HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
3 September 2014

VECTIBIX, 20 mg/ml, concentrate for solution for infusion

B/1 5 ml vial (CIP: 34009 571 818 5 7)
B/1 10 ml vial (CIP: 34009 571 819 1 8)
B/1 20 ml vial (CIP: 34009 571 821 6 8)

Applicant: AMGEN S.A.S

INN	Panitumumab
ATC code (2012)	L01XC08 (monoclonal antibodies)
Reason for the review	**Modification of indication**
List concerned	**Hospital use** (French Public Health Code L.5123 2)
Indications concerned	"VECTIBIX is indicated for the treatment of adult patients with **wild-type RAS** metastatic colorectal cancer (mCRC): - in first-line therapy in combination with FOLFOX. - in second-line therapy 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. "

Actual Benefit	**Substantial**
IAB	**The modification of indication for VECTIBIX, restricting its use to patients with wild-type RAS (KRAS and NRAS) metastatic colorectal cancer within the framework of a stratified strategy, does not change the Transparency Committee's previous assessments in the absence of comparative data versus other biotherapies indicated in these patients in the various lines of treatment.** **Consequently, and given the current state of the data, VECTIBIX does not provide any improvement in actual benefit (level V, non-existent) in the treatment of wild-type RAS metastatic colorectal cancer:** - **in first-line therapy in combination with FOLFOX** - **in second-line therapy in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan)** - **in monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	Initial: 3 December 2007 Variations: - 1st and 2nd line treatment: 10 November 2011, variation of 27 June 2012 - treatment of wild-type RAS mCRC: 25 July 2013 Conditional Marketing Authorisation
Prescribing and dispensing conditions/special status	List I Medicine requiring special monitoring during treatment Prescription restricted to cancer treatment, haematology or medical oncology specialists and departments Medicinal product reserved for hospital use Inclusion on the extra diagnosis-related group list of proprietary medicinal products

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XC	Monoclonal antibodies
	L01XC08	panitumumab

02 BACKGROUND

Since December 2007, VECTIBIX (panitumumab), a totally human-derived monoclonal antibody acting against the Epidermal Growth Factor Receptor (EGFR)[1], has had Marketing authorisation for the treatment of patients with wild-type KRAS (exon 2) metastatic colorectal cancer as onotherapy after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy regimens.
In November 2011, its indication was extended to wild-type KRAS mCRC (exon 2) in two other situations:

- in first-line therapy in combination with FOLFOX (fluorouracil, folinic acid, oxaliplatin),
- in second-line therapy in combination with FOLFIRI (fluorouracil, folinic acid, irinotecan) for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

During the evaluation of the proprietary medicinal product VECTIBIX in these two extensions of indication (opinion of 17 October 2012), the Committee concluded that in the absence of a comparative study versus ERBITUX (cetuximab), VECTIBIX, in combination with chemotherapy, does not provide any improvement in actual benefit (IAB V, non-existent) in the treatment of wild-type KRAS mCRC.

As part of the conditional Marketing Authorisation, the EMA (European Medicines Agency) imposed various follow-up measures for the periodic re-assessment of the benefit/risk ratio for VECTIBIX. One of these measures was based on monitoring the development of new biomarkers.

[1] The other currently marketed monoclonal anti-EGFR antibody is chimeric (ERBITUX, cetuximab).

Thus, a new *post hoc* analysis of the phase III study that led to the extension of indication for panitumumab in 1st line treatment (20050203 or PRIME study) based on subgroups of the RAS and BRAF genes was submitted to the EMA in September 2012.
This analysis and other retrospective analyses have shown that the efficacy of panitumumab, used alone or in combination with chemotherapy, is restricted to patients with wild-type RAS mCRC.

Given these new data, the Marketing Authorisation for VECTIBIX was amended by the EMA on 25 July 2013 so as to no longer restrict the indication of VECTIBIX only to patients with mCRC expressing a wild-type KRAS gene in exon 2, but also to patients with tumours with wild-type RAS genes (corresponding to exons 2, 3, 4 of the KRAS and NRAS genes).[2] The use of VECTIBIX in combination with oxaliplatin-based chemotherapy is now contraindicated in patients who have mCRC with a RAS gene mutation or for whom the RAS mutation status is unknown.

03 THERAPEUTIC INDICATIONS

"VECTIBIX is indicated for the treatment of adult patients with **wild-type RAS** metastatic colorectal cancer (mCRC):
- in first-line therapy in combination with FOLFOX.
- in second-line therapy 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."

