



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

26 February 2015  
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Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

### **Vectibix**

**International non-proprietary name: PANITUMUMAB**

**Procedure No. EMEA/H/C/000741/II/0065**

### **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

5-FU	5-fluorouracil
BSC	best supportive care
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmab	cetuximab
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EU	European Union
FOLFIRI	chemotherapy regimen consisting of irinotecan, infusional 5-FU, and leucovorin
FOLFOX	chemotherapy regimen consisting of oxaliplatin, infusional 5-FU, and leucovorin
HR	hazard ratio
KRAS	Kirsten rat sarcoma-2 viral oncogene
LLD	liver-limited disease
LV	leucovorin
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
NA	not achieved
ND	not determined
NE	not estimable
NR	not reported
NRAS	neuroblastoma RAS viral oncogene
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
Pmab	panitumumab
PRO	patient reported outcomes
RAS	rat sarcoma viral oncogene homolog
TTF	time to treatment failure
TTP	time to progression
TTR	time to relapse
USPI	United States prescribing information
WT	wild-type

# 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 4 November 2014 an application for a variation.

This application concerns the following medicinal product:

<b>Centrally authorised Medicinal product(s):</b>	<b>International non-proprietary name</b>
<b>For presentations: See Annex A</b>	
Vectibix	PANITUMUMAB

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

The Marketing authorisation holder (MAH) applied for an extension of the indication for the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC) to include use in the first-line setting in combination with FOLFIRI. Consequently, the MAH proposed the update of sections 4.1 and 5.1 of the SmPC.

In addition, the MAH took the opportunity to introduce minor editorial updates throughout the PI.

The variation proposed amendments to the Summary of Product Characteristics.

### **Information on paediatric requirements**

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

### **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 and Co-rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings

Co-Rapporteur: Ingunn Hagen Westgaard

Timetable	Actual dates
Submission date	4 November 2014
Start of procedure:	28 November 2014
CHMP Co-Rapporteur Assessment Report	21 January 2015
CHMP Rapporteur Assessment Report	21 January 2015
CHMP comments	16 February 2015
Rapporteur Revised Assessment Report	20 February 2015
Opinion	26 February 2015

## 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, decreased interleukin 8 (IL-8) and vascular endothelial growth factor (VEGF) production. KRAS (Kirsten rat sarcoma 2 viral oncogene homologue) and NRAS (Neuroblastoma RAS viral oncogene homologue) are highly related members of the RAS oncogene family. KRAS and NRAS genes encode small, GTP-binding proteins involved in signal transduction. A variety of stimuli, including that from the EGFR, activate KRAS and NRAS which in turn stimulate other intracellular proteins to promote cell proliferation, cell survival and angiogenesis. Activating mutations in the RAS genes occur frequently in a variety of human tumours and have been implicated in both oncogenesis and tumour progression.

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 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.

The purpose of this variation is to add FOLFIRI as a possible chemotherapy in the first-line combination (first bullet point of the indication). The application is based on two studies:

- a predefined retrospective analysis of Study 20060314 (submitted in 2010) by RAS tumour status
- an investigator-sponsored study (PLANET) comparing FOLFIRI plus panitumumab and FOLFOX plus panitumumab in the first-line setting.

## **2.2. Non-clinical aspects**

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### **2.2.1. Ecotoxicity/environmental risk assessment**

Since the pharmacologically active substance in Vectibix, panitumumab, is a monoclonal antibody, a sequence of amino acids and a protein, it is exempted from the requirement of providing an ERA as in accordance with the Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use (CHMP/SWP/4447/00), it is unlikely to result in significant risk to the environment.

## **2.3. Clinical aspects**

### **2.3.1. Introduction**

The combination of Vectibix with FOLFIRI in the second-line setting was approved based on the results of a Phase III trial (Study 20050181) comparing panitumumab plus FOLFIRI versus FOLFIRI alone in 1186 patients (variation EMEA/H/C/000741/II/0017 approved on 10 November 2011).

Cumulative evidence supporting the use of panitumumab in combination with FOLFIRI for the treatment of patients with wild-type RAS mCRC in the first-line setting has been submitted by the MAH.

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH. The two main studies were conducted in the EU.

- Tabular overview of clinical studies

Study	Setting/ Phase	Regimen	Total Sample Size	RAS Ascertainment n (%)	Primary Endpoint
20080763 (ASPECCT)	3 <sup>rd</sup> line Phase 3	panitumumab vs cetuximab	1010	NA <sup>c</sup>	OS
20060314	1 <sup>st</sup> line Phase 2	FOLFIRI + panitumumab (RAS wild-type vs RAS mutant)	154	143 (93)	ORR
CRYSTAL (EMR 62 202-013) <sup>a</sup>	1 <sup>st</sup> line Phase 3	FOLFIRI + cetuximab vs FOLFIRI	1198	827 (69)	PFS <sup>d</sup>
20050181	2 <sup>nd</sup> line Phase 3	FOLFIRI + panitumumab vs FOLFIRI	1186	1014 (85)	PFS and OS
PLANET (NCT00885885)	1 <sup>st</sup> line Phase 2	FOLFIRI + panitumumab vs FOLFOX + panitumumab	77	64 (83)	ORR
20050203 (PRIME)	1 <sup>st</sup> line Phase 3	FOLFOX + panitumumab vs FOLFOX	1183	1060 (90)	PFS and OS <sup>e</sup>
OPUS (EMR 62 202-047) <sup>b</sup>	1 <sup>st</sup> line Phase 2	FOLFOX + cetuximab vs FOLFOX	337	254 (75)	ORR

### 2.3.2. Pharmacokinetics

No new PK or PD data have been submitted. This is acceptable as the PK and PD of the combination of panitumumab with FOLFIRI has already been assessed in a previous application (EMA/H/C/000741/II/0017).

## **2.4. Clinical efficacy**

### **2.4.1. Main studies**

#### **2.4.1.1. Study Title: A Single Arm Multicentre Phase II Study of Panitumumab in Combination With Irinotecan/5-fluorouracil/Leucovorin in Patients With Metastatic Colorectal Cancer (study 20060314)**

##### **Methods**

Study 20060314 was a MAH-sponsored, Phase II, single-arm study of panitumumab plus FOLFIRI as first-line therapy in subjects with mCRC.

##### **Study participants**

The study included patients with histologically or cytologically-confirmed and radiologically-measurable metastatic colorectal adenocarcinoma. Patients were excluded if they received prior systemic therapy for the treatment of metastatic colorectal carcinoma, with the exception of adjuvant fluoropyrimidine-based chemotherapy given at least 6 months prior to enrolment. Patients with central nervous system metastases, or those with significant cardiovascular disease, were also excluded.

##### **Treatments**

Subjects received panitumumab 6 mg/kg plus FOLFIRI every 2 weeks until disease progression, unacceptable toxicities, or withdrawal of consent; subjects with stabilization of tumour volume who were not appropriate for ongoing chemotherapy could continue to receive panitumumab alone.

##### **Objectives**

The primary objective was to estimate the effect of RAS mutation status on ORR and other measures of efficacy in subjects treated with panitumumab in combination with FOLFIRI as first-line therapy for subjects with mCRC.

The secondary objective was to describe the effect of RAS mutation status on the safety profile of this combination therapy in the first-line setting.

##### **Outcomes/endpoints**

The primary endpoint was objective response rate. Secondary endpoints included disease control rate, duration of objective response, time to objective response, progression-free survival time, time to disease progression, duration of stable disease, time to treatment failure, time to disease relapse, resectability, overall survival time.

##### **Sample size**

This study is a predefined supplemental biomarker analysis of study 20060314.

##### **Randomisation**

As the study was a single arm study, the patients were not randomised.

##### **Blinding (masking)**

The study was a single arm trial; therefore the patients were not blinded.

##### **Statistical methods**

The objective response rate (ORR) by 17 weeks and over the entire study was to be reported by RAS or



RAS/BRAF mutation status along with two-sided exact 95% confidence intervals for the Evaluable for Tumour Response Analysis Sets. Wilson's score method with continuity correction was to be used to calculate a 95% confidence interval for the difference between rates across RAS or RAS/BRAF mutation groups.

