated the combination with FOLFOX (20070509) and from the pivotal monotherapy trial (20020408) were also presented.

Based on these analyses, it is clear that additional RAS mutations outside those initially investigated in the KRAS exon 2 (codons 12/13) improve the efficacy of panitumumab therapy without altering its safety, and therefore, improve the benefit/risk balance of panitumumab in the approved indications. In the most recent survival analysis of the first-line trial, an improvement in overall survival of almost 6 months was shown with the addition of panitumumab to FOLFOX in patients wild-type RAS tumours (hazard ratio = 0.77 [95% CI: 0.64, 0.94]; p = 0.009).

Moreover, the safety profile of panitumumab in patients with wild-type RAS tumour status is indistinguishable from that in patients with wild-type KRAS tumour status and no new safety concerns have been identified in the further restricted target population.

Since these additional mutations (KRAS and NRAS) already tend to be routinely screened for in clinical practice and since new commercial kits are also available, a change in the indication of panitumumab is fully justified.

In conclusion, the CHMP considered the benefit-risk balance of Vectibix in the modified indication:

Vectibix is indicated for the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC):

- 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)
- as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens

as being positive. No change to the conditions of the marketing is proposed other than ones necessary to reflect the updated indication.

4. Recommendations

Outcome

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

Variation accepted		**Type**
C.1.6.a	Change(s) to therapeutic indication(s) Addition of a new therapeutic indication or modification of an approved one	II

Restriction of the indication for the treatment of colorectal cancer to patients with wild-type RAS tumours for Vectibix further to the CHMP request to update the PI in line with new biomarker data

As a consequence, sections 4.1 and 5.1 of the SmPC are updated. In addition, sections 4.2, 4.3, 4.4 and 4.5 of the SmPC are updated in order to amend the safety information regarding use of Vectibix in patients with mutant RAS tumours. The Package Leafle is updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives and to add the details of the Croatian local representative in the Package Leaflet.

Furthermore, the PI is being brought in line with the latest QRD template version 9.0.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

This CHMP recommendation is subject to the following amended conditions:

Conditions and requirements of the marketing authorisation

• Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

• Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

• Additional risk minimisation measures

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 RAS (KRAS and NRAS) 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 RAS and its role in the panitumumab mechanism of action
- Information that in patients with mutant RAS 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 RAS
    - should not be used as monotherapy or in combination with FOLFIRI in patients whose tumours are mutant RAS or patients whose tumours have not been tested for RAS status
    - is contraindicated in combination with FOLFOX in patients with mutant RAS tumours or in patients with unknown RAS tumour status.
- Information on how RAS 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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
To report on the development of new biomarkers with potential to improve the benefit/risk balance of panitumumab: KRAS gene mutations, RAS family members, EGFR signalling pathway genes, EGFR ligands and other circulating growth factors, circulating cell-free tumour genomic DNA, circulating tumour cells. This should include explorative, prospective-retrospective and prospective analyses in their clinical studies.	31/07/2013
A statistical analysis plan for a prospective exploratory hypothesis-generating analysis of outcomes according to selected biomarkers in study 20080763 should be submitted to the CHMP.	31/07/2013

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
To complete a confirmatory trial examining panitumumab monotherapy in licensed indication. In particular to provide the clinical study report of the primary data analysis from the 20080763 study	30/09/2013
To resolve the uncertainties about *KRAS* testing by:	31/12/2013
- collecting information about the range of diagnostic tests conducted in clinical practice and their performance	31/12/2014
- collecting data on and evaluating the compliance of physicians with the recommended use of Vectibix in confirmed cases of wild-type tumours	