04 DOSAGE

"VECTIBIX treatment should be supervised by a physician experienced in the use of anti-cancer therapy.
Evidence of wild-type RAS (KRAS and NRAS) status is required before initiating treatment with VECTIBIX. Mutation status should be determined by an experienced laboratory using validated test methods for detection of KRAS (exons 2, 3 and 4) and NRAS (exons 2, 3 and 4) mutations.

Dosage:
The recommended dose of VECTIBIX is 6 mg/kg of bodyweight given once every two weeks. Prior to infusion, VECTIBIX should be diluted in sodium chloride 9 mg/ml (0.9%) solution for injection to a final concentration not to exceed 10 mg/ml (for preparation instructions, see Special precautions for disposal and other handling).
Modification of the dose of VECTIBIX may be necessary in cases of severe (≥ grade 3) dermatological reactions, see Special warnings and Precautions for use.

Special populations:
The safety and efficacy of VECTIBIX have not been studied in patients with renal or hepatic impairment.
There is no clinical data to support dose adjustments in the elderly.

Paediatric population:
There is no relevant use of VECTIBIX in the paediatric population in the indication treatment of colorectal cancer.

[2] In the remainder of the opinion, RAS designates KRAS (exons 2, 3 and 4) and NRAS (exons 2, 3 and 4) genes.

Method of administration:
VECTIBIX must be administered as an intravenous infusion via an infusion pump, using a low protein binding 0.2 or 0.22 micrometre in-line filter, through a peripheral line or indwelling catheter. The recommended infusion time is approximately 60 minutes. If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes. Doses higher than 1000 mg should be infused over approximately 90 minutes (for handling instructions, see Special precautions for disposal and other handling). "
The infusion line should be flushed with sodium chloride solution before and after VECTIBIX administration to avoid mixing with other medicinal products or intravenous solutions.
A reduction in the rate of infusion of VECTIBIX may be necessary in cases of infusion-related reactions (see Special warnings and precautions for use).
VECTIBIX must not be administered as an intravenous push or bolus.
For instructions on dilution of the medicinal product before administration, see Special precautions for disposal and other handling.

Determination of RAS mutation status:[3]
The expansion of the diagnostic test associated with VECTIBIX (panitumumab), to identify RAS gene mutations following changes to the wording of the Marketing Authorisation, uses the same detection methods as those used to identify KRAS mutations (exon 2).
Currently this test looks for mutations in exons 2, 3 and 4 of KRAS and NRAS oncogenes and, in France, is sponsored by the hospital as it is performed within hospital molecular genetic platforms for cancers funded by the National Cancer Institute and the General Directorate General of Healthcare. These platforms are spread out over the entire country - there is roughly one per region - and: "their aim is to perform innovative molecular tests for all patients in the region regardless of the establishment in which they are being treated." The need represented by this examination, which is a pre-requisite for using VECTIBIX, is therefore covered by these platforms. Therefore so far, it is not the inclusion on the list of procedures and services referred to in Article L. 162-1-7 of the French Social Security Code that ensures financial coverage for the test by the hospital. This inclusion is planned and will require a prior evaluation by HAS.

[3] HAS methodological guide: Companion diagnostic test associated with a targeted therapy: definitions and assessment method. February 2014.

05 THERAPEUTIC NEED

With 42,152 new cases estimated in 2012, 55% of which occur in men, colorectal cancer is the 3rd most common cancer in France.[4] The stage of the cancer at the time of diagnosis is the most relevant factor regarding prognosis. The survival rate at five years ranges from 93% for a stage I disease to less than 10% for stage IV (metastatic). Between 20 and 25% of patients immediately have a stage IV disease and up to 50% will progress to this stage during the course of the disease.[5] The survival rate at five years ranges from 5 to 15% in patients with generalised metastatic disease.[6]

The treatment of metastatic colorectal cancer has changed substantially in recent years. First of all, overall survival has increased significantly thanks to the use in current practice of irinotecan and oxaliplatin, in combination with 5-fluorouracil (5FU) and folinic acid (FA) in the form of LV5FU2, combinations called FOLFIRI and FOLFOX respectively. A study had shown, in first- and second-line treatment, that the sequences FOLFIRI-FOLFOX and FOLFOX-FOLFIRI had equivalent efficacy.[7]

With the appearance of biotherapies, the value of a combination of biotherapy and chemotherapy as first- and second-line treatments was established[8].