A logistic regression model was to be employed to estimate the effect of RAS or RAS/BRAF mutation status on ORR. The odds ratio and 95% confidence interval using the Wald method were to be provided.

The analysis of all secondary efficacy endpoints was to be performed by RAS or RAS/BRAF mutation status for the Efficacy Analysis Sets or Evaluable for Tumour Response Analysis Sets as applicable.

## Results

### Outcomes and estimation

#### Disposition of Subjects and Baseline Characteristics

A total of 154 subjects were enrolled in the study. Of the 154 enrolled subjects, 143 subjects (93%) were evaluable for RAS status, including 69 (45%) with wild-type RAS tumors and 74 (48%) with mutant RAS tumors.

**Table 1: Demographics and key baseline disease characteristics RAS efficacy/safety analysis set**

	Panitumumab plus FOLFIRI		
	Wild-type RAS (N = 69)	Mutant RAS (N = 74)	Total (N = 143)
<b>Sex – n (%)</b>			
Men	55 (80)	42 (57)	97 (68)
Women	14 (20)	32 (43)	46 (32)
<b>Race/ethnicity – n (%)</b>			
White or Caucasian	66 (96)	73 (99)	139 (97)
Black or African American	2 (3)	0 (0)	2 (1)
Hispanic or Latino	0 (0)	1 (1)	1 (1)
Japanese	1 (1)	0 (0)	1 (1)
<b>Baseline age – years</b>			
N	69	74	143
Mean	62.2	63.7	63.0
SD	10.5	9.5	10.0
Median	65.0	64.0	64.0
Q1, Q3	54.0, 70.0	57.0, 72.0	55.0, 72.0
Min, Max	38, 84	37, 80	37, 84
<b>Baseline age group – n (%)</b>			
<65 years	34 (49)	38 (51)	72 (50)
≥65 years	35 (51)	36 (49)	71 (50)
<75 years	63 (91)	64 (86)	127 (89)
≥75 years	6 (9)	10 (14)	16 (11)
<b>Primary tumor type – n (%)</b>			
Colon cancer	40 (58)	48 (65)	88 (62)
Rectal cancer	29 (42)	26 (35)	55 (38)
<b>Adenocarcinoma differential of primary tumor – n (%)</b>			
Well differentiated	10 (14)	17 (23)	27 (19)
Moderately differentiated	39 (57)	39 (53)	78 (55)
Poorly differentiated	15 (22)	11 (15)	26 (18)
Unknown	5 (7)	7 (9)	12 (8)
<b>Months since primary diagnosis<sup>a</sup></b>			
N	66	73	139
Mean	11.0	10.8	10.9
SD	18.0	17.8	17.8

	Panitumumab plus FOLFIRI		
	Wild-type RAS (N = 69)	Mutant RAS (N = 74)	Total (N = 143)
Median	1.6	1.5	1.6
Q1, Q3	1.0, 17.6	1.0, 17.2	1.0, 17.4
Min, Max	0, 73	0, 84	0, 84
Months since metastatic disease diagnosis <sup>a</sup>			
N	67	73	140
Mean	1.9	2.4	2.2
SD	3.7	5.9	5.0
Median	1.1	1.2	1.1
Q1, Q3	0.7, 1.7	0.8, 1.8	0.7, 1.7
Min, Max	0, 29	0, 44	0, 44
Number of sites of metastatic disease			
1	30 (43)	31 (42)	61 (43)
2	22 (32)	25 (34)	47 (33)
≥ 3	17 (25)	18 (24)	35 (24)
Location of sites of metastatic disease			
Liver only	26 (38)	20 (27)	46 (32)
Liver plus other sites	33 (48)	35 (47)	68 (48)
Other sites only	10 (14)	19 (26)	29 (20)
ECOG performance status – n (%)			
0	35 (51)	45 (61)	80 (56)
1	31 (45)	24 (32)	55 (38)
2	3 (4)	4 (5)	7 (5)
3	0 (0)	1 (1)	1 (1)
Baseline LDH concentration			
< 1.5 x ULN	39 (57)	51 (69)	90 (63)
≥ 1.5 x ULN	28 (41)	22 (30)	50 (35)
Missing/Unknown	2 (3)	1 (1)	3 (2)
< 2.0 x ULN	47 (68)	59 (80)	106 (74)
≥ 2.0 x ULN	20 (29)	14 (19)	34 (24)
Missing/Unknown	2 (3)	1 (1)	3 (2)
Alkaline phosphatase			
< 2.0 x ULN	47 (68)	58 (78)	105 (73)
≥ 2.0 x ULN	19 (28)	16 (22)	35 (24)
Missing/Unknown	3 (4)	0 (0)	3 (2)

ECOG = Eastern Cooperative Oncology Group; FOLFIRI = irinotecan, 5-fluorouracil, and leucovorin; LDH = lactate dehydrogenase; RAS = rat sarcoma viral oncogene homolog; SD = standard deviation; ULN = upper limit of normal

<sup>a</sup> Date of enrollment minus date of primary diagnosis or metastatic disease.

<sup>b</sup> Sites of disease are not mutually exclusive.

Source: [Table 14-2.2.2](#) and [Table 14-2.3.1](#).

Among the subjects evaluable for *RAS* status, median follow-up time as of the final analysis data cutoff date was 34.0 weeks (range 5 to 223). The most frequently reported reason for discontinuing both panitumumab (43%) and FOLFIRI (37%) was disease progression.

#### *Efficacy outcomes*

The results in patients with wild-type *RAS* mCRC and mutant *RAS* mCRC from the primary analysis are presented in the table below.

**Table 2: Study 20060314: Key efficacy results (RAS Efficacy Analysis Set)**

	Wild-type RAS Panitumumab plus FOLFIRI (N = 69)	Mutant RAS Panitumumab plus FOLFIRI (N = 74)
Objective tumor response <sup>a</sup>		
Subjects responding – n (%)	40 (59)	30 (41)
Response Rate (95% CI) - %	58.82 (46.23, 70.63)	41.10 (29.71, 53.23)
Unadjusted common treatment odds ratio <sup>b</sup>	2.05 (0.99, 4.23)	
Duration of response (months) <sup>c</sup>		
Subjects with disease progression	15 (38)	24 (80)
Median time (95% CI), months	13.0 (9.3, 15.7)	5.8 (3.9, 7.8)
Progression-free survival		
Subjects who progressed/died – n (%)	38 (55)	61 (82)
Median time (95% CI), months	11.2 (7.6, 14.8)	7.3 (5.8, 7.5)
Hazard ratio (95% CI) <sup>d</sup>	0.37 (0.24, 0.58)	
Overall survival		
Subjects who died – n (%)	5 (7)	11 (15)
Median time (95% CI), months	NE (NE, NE)	NE (12.6, NE)
Hazard ratio (95% CI) <sup>d</sup>	0.42 (0.15, 1.23)	
Time to disease progression		
Subjects with disease progression, n (%)	34 (49)	55 (74)
Median time (95% CI), months	13.2 (7.8, 17.0)	7.3 (6.1, 7.6)

CI = confidence interval; FOLFIRI = irinotecan, 5-fluorouracil, and leucovorin; NE = not estimable; RECIST = Response Evaluation Criteria In Solid Tumors

Disease assessments were based on investigator review of scans using modified-RECIST V1.0 criteria.