In metastatic colorectal cancer, the anti-VEGF antibody bevacizumab (AVASTIN) and the anti-EGFR antibodies panitumumab (VECTIBIX) and cetuximab (ERBITUX) can be used as first-line treatment in combination with chemotherapy. Determination of the RAS (exons 2, 3 and 4 of KRAS and NRAS) gene mutation status of the tumour (for the initial tumour or for the metastases) is useful in selecting the therapeutic strategy8. Testing the EGFR status by immunohistochemistry is no longer recommended since the method is not reliable and is not predictive of response. Checking for a BRAF mutation, a poor prognosis factor, is optional because it is not predictive of response to anti-EGFR treatment. The indication of panitumumab and cetuximab is now limited to patients with a wild-type RAS status, contrary to bevacizumab which can be used regardless of the RAS status.

In second-line treatment, in the event of progression with chemotherapy plus biotherapy, the choice is either to change the chemotherapy (irinotecan or oxaliplatin depending on the first-line regimen received), or to change the biotherapy.

In a third-line treatment, in the event of progression with irinotecan and oxaliplatin (with or without bevacizumab):

- no RAS gene mutation:
  - either panitumumab
  - or cetuximab
- presence of a RAS mutation: palliative care or therapeutic trial.

As a last line of treatment, in the event of failure or ineligibility for the available treatments, particularly anti-VEGF and anti-EGFR treatment, a treatment with the protein kinase inhibitor regorafenib (STIVARGA) may be considered.

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[4] Binder-Foucard F, Belot A, Delafosse P, Remontet L, Woronoff AS, Bossard N. Estimation nationale de l'incidence et de la mortalité par cancer en France entre 1980 et 2012. Partie 1 – Tumeurs solides. Saint-Maurice (Fra): Health Monitoring Institute, 2013.

[5] Schmoll HJ, Van CE, Stein A et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol 2012; 23: 2479-516.

[6] Brenner H, Bouvier AM, Foschi R, et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EUROCARE study. Int J Cancer 2012; 131: 1649-58.

[7] Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A.J Clin Oncol. 2004 Jan 15; 22(2): 229-37.

[8] French National Society of Gastroenterology (SNFGE) thesaurus of gastrointestinal oncology, metastatic colon cancer. Updated 18/02/2014

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

INN	Identical TC*	Name (Company)	Indication	Date of opinion	AB	IAB
Cetuximab	Yes	ERBITUX (Merck Serono)	mCRC with epidermal growth factor receptor (EGFR-expressing, RAS wild-type) • in combination with chemotherapy,[9]	2009	Substantial	1st and 2nd line in combination: V
			• as a single agent in patients who have failed oxaliplatin- and irinotecan based therapy and who are intolerant to irinotecan.			after failure, as monotherapy: IV
Bevacizumab	Yes	AVASTIN (Roche)	MCRC in combination with fluoropyrimidine-based chemotherapy	1st line: 2005	Substantial	II
				2nd line: 2009	Substantial	IV compared with FOLFOX-4 alone and in combination with FOLFOX-4

TC = therapeutic class
mCRC: metastatic colorectal cancer.

Conclusion

In the treatment of patients with wild-type RAS metastatic colorectal cancer, the clinically relevant comparator medicine is ERBITUX (cetuximab), another anti-EGFR antibody with a similar indication to that of VECTIBIX (panitumumab) and also limited to tumours with wild-type RAS status.
AVASTIN (bevacizumab), an anti-VEGF antibody, has a broader indication, independent from the mutation status of the RAS genes.

[9] The wording of the indication for ERBITUX was restricted to use in combination with an irinotecan-based regimen or with FOLFOX-4 on 23 June 2011, then on 13 January 2012 to first-line treatment in combination with FOLFOX. The wording now reads: "ERBITUX is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer
• in combination with an irinotecan-based chemotherapy,
• in first-line combination with FOLFOX,
• as a single agent in patients who have failed oxaliplatin- and irinotecan based therapy and who are intolerant to irinotecan. "

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Management (patients with wild-type KRAS status)	
	1st and 2nd line in combination	Monotherapy
Germany	Yes	Yes
United Kingdom	No (not requested)	No (rejected by NICE and SMC)
United States	No	Yes
Canada	No (no regulatory approval)	Yes for certain provinces
Australia	2nd line only	Yes