<sup>a</sup> A subject was considered a responder if the best response was either a complete or partial response. Objective response was calculated using the Tumor Response Analysis Set: n = 68 wild-type RAS, n = 73 mutant RAS

<sup>b</sup> Odds ratio presented as wild-type : mutant strata

<sup>c</sup> Duration of response for responders is calculated using Tumor Response Analysis Set responders: wild-type RAS n = 40, mutant RAS n = 30

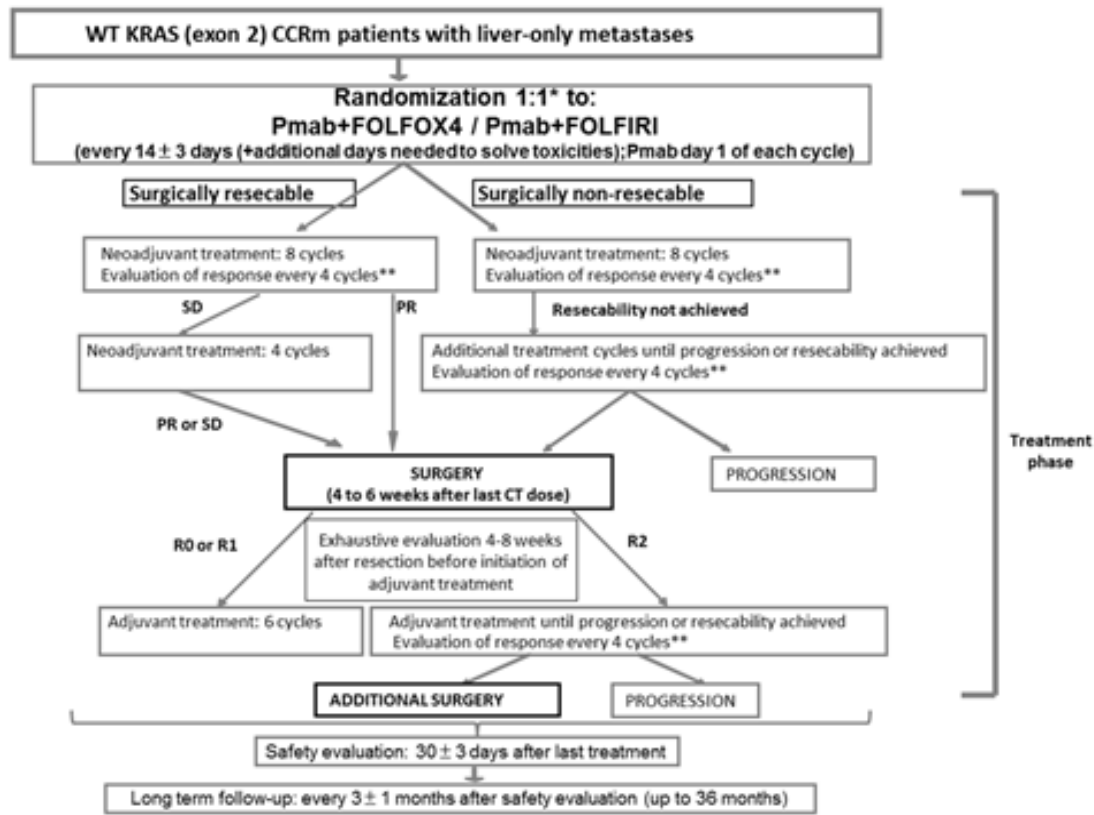
<sup>d</sup> Hazard ratio presented as wild-type : mutant strata

**2.4.1.2. Study Title: An Open label Randomized, Multi-Center Exploratory Phase II Study to evaluate the efficacy and safety of the combination of Panitumumab with FOLFOX 4 Chemotherapy or Panitumumab with FOLFIRI Chemotherapy in Subjects with Wild-Type KRAS Colorectal Cancer and liver-only Metastases (PLANET)**

**Methods**

PLANET is an investigator-led (non-Amgen sponsored), Phase II, randomized, open-label study of panitumumab plus FOLFIRI and panitumumab plus FOLFOX as first-line treatment of liver-limited, wild-type KRAS exon 2 mCRC. The study is conducted by the Spanish Cooperative Group for Digestive Tumor Therapy

at 15 centres in Spain. It was initiated in May 2009 and is still ongoing; the cut-off date of the results submitted is 01 August 2013.



**Figure 1: Study design**

### **Study participants**

Eligible subjects were > 18 years of age, with Karnofsky performance status  $\geq 70\%$  and wild-type *KRAS* exon 2 mCRC with synchronous or metachronous liver-only metastases deemed resectable or unresectable (including subjects who had undergone complete resection of the primary tumour at least 4 weeks before randomization), fulfilling one of the following criteria:  $\geq 4$  metastases; at least 1 metastasis > 10 cm in diameter; or liver metastases technically not resectable (vascular compromise and/or location in which complete resection is impossible and/or 25% to 30% of healthy liver would not remain functional after resection).

### **Treatments**

Panitumumab 6 mg/kg plus FOLFIRI or FOLFOX4 was administered every 14 days for 4 to 8 cycles. Subjects with resectable disease were eligible for surgery, which was performed 4 to 6 weeks after the last chemotherapy dose, followed by adjuvant treatment.

Patients with R0 (tumour free margin, no evidence of microscopic or macroscopic residual disease) or R1 (positive microscopic tumour margins) received 6 cycles of adjuvant treatment and patients with R2 received adjuvant treatment until disease progression or resectability achieved. Subjects with stable disease or in whom resectability was not achieved received additional cycles until disease progression, unacceptable toxicity, or withdrawal of consent.

A resection analysis was performed among patients that underwent an R0 or R1 resection.

## **Objectives**

The primary objective of the study was to compare the ORR (per modified RECIST criteria Version 1.1) in the two treatment arms during the treatment period. Tumour assessments were performed by investigators 8-weekly during the treatment phase.

Secondary objectives were to evaluate other efficacy variables (proportions of tumours becoming resectable, DOR, TTR, PFS, OS), safety, and also to assess hypomagnesaemia as a predictor of efficacy. Exploratory objectives were to explore possible differences in outcomes according to other predictive biomarkers (eg, *RAS* mutations).

## **Sample size**

An objective response rate of at least 30% is commonly thought to be achievable in mCRC subjects with liver-only metastases treated in the 1stline with FOLFOX4 or FOLFIRI alone. The randomized two-arm phase II design by Simon, Wittes and Ellenberg was used to establish the sample size requirements. In order to have 90% probability of correctly selecting the better treatment when the difference in the true objective response rates is 15% or greater, 37 subjects per arm are required. Such a trial has at least 80% probability of correctly selecting the better treatment if the absolute difference in the true response rates is only 10%. Based on these requirements a total of 80 subjects will be randomized to the study, 40 to each treatment arm.

## **Randomisation**

Subjects were randomized in a 1:1 ratio, with randomization stratified by prior adjuvant FOLFOX therapy and resectability of liver metastasis.

## **Blinding (masking)**

N/A

## **Results**

### **Participant flow**

Eighty patients were randomized; three of them did not take medication and were not included in the safety population. Of the 77 WT *KRAS* patients included in the safety population, 38 received panitumumab plus FOLFOX4 (Group A) and 39 panitumumab plus FOLFIRI (Group B) (Figure 2).

Thirty-seven patients of Group A and 36 patients of Group B had discontinued the treatment at the cut-off date. The most frequent reasons for panitumumab discontinuation were:

- disease progression: 13 (Group A) vs. 10 (Group B)
- treatment completed: 10 vs. 7, respectively
- investigator's decision: 3 vs. 11, respectively
- non-acceptable toxicity: 6 vs. 3, respectively

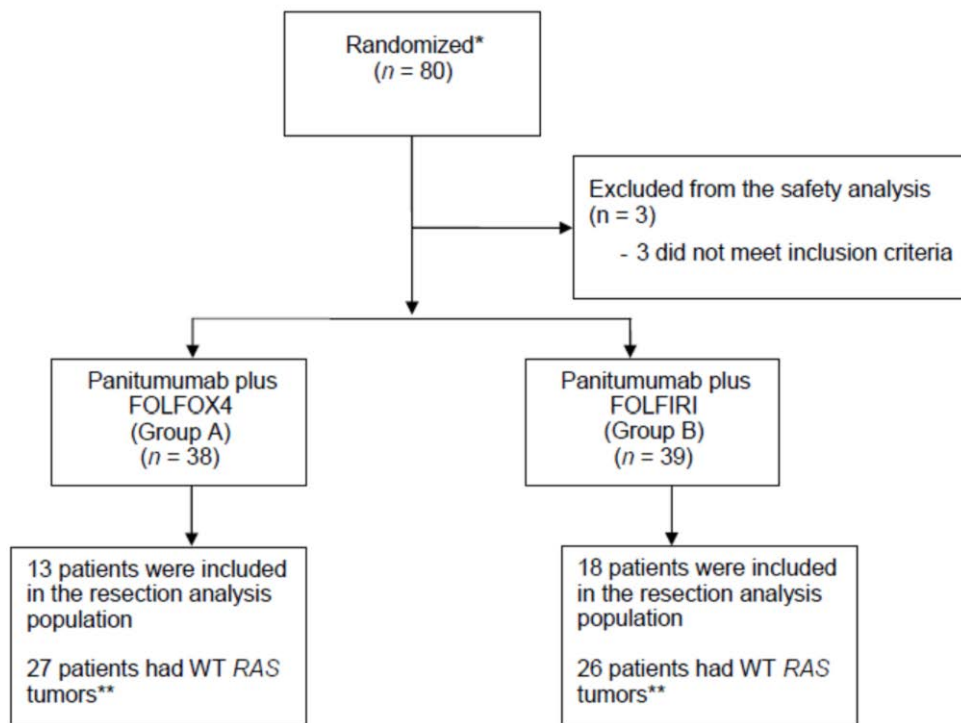
The most frequent reasons for chemotherapy discontinuation were:

- disease progression: 12 (Group A) vs. 10 (Group B)
- treatment completed: 10 vs. 8, respectively
- investigator's decision: 3 vs. 9, respectively
- non-acceptable toxicity: 7 vs. 2, respectively

The resection analysis population included 13 patients from Group A and 18 patients from Group B.

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In addition, *RAS* status (mutations in *KRAS* exon 3 or 4; *NRAS* exon 2, 3 or 4) was determined in 64 (83.1%) patients of the safety population. Of those patients, 53 (82.8%) were identified as having tumours with non-mutated *RAS*: 27 patients of Group A and 26 patients of Group B.



\* Mutations in *KRAS* exon 2

\*\*Mutations in *KRAS* exon 3 or 4 or *NRAS* exon 2, 3 or 4

**Figure 2: Patient disposition**

### Demographics

The main demographic and clinical data at baseline are summarised in Table 2.

**Table 2: PLANET Study: Demographics and baseline data (Safety population)**

Characteristic	Panitumumab plus FOLFOX4	Panitumumab plus FOLFIRI	Total (n= 77)
	Group A (n= 38)	Group B (n= 39)	
Male, n (%)	31 (81.6)	28 (71.8)	59 (76.6)
White/Caucasian, n (%)	38 (100.0)	38 (97.4)	76 (98.7)
Mean age, years (SD)	63.2 (10.0)	60.4 (12.2)	61.8 (11.2)
Mean time since primary diagnosis of CRC, months (SD)	21.6 (36.6)	12.6 (21.2)	16.3 (28.5)
Primary tumor site, n (%)			
Colon	28 (73.7)	27 (69.2)	55 (71.4)
Rectum	9 (23.7)	11 (28.2)	20 (26.0)
Colon & rectum	1 (2.6)	1 (2.6)	2 (2.6)
TNM at diagnosis, n (%)			
I	1 (2.6)	2 (5.1)	3 (3.9)
II	0 (0.0)	1 (2.6)	1 (1.3)
III	5 (13.2)	3 (7.7)	8 (10.4)
IV	32 (84.2)	32 (82.1)	64 (83.1)
Prior surgery, n (%)	26 (68.4)	22 (56.4)	48 (62.3)
Prior therapy, n (%)	6 (15.8)	4 (10.3)	10 (13.0)
Chemotherapy*	12 (75.0)	6 (75.0)	18 (75.0)
Radiotherapy*	4 (25.0)	2 (25.0)	6 (25.0)

## Efficacy

The main objective of this study was to determine the ORR over the entire panitumumab plus chemotherapy treatment period. Results of unconfirmed response are reported because surgery resection was performed in some patients before radiological response confirmation.

In the overall WT KRAS patient population, the ORR was 73.7% (95% CI: 59.7% to 87.7%) in Group A (P+FOLFOX4) and 66.7% (95% CI: 51.9% to 81.5%) in Group B (P+FOLFIRI).

In the WT RAS population, ORR was 77.8% (95% CI: 62.1% to 93.5%) in Group A and 73.1% (95% CI: 56.0% to 90.1%) in Group B, respectively. Among patients with mutated RAS, ORR was 50% (95% CI: 1% to 99%) in Group A and 57.1% (95% CI: 20.5% to 93.8%) in Group B.

Surgery resection of liver metastases was performed in 40 (52%) of the 77 patients included in the safety population: in 17 (44.7%) patients of Group A and in 23 (59.0%) patients of Group B. Hepatic resection rate defined as the proportion of patients with R0 or R1 resection was 40.3% for the safety population (31 patients, 77.5% for the whole resected population): 13 subjects in Group A (34.2%) and 18 in Group B (46.2%). Median time to resection was 7.1 months in Group A and 6.2 months in Group B (no significant difference). Regarding hepatic resection results in the WT RAS population, 25.9% (7 of 27) of patients of Group A and 53.8% (14 of 26) of patients of Group B presented R0 or R1 resection.

A summary of the results in the RAS WT population is presented in Table 3 and Figures 3 and 4.

**Table 3: PLANET Study: Key efficacy results (RAS WT population)**

	Panitumumab + FOLFIRI (n = 26)	Panitumumab + FOLFOX (n = 27)
Objective tumor response (unconfirmed), % (95% CI)	73.1 (56.0, 90.1)	77.8 (62.1, 93.5)
Progression-free survival		
Median, months (95% CI)	14.8 (7.1, 18.7)	12.8 (6.2, 22.0)
Hazard ratio (95% CI) <sup>a</sup>	0.86 (0.47, 1.56)	
Overall Survival		
Median, months (95% CI)	45.8 (32.8, 51.5)	39.0 (26.5, NE)
Hazard ratio (95% CI) <sup>a</sup>	0.97 (0.41, 2.28)	
Hepatic Resection Rate <sup>b</sup> , n (%)	14 (53.8)	7 (25.9)

CI = confidence interval; NE = not estimable

<sup>a</sup> Hazard ratio presented as panitumumab plus FOLFIRI: panitumumab plus FOLFOX

<sup>b</sup> Defined as the proportion of subjects with R0 or R1 resection



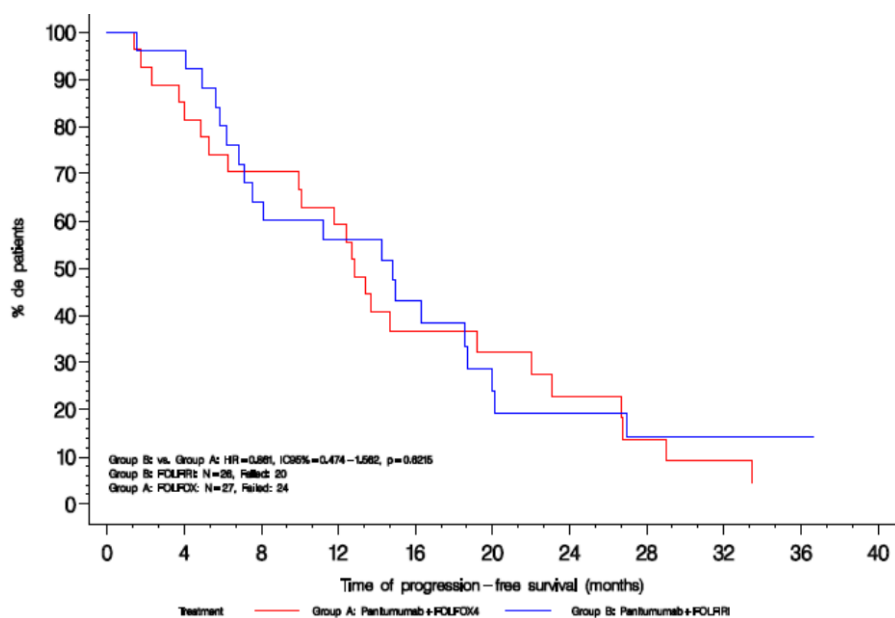


Figure 3: Progression-free survival (RAS WT population)