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion	**30 April 2008 (inclusion for hospital use)**
Indication	EGFR-expressing mCRC with wild-type KRAS, as **monotherapy**, after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy regimens.
AB	**Substantial**
IAB	In the absence of comparative data based on rigorous methodology, it is not possible to assess the therapeutic benefit of this medicine in this clinical situation. Consequently, the Transparency Committee considers that, in the current state of knowledge, the proprietary medicinal product VECTIBIX does not provide any improvement in actual benefit (**level V**) in the management of patients with EGFR-expressing metastatic colorectal carcinoma with wild-type KRAS, after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.
Studies requested	The Transparency Committee would like to set up a descriptive study following up patients treated with VECTIBIX in France for colorectal cancer. The objective is to document the circumstances in which this product is used in real-life treatment situations: - characteristics of the prescribing physicians (discipline, practice type, etc.) - characteristics of the patients treated: age, gender, disease stage, previous treatments, diagnostic factors (EGFR status, KRAS gene expression, etc.) - dosage used and combined treatments. The duration of the study will need to be justified by an independent scientific committee. If scheduled or ongoing studies, in particular within the remit of the European Risk Management plan, fail to answer all the questions raised by the Transparency Committee, a specific study will need to be conducted.
Date of opinion	**17 October 2012 (extension of indication)**

Indications	Wild-type KRAS mCRC: **- in first-line therapy in combination with FOLFOX.** **- in second-line therapy 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.
AB	**Substantial**
IAB	Without a comparative study versus ERBITUX, VECTIBIX does not provide any improvement in actual benefit (**level V**) in the treatment of wild-type KRAS metastatic colorectal cancer: - in first-line therapy in combination with FOLFOX - in second-line therapy in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

09 ANALYSIS OF AVAILABLE DATA

Comparative, randomised, open-label phase III studies carried out in the various indications for VECTIBIX have been presented in the Transparency Committee's previous opinions:

- Study 20020408 (opinion of 30 April 2008[10]): evaluating the efficacy and safety of panitumumab combined with a palliative treatment versus a palliative treatment alone in patients in whom fluoropyrimidine-, oxaliplatin and irinotecan based chemotherapy regimens failed.
- 20050181 or PEETERS study (opinion of 17 October 2012[11]): evaluating the efficacy and safety of panitumumab in combination with FOLFOX-4 versus FOLFOX-4 alone as a second-line treatment in patients previously treated with a fluoropyrimidine-based chemotherapy regimen (excluding irinotecan).
- 20050203 or PRIME study (opinion of 17 October 2012[11]): evaluating the efficacy and safety of panitumumab in combination with FOLFOX-4 versus FOLFOX-4 alone as a first-line treatment.

No new clinical data were provided with a view to restrict the indication of VECTIBIX in patients with wild-type RAS mCRC. This restriction of indication is based solely on the results of *post hoc* exploratory subgroup analyses of these phase III studies.

09.1 Efficacy

Summary of the primary results of these phase III studies:

- Study 20020408 (opinion of 30 April 2008): the results of the prospective analysis of this study led the Committee for Medicinal Products for Human Use (CHMP) to issue an opinion against granting VECTIBIX a Marketing Authorisation on 24 May 2007. This analysis, carried out in the overall study population, did not show a clinically relevant gain with an absolute gain of 5 days in terms of progression-free survival (primary endpoint) in the VECTIBIX group and no difference in terms of overall survival. A retrospective analysis was performed *post hoc* to include the presence or absence of exon 2 KRAS gene mutation and made it possible to obtain the Marketing Authorisation. Among the 427 patients eligible for this analysis: 184 (43%) had a tumour with the mutation and 243 (57%) had a tumour without this mutation. For patients with a wild-type KRAS gene (Marketing Authorisation population), the median progression-free survival was 16 weeks in the VECTIBIX group

[10] Transparency Committee Opinion, 30 April 2008, VECTIBIX 20 mg/ml.
[11] Transparency Committee Opinion, 17 October 2012, VECTIBIX 20 mg/ml.

versus 8 weeks in the palliative care alone group; no difference in overall survival was observed between the two groups.

- 20050181 or PEETERS study (opinion of 17/10/2012): the principal analysis carried out within the subgroup of 597 patients (55%) with a wild-type KRAS gene showed an extension in median progression-free survival (co-primary endpoint) of 2 months (5.9 months versus 3.9 months, HR = 0.73; [0.59-0.90]; p = 0.004) in the VECTIBIX + FOLFIRI group; no change to the median overall survival (the other co-primary endpoint).
- 20050203 or PRIME study (opinion of 17/10/2012): the principal analysis carried out within the subgroup of 656 previously untreated patients (60%) with a wild-type KRAS gene showed a modest increase in progression-free survival of 1.6 months (primary endpoint, 9.6 months versus 8 months, HR = 0.80; [0.66-0.97]; p = 0.02) with no impact on the overall survival in the VECTIBIX + FOLFOX-4 group.