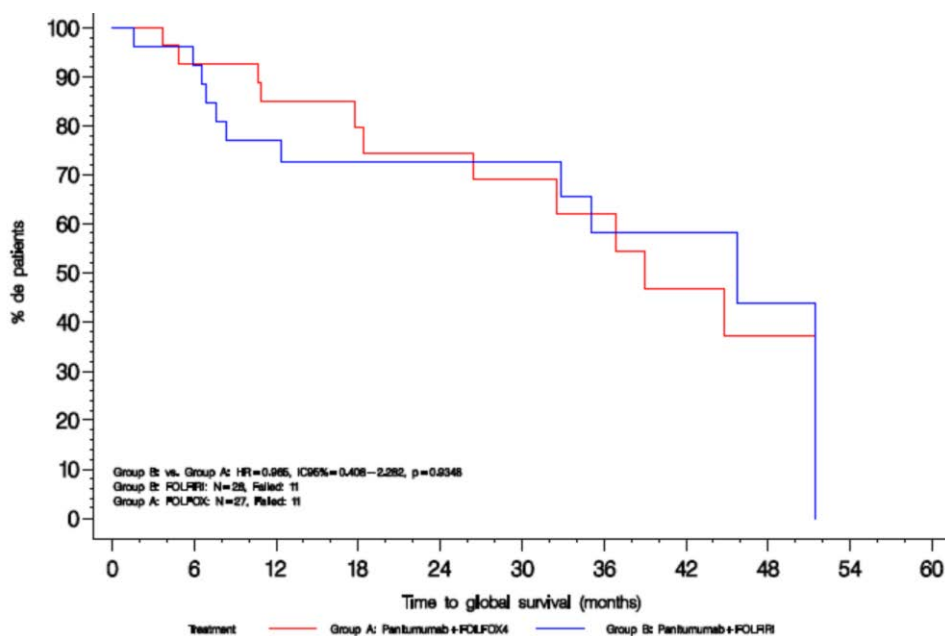


Figure 4: Overall survival (RAS WT population)

**Supportive studies**

Study 20080763 was a randomised, multicentre, open-label study designed to compare the efficacy and safety of panitumumab and cetuximab in subjects with previously treated, wild-type *KRAS* exon 2 mCRC. It showed that panitumumab was non inferior to cetuximab for OS; median OS was 10.4 months (95% CI: 9.4, 11.6) in the panitumumab arm and 10.0 months (95% CI: 9.3, 11.0) in the cetuximab arm.

The results of the two main studies previously described (20060314 and PLANET) are presented with those of other first-line studies supporting the use of panitumumab in the first line setting in combination with FOLFIRI (Table 4):



- Phase III CRYSTAL study, which evaluated cetuximab plus FOLFIRI (n = 599) compared to FOLFIRI alone (n = 599), a retrospective analysis of the results by RAS tumour status was recently published<sup>1</sup>;
- Phase III Study 2005203, which compared panitumumab plus FOLFOX versus FOLFOX alone;
- Phase II OPUS study, which evaluated cetuximab plus FOLFOX versus FOLFOX alone (n = 337), a retrospective analysis of the results by RAS tumour status was recently published<sup>2</sup>.

**Table 4: Key first-line studies: evaluable subjects (RAS WT population)**

	CRYSTAL <sup>a</sup>		20060314	PLANET		20050203	OPUS <sup>b</sup>
	Cetuximab + FOLFIRI	FOLFIRI alone	Panitumumab + FOLFIRI	Panitumumab + FOLFIRI	Panitumumab + FOLFOX	Panitumumab + FOLFOX	Cetuximab + FOLFOX
Total number of subjects enrolled in panitumumab/cetuximab arm of the study	599	599	154	39	38	593	169
Wild-type RAS							
Evaluable for PFS and OS, n (%)	178 (30)	189 (32)	69 (45)	26 (67)	27 (71)	259 (44)	38 (22)
Evaluable for ORR, n (%)	NR	NR	68 (44)	26 (67)	27 (71)	254 (43)	38 (22)

PFS = progression-free survival; ORR = objective response rate; OS = overall survival

<sup>a</sup> Ciardello et al, 2014; Van Cutsem et al, 2011

<sup>b</sup> Bokemeyer, et al 2014; Bokemeyer et al, 2011

Demographics and baseline characteristics were generally comparable across studies: most patients were male (60-80%), median age 60-65 years, with colon as the primary tumour (60-70%) and ECOG stage 0-1. The exception was in the OPUS study where there were about as many females as male patients and as many rectal as colon tumours.

The key efficacy results are presented in Table 4.

**Table 5: Key first-line studies: efficacy results (RAS WT population)**

	CRYSTAL <sup>a</sup>		20060314	PLANET		20050203	OPUS <sup>b</sup>
	Cetuximab + FOLFIRI	FOLFIRI Alone	Panitumumab + FOLFIRI	Panitumumab + FOLFIRI	Panitumumab + FOLFOX	Panitumumab + FOLFOX	Cetuximab + FOLFOX
Total number of subjects enrolled per treatment arm	599	599	154	39	38	593	169
Overall RAS ascertainment rate <sup>c</sup>	65%		93%	83%		90%	66%
Number of subjects with wild-type RAS status	178	189	69	26	27	259	38
ORR, %	66.3	38.6	58.8	73.1	77.8	58.7	57.9
PFS							
Median, months (95% CI)	11.4 <sup>d</sup> (NR)	8.4 (NR)	11.2 (7.6, 14.8)	14.8 (7.1, 18.7)	12.8 (6.2, 22.0)	10.1 (9.3, 12.0)	12.0 <sup>d</sup> (NR)
Hazard ratio vs control arm (95% CI)	0.56 <sup>d</sup> (0.41, 0.76)		NA	0.86 (0.47, 1.56)		0.72 (0.58, 0.90)	0.53 <sup>d</sup> (0.27, 1.04)
OS							
Median OS, months (95% CI)	28.4 (NR)	20.2 (NR)	NE	45.8 (32.8, 51.5)	39.0 (26.5, NE)	26.0 (21.7, 30.4)	19.8 (NR)
Hazard ratio versus control arm (95% CI)	0.69 (0.54-0.88)		NA	0.97 (0.41, 2.28)		0.78 (0.62, 0.99)	0.94 (0.56, 1.56)

CI = confidence interval; NA = not applicable; NE = not estimable; NR = not reported; ORR = objective response rate; PFS=progression-free survival, OS=overall survival

<sup>a</sup> Ciardello et al, 2014; Van Cutsem et al, 2011

<sup>b</sup> Bokemeyer et al, 2014; Bokemeyer et al, 2011

<sup>c</sup> Includes control arm, where applicable

<sup>d</sup> PFS defined as time from randomization to disease progression or death from any cause within 60 days after the last tumor assessment or after randomization

<sup>1</sup> Ciardello F, Lenz H-J, Kohne C-H, E, et al. Treatment outcome according to tumor RAS mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab. J Clin Oncol. 2014;32:5s (suppl; abstr 3506).

<sup>2</sup> Bokemeyer C, Kohne C-H, Ciardello F, et al. Treatment outcome according to tumor RAS mutation status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX 4 with/without cetuximab. J Clin Oncol. 2014; 32:5s (suppl; Abstract 3505).

## 2.4.2. Discussion on clinical efficacy

The rationale for expanding the indication for panitumumab to include use in first-line in combination with FOLFIRI includes evidence that the efficacy and safety of panitumumab has been demonstrated across lines of therapy with different chemotherapy backbones and appears very similar to that for cetuximab in these settings.

### Design and conduct of clinical studies

The combination of panitumumab to FOLFIRI in the first-line setting has been studied in a Phase II single-arm trial and in a small investigator-sponsored trial comparing the combination of panitumumab to either FOLFIRI or FOLFOX. The latter trial was a superiority trial, which was only powered to detect a large difference between the two combinations. As these data cannot be considered pivotal, the MAH rationale is also based on the comparison of panitumumab with cetuximab, which has an indication for the combination with irinotecan-based chemotherapy in all treatment lines. This is because the two anti-EGFR monoclonal antibodies have shown similar efficacy in a large head-to-head comparative trial in the third-line monotherapy setting. Therefore, the key efficacy results of all first-line combination studies for the two products in the RAS WT population have been presented to support this extension of indication.