Within the scope of the restriction of indication to patients whose tumours have RAS mutations, which is the subject of this opinion, the new data provided by the laboratory are from the *post hoc* retrospective exploratory analyses carried out according to the KRAS and NRAS mutation status in exons 2, 3 and 4.

9.1.1 Study 20020408 (monotherapy)[10]

Preliminary hypotheses regarding the existence of biomarkers that predict the response to treatment are taken from this phase III study for the Marketing Authorisation for VECTIBIX as monotherapy in the 3rd line treatment or beyond.

Results of the retrospective analysis by RAS status:
A new retrospective analysis of the study was performed *post hoc* to include the presence or absence of RAS gene mutation. It was possible to determine the status of the RAS gene for 361 of the 463 patients included (78%): 133 (37%) had wild-type RAS genes and 228 (63%) had at least one muted-type RAS gene (22 of whom had a wild-type KRAS exon 2 status). In the subgroup of patients with wild-type RAS genes in their tumours, progression-free survival (PFS) was 12.3 weeks in the VECTIBIX group versus 6.9 weeks in the palliative care alone group, i.e. an absolute gain of 5.4 weeks in favour of panitumumab (HR = 0.38; [0.27-0.56]); no change in the median overall survival (OS) was observed between the two treatment groups (see Table 1).

This retrospective analysis is consistent with the assumption that RAS mutations are negative predictive markers for treatment with panitumumab.

Table 1: Efficacy results from study 20020408 by RAS and KRAS mutation status

		New exploratory analysis						Initial exploratory analysis			
		Wild-type RAS		Muted-type RAS		Wild-type KRAS exon 2/mutated RAS		Wild-type KRAS exon 2		Muted-type KRAS exon 2	
		Pmab + pall (n = 72)	Pall alone (n = 61)	Pmab + pall (n = 95)	Pall alone (n = 111)	Pmab + pall (n = 11)	Pall alone (n = 11)	Pmab + pall (n = 124)	Pall alone (n = 119)	Pmab + pall (n = 84)	Pall alone (n = 100)
PFS (primary endpoint)	**Median (weeks) [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]
	Difference in medians (weeks)	5.4		0.1		-0.5		5		0.1	
	Relative risk [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]	
OS	**Median (months) [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]
	Difference in medians (months)	0.6		0.8		1		0.5		0.5	
	Relative risk [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]	

Pmab: panitumumab; Pall: palliative treatment.

9.1.2 20050203 – PRIME study

A retrospective analysis of this open-label, randomised, controlled phase III study that assessed the efficacy and safety of panitumumab (VECTIBIX) in combination with FOLFOX-4 versus FOLFOX-4 alone in previously untreated patients was performed *post hoc* by presence or absence of RAS gene mutations.

As a reminder, this study was in progress when the *post hoc* analysis of study 20020408 showed that the efficacy of panitumumab as monotherapy was restricted to patients with a wild-type KRAS gene in exon 2. The protocol was thus amended after randomisation of 974 patients to enable a prospective analysis of the efficacy of panitumumab depending on the KRAS gene status. A total of 1183 patients were randomised: 593 patients in the panitumumab combined with FOLFOX-4 group and 590 in the FOLFOX-4 alone group. The average age was 62 years and 9% of patients were aged over 75 years. The majority of patients had an ECOG performance index of 0 or 1 (94%). Approximately two-thirds of patients had colon cancer and one-third had rectal cancer.

Results of the principal analysis in the "muted-type KRAS gene" and "wild-type KRAS gene" patient subgroups were presented in the Committee's previous assessment (opinion of 17 October 2012[11]). In this analysis, only the seven most common KRAS mutations (in codons 12 and 13 of exon 2) were determined[12,13]. Therefore, these KRAS gene mutations were the only negative predictive biomarkers of efficacy validated in mCRC. In the principal analysis, the status of the KRAS gene was known for 1096 of the 1183 randomised patients (93%): 656 (60%) had a wild-type KRAS gene and 440 (40%) had a mutant KRAS gene. In the subgroup of 656 previously untreated patients with a wild-type KRAS gene, the addition of panitumumab to FOLFOX-4 alone was associated with a modest gain of 1.6 months in the median progression free survival (primary endpoint, 9.6 months versus 8 months, HR = 0.80 [0.66; 0.97]; p = 0.02) with no impact shown on the overall survival (23.9 months versus 19.7 months, HR = 0.83; [0.67 to 1.02]; NS) (see Table 2).

Table 2: Efficacy results from the PRIME study by KRAS mutation status (ITT)

		Main analysis			
		Wild-type KRAS exon 2 (Previous MA)		Muted-type KRAS exon 2	
		Pmab + FOLFOX-4 (n = 325)	FOLFOX-4 (n = 331)	Pmab + FOLFOX-4 (n = 221)	FOLFOX-4 (n = 219)
PFS (primary endpoint)	**Median (months) [95% CI]**	9.6 [9.2; 11.1]	8.0 [7.5; 9.5]	7.3 [6.3; 8.0]	8.8 [7.7; 9.4]
	Difference in medians (months)	1.6		-1.5	
	Relative risk [95% CI]; p	0.80 [0.66; 0.97]; p = 0.02		1.28 [1.04; 1.62]; p = 0.02	
OS	**Median (months) [95% CI]**	23.9 [20.3; 28.3]	19.7 [17.6; 22.7]	15.5 [13.1; 17.6]	19.3 [16.5; 21.8]
	Difference in medians (months)	4.2		-3.8	
	Relative risk [95% CI]; p	0.83 [0.67; 1.02]; NS		1.24 [0.98; 1.57]; NS	

Pmab: panitumumab.

Additional mutations in the NRAS gene at exons 2, 3 and 4 and the KRAS gene at exons 3 and 4 were subsequently identified. A *post hoc* retrospective analysis was thus performed according to the subgroups of the newly identified RAS mutations. The statistical assumptions required for this analysis were not provided for in the protocol and were the subject of an additional statistical

[12] Amado RG, Wolf M, Peeters M et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008; 26: 1626-34.

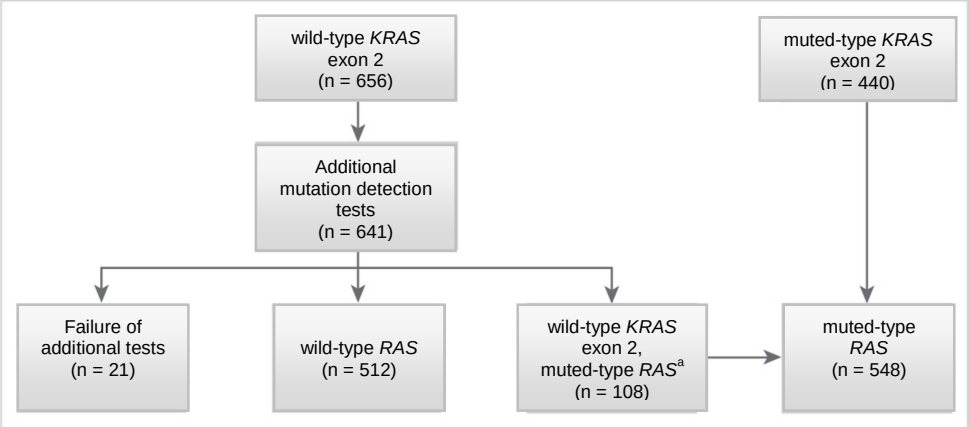
[13] Douillard JY, Siena S, Cassidy J et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010; 28: 4697-705.

analysis plan. To perform this analysis, samples of KRAS exon 2 wild-type tumours (codons 12 and 13) were tested to verify the existence of pre-defined mutations in the exons:

- 3 (codons 61) and 4 (codons 117 and 146) of the KRAS gene
- 2 (codons 12 and 13), 3 (codons 61) and 4 (codons 117 and 146) of the NRAS gene
- 15 (codon 600) of the BRAF gene

Patients whose tumours have a muted-type KRAS gene in exon 2 were classified as having a muted-type RAS status and were not tested for additional RAS mutations.
Among the 1060 patients for whom the RAS status could be determined: 548 (52%) had a tumour with at least one mutation and 512 (48%) had a tumour without mutations (see Fig. 1). Approximately 9% of patients (n = 60) presented with mutations at exons 3 and 4 of the KRAS gene, and 7% (n = 48) at exons 2 and 3 of the NRAS gene; no mutation at exon 4 of the NRAS gene was detected. BRAF gene mutations were reported in 10 to 15% of the wild-type KRAS tumours.