### Efficacy data and additional analyses

The efficacy results (ORR and PFS) of panitumumab in the first-line setting are very similar regardless of the backbone chemotherapy as indicated by the outcomes of the pivotal trial 20050203 (with FOLFOX) and those of the single-arm trial 20060314 (with FOLFIRI): ORR of 59% and median PFS of 10-11 months.

The small PLANET trial comparing these two combinations in a population of patients with liver metastases only failed to detect any significant difference in ORR (73% with FOLFIRI vs. 78% with FOLFOX) but this could be expected given the study power. Of note, the reason for a higher rate of treatment discontinuations in the FOLFIRI arm due to investigator's decision is unclear. Nevertheless, median PFS and OS were broadly comparable and in line with those observed in a similar subset of patients from the pivotal FOLFOX combination trial (20050203). Taken together, these results suggest that the two combinations do not differ substantially.

The review of available data has shown that the efficacy of panitumumab and cetuximab in combination with FOLFIRI as first-line treatment for mCRC is similar. The positive benefit-risk of panitumumab with FOLFIRI has been established in previously treated wild-type RAS mCRC with Phase III Study 20050181.

Study 20060314 demonstrated the clinical benefit of panitumumab plus FOLFIRI in the first line setting in a Phase II uncontrolled study. The CRYSTAL study, which supported approval of the indication for cetuximab in combination with irinotecan-based chemotherapy, showed significant improvements in PFS and OS for cetuximab plus FOLFIRI vs FOLFIRI alone in a randomised Phase III trial. A cross-study comparison between Study 20060314 and the CRYSTAL study showed similar clinical outcomes in subjects with wild-type RAS mCRC. In Study 20060314 vs CRYSTAL, ORR was 58.8% vs 66.3%, and median PFS was 11.2 months vs 11.4 months, respectively.

The positive benefit-risk of panitumumab with FOLFOX in previously untreated wild-type RAS mCRC has been established with Phase III Study 20050203. The first-line PLANET study showed comparable efficacy for panitumumab plus FOLFIRI and panitumumab plus FOLFOX in subjects with wild-type RAS tumours and metastases limited to the liver only (PFS hazard ratio FOLFIRI arm vs FOLFOX arm = 0.86 [95% CI: 0.47, 1.56]; ORR = 73% vs 78% FOLFIRI vs FOLFOX arms). The median PFS (11.3 months) and OS (40.7 months) in subjects with liver-limited disease in Study 20050203 are similar to the median PFS (12.8 months) and OS (39.0 months) for subjects in the PLANET study who received panitumumab plus FOLFOX.

Together, these results suggest that the clinical benefit of panitumumab in combination with FOLFOX or FOLFIRI in the first line setting is consistent with the proposed labelling.

### 2.4.3. Conclusions on the clinical efficacy

The comparison of the two panitumumab combinations (to FOLFOX and FOLFIRI) used as first line treatment in the PLANET trial and the cross-study comparison between the efficacy results of Study 20060314 with FOLFIRI and Study 20050203 with FOLFOX support the proposed extension of indication for the FOLFIRI combination.

## 2.5. Clinical safety

### Introduction

This Summary of Clinical Safety presents recent safety data from two studies of panitumumab in combination with FOLFIRI in the setting of first-line mCRC (Study 20060314 and PLANET study) and provides a qualitative comparison of data from these studies with previous key studies of panitumumab and cetuximab in first-line mCRC. In addition, the safety profile of the combination of panitumumab with FOLFIRI in the second-line setting (Study 20050181) has been summarised.

### Patient exposure

Table 6 presents the total numbers of subjects randomized and the numbers of subjects with wild-type *RAS* and wild-type *KRAS* exon 2 mCRC receiving panitumumab or cetuximab for all studies included in this review.

**Table 6: Patient exposure**

Study	Setting/ Phase	Regimen	Number of Subjects		
			Sample Size	Wild-type <i>KRAS</i> exon 2 (Pmab or Cmab)	Wild-type <i>RAS</i> (Pmab or Cmab)
20060314	1 <sup>st</sup> line Phase 2	FOLFIRI + Pmab	154	86	69
PLANET	1 <sup>st</sup> line Phase 2	FOLFIRI + Pmab or FOLFOX + Pmab	77	77	53
CRYSTAL	1 <sup>st</sup> line Phase 3	FOLFIRI +/- Cmab	1198	316	178
20050203	1 <sup>st</sup> line Phase 3	FOLFOX +/- Pmab	1183	325	259
OPUS	1 <sup>st</sup> line Phase 2	FOLFOX +/- Cmab	337	82	36
20050181	2 <sup>nd</sup> line Phase 3	FOLFIRI +/- Pmab	1186	303	208

### Adverse events

The overall subject incidence of adverse events, grade 3/4 adverse events, and fatal events was similar across the studies evaluated, although limited data were available for the CRYSTAL study. The subject incidence of serious adverse events was higher in subjects with wild-type *RAS* mCRC receiving panitumumab plus FOLFIRI in Study 20060314 (58%) than in the other studies (22% to 43%), primarily due to a higher subject incidence of serious diarrhoea. The subject incidence of adverse events leading to discontinuation of

treatment varied between studies, but no consistent pattern based on epidermal growth factor receptor (EGFR) inhibitor type or chemotherapy backbone was observed.

**Table 7: Safety summary in first-line studies of panitumumab or cetuximab (RAS WT subjects)**

Subjects enrolled in study	CRYSTAL <sup>a</sup>	20060314	PLANET		20050203	OPUS <sup>b</sup>
	Cmab + FOLFIRI n = 599 <sup>c</sup>	Pmab + FOLFIRI n = 154	Pmab + FOLFIRI n = 39	Pmab + FOLFOX n = 38	Pmab + FOLFOX n = 593	Cmab + FOLFOX n = 338 <sup>d</sup>
Subjects with wild-type RAS status	n = 178	n = 69	n = 26	n = 27	n = 256 <sup>d</sup>	n = 36
Subjects with any adverse event	NR	69 (100%)	26 (100%)	27 (100%)	256 (100%)	36 (100%)
Worst grade of 3 or 4	144 (81%)	56 (81%)	19 (73%)	21 (78%)	217 (85%)	28 (78%)
Worst grade of 5	NR	3 (4%)	1 (4%)	1 (4%)	14 (5%)	1 (3%)
Any Serious	NR	40 (58%)	7 (27%)	6 (22%)	111 (43%)	15 (42%)
Leading to permanent discontinuation of any study drug	NR	21 (30%)	3 (12%)	15 (56%)	66 (26%)	17 (47%)

NR: not reported

In Study 20060314, the most frequently reported adverse events ( $\geq 40\%$ ) in subjects with wild-type RAS mCRC were diarrhoea (80%), nausea (52%), dry skin (48%), and rash (41%), consistent with the known safety profile of EGFR inhibitors administered in combination with chemotherapy. Similar results were observed for the panitumumab plus FOLFIRI arm of the PLANET study, in which diarrhoea (65%), rash (65%), asthenia (58%), and mucosal inflammation (54%) were the most frequently reported events.

The adverse event profile of panitumumab plus FOLFIRI was also consistent with that of panitumumab plus FOLFOX in subjects with wild-type RAS mCRC in the first-line setting, with the exception of known differences based on chemotherapy backbone. In the panitumumab plus FOLFOX arm of the PLANET study, the most frequently reported adverse events were diarrhoea (74%), asthenia (70%), neurotoxicity (59%), mucosal inflammation (56%), neutropenia (52%), rash (48%), and constipation (48%). These adverse events were similar to those frequently observed in subjects receiving panitumumab plus FOLFOX in Study 20050203, which included diarrhoea (65%), neutropenia (62%), rash (55%), and nausea (46%).

### Serious adverse event/deaths/other significant events

Fatal adverse events were consistent with those observed in previous studies of EGFR inhibitors. In Study 20060314, fatal adverse events were reported in 3 subjects (4%) with wild-type RAS mCRC. The fatal adverse events were hepatic failure, intestinal obstruction, and septic shock (1 subject each). None of these events were considered related to panitumumab by the investigator.

In the PLANET study, fatal adverse events were reported for 1 subject (4%) in the panitumumab plus FOLFIRI arm (pulmonary embolism) and 1 subject (4%) in the panitumumab plus FOLFOX arm (pneumomediastinum). These events were not considered related to treatment by the investigator.