Figure 1: Distribution of patients in the analysis of the RAS mutation status



Results of the retrospective analysis by RAS status:

In the subgroup of "RAS wild-type status" patients (Marketing Authorisation population)

The median progression-free survival (primary endpoint) was:

- 10.1 months in the panitumumab + FOLFOX-4 group (n = 259),
- 7.9 months in the FOLFOX-4 group (n = 253),

i.e. an absolute gain of 2.2 months in favour of the combination of panitumumab and FOLFOX-4 (HR = 0.72; [0.58-0.90]; p = 0.004).
The overall median survival time (secondary endpoint for which the primary analysis was scheduled after the occurrence of at least 380 events) was:

- 26 months in the panitumumab + FOLFOX-4 group (n = 259),
- 20.2 months in the FOLFOX-4 group (n = 253),

i.e. an absolute gain of 5.8 months in favour of the combination of panitumumab and FOLFOX-4 (HR = 0.78; [0.62-0.99]; p = 0.043) (see Table 3).

Results are consistent in the analysis of the subgroup except for two subgroups for which an HR greater than 1 was observed:

- subgroup of patients aged over 75 years (n = 48):
  - median progression-free survival: HR = 1.21; [0.62-2.38]
  - overall median survival: HR = 1.06; [0.53-2.11]
- subgroup of patients with an ECOG score of 2 (n = 32):
  - median progression-free survival: HR = 1.69; [0.75-3.82]
  - overall median survival: HR = 1.34; [0.63-2.89].

It should be noted that the SPC states that a positive risk-benefit relationship has not been documented in patients with an ECOG score of 2.

In the subgroup of “RAS muted-type status” patients:
The median progression-free survival was:

- 7.3 months in the panitumumab + FOLFOX-4 group (n = 272),
- 8.7 months in the FOLFOX-4 group (n = 276),

i.e. a statistically significant difference of 1.4 months not in favour of panitumumab + FOLFOX-4 (HR = 1.31; [1.07-1.60]; p = 0.008).
The overall median survival was:

- 15.6 months in the panitumumab + FOLFOX-4 group (n = 272),
- 19.2 months in the FOLFOX-4 group (n = 276),

i.e. a non-statistically significant difference of 3.6 months not in favour of panitumumab + FOLFOX-4 (HR = 1.25; [1.02-1.55]; NS) (see Table 3).
According to these results (shorter PFS and OS in patients receiving panitumumab in addition to FOLFOX), the use of panitumumab is contraindicated in patients with a known or undetermined RAS gene mutation. Determination of the RAS status is vital before treatment is started.

In this analysis, BRAF gene mutations were found to be prognostic of worse outcome but not predictive of non-response to panitumumab treatment.

Since this analysis, additional mutations in KRAS and NRAS genes in exon 3 (codon 59) were subsequently identified (n = 7). A new retrospective exploratory analysis showed similar results to those observed in patients whose tumours have a RAS gene without consideration of codon 59 in exon 3.

Table 3: **Efficacy results from the PRIME study by RAS and KRAS mutation status (ITT)**

		Exploratory analysis				Main analysis			
		Wild-type RAS (MA population)		Muted-type RAS		Wild-type KRAS exon 2 (Previous MA)		Muted-type KRAS exon 2	
		Pmab + FOLFOX-4 (n = 259)	FOLFOX-4 (n = 253)	Pmab + FOLFOX-4 (n = 272)	Pmab + FOLFOX-4 (n = 276)	Pmab + FOLFOX-4 (n = 325)	FOLFOX-4 (n = 331)	Pmab + FOLFOX-4 (n = 221)	FOLFOX-4 (n = 219)
PFS (primary endpoint)	**Median (months) [95% CI]**	10.1 [9.3; 12]	7.9 [7.2; 9.3]	7.3 [6.3; 7.9]	8.7 [7.6; 9.4]	9.6 [9.2; 11.1]	8.0 [7.5; 9.5]	7.3 [6.3; 8.0]	8.8 [7.7; 9.4]
	Difference in medians (months)	2.2		-1.4		1.6		-1.5	
	Relative risk [95% CI]; p	0.72 [0.58; 0.90]; p = 0.004		1.31 [1.07; 1.60]; p = 0.008		0.80 [0.66; 0.97]; p = 0.02		1.28 [1.04; 1.62]; p = 0.02	
OS	**Median (months) [95% CI]**	26.0 [21.7; 30.4]	20.2 [17.7; 23.1]	15.6 [13.4; 17.9]	19.2 [16.7; 21.8]	23.9 [20.3; 28.3]	19.7 [17.6; 22.7]	15.5 [13.1; 17.6]	19.3 [16.5; 21.8]
	Difference in medians (months)	5.8		-3.6		4.2		-3.8	
	Relative risk [95% CI]; p	0.78 [0.62; 0.99]; p = 0.043		1.25 [1.02; 1.55]; p = 0.034		0.83 [0.67; 1.02]; NS		1.24 [0.98; 1.57]; NS	

Pmab: panitumumab:

9.1.3 20070509 – PEAK study

The PEAK study is a randomised, controlled, open-label phase II study that evaluated panitumumab in combination with FOLFOX-6 versus bevacizumab in combination with FOLFOX-6 in previously untreated patients whose tumours express wild-type KRAS in exon 2. The primary objective of this study was to obtain a point estimate of the median progression-free survival with each treatment.