The subject incidence of fatal adverse events was similar across studies of panitumumab or cetuximab plus FOLFIRI or FOLFOX in subjects with wild-type RAS mCRC in the first-line setting, ranging from 3% to 5% (Table 7).

In Study 20060314, serious adverse events were reported in 40 subjects (58%) with wild-type RAS mCRC. The most frequent serious adverse events ( $\geq 5\%$  of subjects) were diarrhoea (19%) and pulmonary embolism and vomiting (6% each).

The subject incidence of serious adverse events in subjects with wild-type RAS mCRC was higher in Study 20060314 (58%) than in the other studies of panitumumab or cetuximab in combination with chemotherapy in the first-line setting (22% to 43%). In particular, the incidence of serious diarrhoea was higher in Study 20060314 (19%) than in the PLANET study (no events of serious diarrhoea) or Study 20050203 (9% panitumumab plus FOLFOX). All but one event of serious diarrhoea in Study 20060314 resolved, and no subject discontinued panitumumab due to diarrhoea. No adverse event of serious diarrhoea was associated with acute renal failure. Diarrhoea is included in Section 4.4 Warnings and Precautions for Use and Section

#### 4.8 Undesirable Effects of the prescribing information for panitumumab.

##### Adverse events of interest

In Study 20060314, 68 of 69 subjects (99%) with wild-type *RAS* mCRC experienced an adverse event of interest (Table 7). The most frequently reported adverse events of interest were skin toxicity (99%) and diarrhoea (80%). The types of events and incidence rates were consistent with those expected for an EGFR inhibitor in combination with FOLFIRI.

**Table 8: Study 20060314 – AEs of interest (RAS WT population)**

	N = 69
Subjects with any adverse events of interest - n(%)	68 (99)
Hypomagnesemia	17 (25)
Hypocalcemia	2 (3)
Diarrhoea	55 (80)
Cardiac Toxicity	10 (14)
Pulmonary Toxicity	12 (17)
Vascular Toxicity	23 (33)
Stomatitis/Oral Mucositis	30 (43)
Integument Toxicities	68 (99)
Skin	68 (99)
Eye	36 (52)
Hair	21 (30)
Nail	20 (29)
Cheilitis	2 (3)
Infusion Reactions	
USPI	0 (0)
CTCAE	13 (19)
Reported AE	0 (0)

Grade 3/4 adverse events of interest across studies of EGFR inhibitors administered in combination with chemotherapy in subjects with wild-type *RAS* mCRC in the first-line setting are provided in Table 9.

**Table 9: Selected Grade 3/4 AEs in first-line studies (RAS WT population)**

	CRYSTAL <sup>a</sup>	20060314	PLANET		20050203	OPUS <sup>b</sup>
Subjects enrolled in study	Cmab + FOLFIRI n = 599	Pmab + FOLFIRI n = 154	Pmab + FOLFIRI n = 39	Pmab + FOLFOX n = 38	Pmab + FOLFOX n = 593	Cmab + FOLFOX n = 338 <sup>c</sup>
Subjects in the wild-type <i>RAS</i> Safety Analysis Set	n=178	n= 69	n = 26	n = 27	n=256	n = 36
All Skin Reactions	21%	NR	46%	37%	38%	NR
Dermatitis acneiform	5%	6%	8%	0%	10%	
Rash	9%	10%	19%	19%	17%	
Diarrhea	15%	28%	8%	11%	19%	NR
Hypomagnesemia	NR	4%	0%	0%	7%	NR
Neutropenia	31%	13%	8%	26%	42%	NR
Febrile neutropenia	NR	1%	0%	4%	2%	NR
Infusion reaction <sup>d</sup>	2%	0%	NR	NR	3%	NR
Fatigue	7%	7%	NR	NR	10%	NR
Deep vein thrombosis	6%	1%	4%	4%	4%	NR

<sup>a</sup> Ciardiello et al, 2014.

<sup>b</sup> Bokemeyer et al, 2014; Cetuximab EPAR, 2013

<sup>c</sup> Safety Analysis Set

<sup>d</sup> For Amgen-sponsored studies, per USPI

##### Safety in the second-line setting

Study 20050181 was a phase III, multicenter, randomized, open-label, comparative study to evaluate the efficacy of panitumumab in combination with FOLFIRI chemotherapy relative to FOLFIRI alone as second-line treatment in subjects with mCRC. Eligible subjects were randomized in a 1:1 ratio to receive panitumumab as an intravenous (IV) infusion at a dose of 6 mg/kg plus FOLFIRI chemotherapy or FOLFIRI

alone every 14 days  $\pm$  3 days until disease progression or unacceptable toxicity occurred. This study supported the extension of indication of panitumumab in combination with FOLFIRI as second line treatment in mCRC (EMA/H/C/000741/II/0017).

Nearly all subjects with wild-type *RAS* mCRC in both treatment arms had adverse events. Grade 3/4 adverse events, serious adverse events, and adverse events leading to discontinuation of any study medication were more frequently reported in the panitumumab plus FOLFIRI arm compared with the FOLFIRI alone arm, and were consistent with the known safety profile of panitumumab added to a chemotherapy backbone. Subject incidences of grade 5 (fatal) adverse events were similar in the two treatment arms (Table 10).

**Table 10: Study 20050181 – Safety summary (RAS WT population)**

	Pmab + FOLFIRI (n = 207)	FOLFIRI Alone (n = 213)
Subjects with any adverse event, n(%)	207 (100)	211 (99)
Worst grade of 3	114 (55)	78 (37)
Worst grade of 4	41 (20)	35 (16)
Worst grade of 5	8 (4)	13 (6)
Serious	94 (45)	67 (31)
Leading to permanent discontinuation of any study drug	50 (24)	25 (12)

The most frequently reported serious adverse event in both treatment arms was diarrhoea (6% panitumumab plus FOLFIRI and 4% FOLFIRI alone). No serious adverse event was reported with >5% difference between treatment arms.

Fatal adverse events were reported in 8 subjects (4%) receiving panitumumab plus FOLFIRI and 13 subjects (6%) receiving FOLFIRI alone. Fatal adverse events occurring in more than a single subject in either treatment arm were ileus (1% panitumumab plus FOLFIRI and 0% FOLFIRI alone) and mCRC (0% and 1%).

The most frequently reported adverse events among subjects with wild-type *RAS* mCRC in the panitumumab plus FOLFIRI and FOLFIRI alone arms, respectively, were diarrhoea (69% and 57%), nausea (50% and 50%), fatigue (39% and 32%), and neutropenia (38% and 41%). Other frequently occurring adverse events reported for subjects in the panitumumab plus FOLFIRI arm included those known to be associated with panitumumab and other EGFR inhibitors, such as rash (54% and 8%), hypomagnesaemia (29% and 2%), and dermatitis acneiform (28% and 1%).

Adverse events of interest for panitumumab that differed by at least 5% between the panitumumab plus FOLFIRI and FOLFIRI alone arms were integument toxicities (95% and 52%), diarrhoea (69% and 57%), stomatitis/oral mucositis (46% and 27%), hypomagnesaemia (31% and 2%), pulmonary toxicity (24% and 19%), and hypocalcaemia (7% and < 1%).

### Post marketing experience

For the reporting period of the last PSUR covering the period from 1 October 2013 to 30 March 2014 (EMA/H/C/000741/PSUV/0062), the estimated exposure to panitumumab in the post-marketing setting was 4654 patient-years. Cumulatively, since the IBD through the end of the reporting period, the estimated exposure to panitumumab in the marketed setting was 46,104 patient-years. Over 6000 subjects have been exposed to panitumumab as monotherapy or in combination with chemotherapy in clinical studies.

As of 31 March 2014, Amgen received a cumulative total of 6392 adverse drug reactions from medically confirmed and unconfirmed spontaneous sources; 2445 of the 6392 were serious adverse drug reactions



and 3947 were non-serious adverse drug reactions. In addition, a cumulative total of 902 serious adverse reactions were received from non-interventional post-marketing sources.

The most frequent spontaneously reported adverse drug reactions were from the System Organ Classes of Skin and Subcutaneous Tissue Disorders (n = 2410), General Disorders and Administrative Site Conditions (n = 661), and Gastrointestinal Disorders (n = 524). Overall, frequently reported adverse drug reactions such as rash (n = 533), skin toxicity (n = 204), skin reaction (n = 203), dermatitis acneiform (n = 195), diarrhoea (n = 133), pruritus (n = 133), erythema (n = 117), and paronychia (n = 111), were consistent with the known safety profile of panitumumab and its mechanism of action. Other adverse events such as fatigue (n = 47), general physical health deterioration (n = 26), sepsis (n = 12), and pneumonia (n = 7) would be expected in a patient population with underlying metastatic cancer.

### **2.5.1. Discussion on clinical safety**

The data from the two main trials in the first-line setting are consistent with the known safety profile of the combination. No conclusions can be drawn from certain differences observed between studies such as a lower SAE rate in general for the PLANET study compared with all other company-sponsored trials or the higher rate of serious diarrhoea in the first-line setting compared with the second-line setting for the combination of panitumumab with FOLFIRI. However these differences do not impact the known safety profile of the product.

In addition, the adverse events observed in combination with FOLFIRI in the post-marketing setting did not identify any new safety signals compared with those observed in clinical studies. The safety profile of panitumumab, including use in combination with FOLFIRI, is well established, and the risks are managed through the routine and additional risk minimization measures in the approved Risk Management Plan.

### **2.5.2. Conclusions on clinical safety**

The safety of the combination of panitumumab with FOLFIRI has been well characterised from clinical trials and post-marketing experience. No new safety concern has arisen from the new data submitted.

### **2.5.3. PSUR cycle**

The PSUR cycle remains unchanged.

## **2.6. Risk management plan**

The current Risk Management Plan (RMP) for panitumumab (version 14 dated 9 April 2014) covers its use in combination with FOLFIRI. With this proposed extension of the indication to include use of panitumumab in combination with FOLFIRI in the first-line setting, no new safety signals were identified and there were no new toxicities. No new risk minimisation measures are proposed and the risk-management system has not been modified, the justification for not updating the RMP with this variation application is considered acceptable.

## **2.7. Update of the Product information**

As a consequence of this new indication, sections 4.1 and 5.1 of the SmPC have been updated (new text underlined).

## 4.1 Therapeutic indications

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

- in first-line in combination with FOLFOX or FOLFIRI.
- 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.

[...]

## 5.1 Pharmacodynamic properties

*Combination with FOLFIRI*

[...]

The efficacy of Vectibix in first-line in combination with FOLFIRI was evaluated in a single-arm study of 154 patients with the primary endpoint of objective response rate (ORR). Other key endpoints included the progression-free survival (PFS), time to response, time to progression (TTP), and duration of response.

A predefined retrospective subset analysis of 143 patients of the 154 patients with wild-type *KRAS* (exon 2) mCRC was performed, where tumour samples from these patients were tested for additional *RAS* mutations. The incidence of these additional *RAS* mutations (*KRAS* exons 3, 4 and *NRAS* exons 2, 3, 4) in the wild-type *KRAS* (exon 2) population was approximately 10%.

Results in patients with wild-type *RAS* mCRC and mutant *RAS* mCRC from the primary analysis are presented in the table below.

	<b>Panitumumab + FOLFIRI</b>	
	<b>Wild-type <i>RAS</i> (n = 69)</b>	<b>Mutant <i>RAS</i> (n = 74)</b>
<u>ORR (%)</u> <u>(95% CI)</u>	<u>59</u> <u>(46, 71)</u>	<u>41</u> <u>(30, 53)</u>
<u>Median PFS (months)</u> <u>(95% CI)</u>	<u>11.2</u> <u>(7.6, 14.8)</u>	<u>7.3</u> <u>(5.8, 7.5)</u>
<u>Median Duration of response (months)</u> <u>(95% CI)</u>	<u>13.0</u> <u>(9.3, 15.7)</u>	<u>5.8</u> <u>(3.9, 7.8)</u>
<u>Median TTP (months)</u> <u>(95% CI)</u>	<u>13.2</u> <u>(7.8, 17.0)</u>	<u>7.3</u> <u>(6.1, 7.6)</u>

## 3. Benefit-Risk Balance

### Benefits

#### Beneficial effects

The benefit of the combination of panitumumab with FOLFIRI in the first-line therapy of *RAS* WT mCRC appears similar in a cross-study comparison to that of the combination with FOLFOX (ORR=59%, median PFS of 10-11 months). This finding is supported by a small trial comparing the two combinations and showing broadly comparable outcomes.

#### Uncertainty in the knowledge about the beneficial effects

Although no pivotal trial (comparing the combination to FOLFIRI alone) has been conducted with this specific combination in the first line setting, a review of all trials with panitumumab and cetuximab supports that their efficacy is comparable across all lines of therapy.



## Risks

### Unfavourable effects

The most frequent adverse reactions due to the addition of panitumumab to FOLFIRI are skin toxicities, increased diarrhoea, and hypomagnesaemia; the occurrence of nausea, fatigue, and neutropenia, which are related to FOLFIRI, remains unchanged. The types of events and incidence rates are consistent with those expected for an EGFR inhibitor in combination with FOLFIRI.

### Uncertainty in the knowledge about the unfavourable effects

The safety of the combination is well known as it is already administered in the second line setting. No new signal has been detected in the first-line trials.

### Benefit-Risk Balance

#### Importance of favourable and unfavourable effects

Significant survival improvement has been demonstrated for panitumumab in combination with FOLFIRI in the second-line setting and with FOLFOX in the first-line setting. In the latter, comparable results were observed with FOLFIRI in a single-arm trial.

The safety profile of the combination is well-known and the toxicities are considered manageable.

#### Benefit-risk balance

The benefit-risk balance of this combination is considered positive.

### Discussion on the Benefit-Risk Balance

In the EU, the choice of first-line backbone chemotherapy (FOLFIRI or FOLFOX) combined with anti-EGFR therapy is per clinician's choice. However, there is an additional benefit for the FOLFIRI combination compared to the FOLFOX combination, which is that the combination with FOLFIRI has never been shown to produce harmful effects in patients with RAS mutant tumours in stark contrast with the combination with FOLFOX.

The CHMP conclusion on the benefit-risk of this combination is further supported by the recent ESMO treatment guideline stating that "all chemotherapy (FOLFOX/FOLFIRI)-antibody (note that this also includes bevacizumab) combination should be regarded as appropriate and the decision-making will be a complex surrogate, taking into account many clinical factors, as well as patient preferences"<sup>3</sup>. This recommendation is mainly based on the recent results of the US Intergroup CALGB/SWOG 80405 study, showing no difference between bevacizumab and cetuximab-based therapy in patients with RAS WT tumours<sup>4</sup>. The choice between FOLFOX and FOLFIRI (in combination with cetuximab or bevacizumab) was left to physician's preference and 73% of the patients received FOLFOX, which is in accordance with North-American practice. Therefore, the expected subgroup analysis between the two chemotherapies might be of limited value. The benefit-risk balance of panitumumab in the first-line treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC) in combination with FOLFIRI is considered positive.

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<sup>3</sup> Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology 25 (Supplement 3): iii1–iii9, 2014

<sup>4</sup> Lenz, H. et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with expanded RAS analyses untreated metastatic adenocarcinoma of the colon or rectum (mCRC). Ann. Oncol. 25 (Suppl. 4), A5010 (2014).

## 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 changes:

<b>Variation requested</b>		<b>Type</b>
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Extension of Indication to include use in the first-line setting in combination with FOLFIRI in the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC) for Vectibix; as a consequence, sections 4.1 and 5.1 of the SmPC have been updated. In addition, the MAH took the opportunity to introduce minor editorial updates throughout the PI.

The requested variation proposed amendments to the SmPC.

## 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

### **Scope**

Extension of Indication to include use in the first-line setting in combination with FOLFIRI in the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC) for Vectibix; as a consequence, sections 4.1 and 5.1 of the SmPC have been updated. In addition, the MAH took the opportunity to introduce minor editorial updates throughout the PI.

### **Summary**

Refer to scientific discussion Vectibix-H-C-741-II-65