A total of 285 patients were randomised: 142 patients in the panitumumab combined with FOLFOX-6 group and 143 in the bevacizumab combined with FOLFOX-6 group. The average age was 62 years and 9% of patients were aged over 75 years. Only one patient had an unknown ECOG performance index, the others all had an ECOG score of 0 or 1. Approximately two-thirds of patients had colon cancer and one-third had rectal cancer.

This study was also the subject of a *post hoc* retrospective analysis carried out according to the RAS gene mutation status (exons 2, 3 and 4 of KRAS and NRAS genes). Among the 207 patients for whom the RAS status could be determined: 47 (23%) had a tumour with at least one mutation and 160 (77%) had a tumour without mutations.

Results of the retrospective analysis by RAS status:

The results of the *post hoc* analysis by the other RAS biomarkers were comparable with those of the primary analysis by the KRAS exon 2 status (see Table 4).
In the subgroup of patients whose tumours have wild-type RAS genes, improved progression-free survival and overall survival were observed in the group treated with panitumumab + FOLFOX-6 compared with the group treated with bevacizumab + FOLFOX-6. Conversely, in the subgroup of patients whose tumours have mutated RAS genes, progression-free survival and overall survival were better in the group treated with bevacizumab + FOLFOX-6. The results of the retrospective analysis of this study by RAS gene mutation status are in agreement with those of the retrospective analyses of the 20020408 and 20050203 studies (PRIME).

Table 4: Results from the PEAK study by RAS and KRAS mutation status (ITT)

		Exploratory analysis				Main analysis	
		Wild-type RAS (MA population)		Muted-type RAS and Wild-type KRAS exon 2		Wild-type KRAS exon 2	
		Pmab + FOLFOX-6 (n = 80)	Bev + FOLFOX-6 (n = 80)	Pmab + FOLFOX-6 (n = 24)	Bev + FOLFOX-6 (n = 23)	Pmab + FOLFOX-6 (n = 142)	Bev + FOLFOX-6 (n = 143)
PFS	**Median (months) [95% CI]**	13.0 [10.9-15.1]	10.1 [9.0-12.7]	7.8 [6.5-9.8]	8.9 [7.3-12.0]	10.9 [9.7-12.8]	10.1 [9.0-12.0]
	Difference in medians (months)	2.9		-1.1		0.8	
	Relative risk [95% CI]	0.66 [0.46-0.95]		1.39 [0.73-2.64]		0.84 [0.64-1.11]	
OS	**Median (months) [95% CI]**	41.3 [28.8-41.3]	28.9 [23.9-31.3]	N/R [13.0, N/R]	21.6 [13.9-25.4]	34.2 [26.6-N/R]	24.3 [21.0-29.2]
	Difference in medians (months)	12.4		-		9.9	
	Relative risk [95% CI]	0.63 [0.39-1.02]		0.72 [0.28-1.83]		0.62 [0.44-0.89]	

Pmab: panitumumab; Bev: bevacizumab; N/R: not reached.

It should be noted that the median overall survival times in the panitumumab + FOLFOX-6 group in the PEAK study were higher than those found in the panitumumab + FOLFOX-4 group in the PRIME study.

9.1.4 Additional data: 20080763 – ASPECCT study[14]

The ASPECCT study is a non-inferiority, controlled, randomised, open-label, phase III study evaluating the efficacy and safety of panitumumab versus cetuximab in previously treated patients whose tumours have wild-type RAS in exon 2. This is the first direct comparison study between the two biotherapies targeting EGFR receptors used in the treatment of mCRC: panitumumab (VECTIBIX) and cetuximab (ERBITUX).

A total of 1010 patients were randomised: 506 patients to the panitumumab group and 504 to the cetuximab group. The average age was 61 years and 82% of patients were aged over 75 years. The majority of patients had an ECOG performance index of 0 or 1 (92%). Approximately two-thirds of patients had colon cancer and one-third had rectal cancer. By that date, there are no data available on the RAS status of the patients included.

This study is currently ongoing but was the subject of an interim analysis on 5 February 2013. To date, corresponding to a median duration of follow-up of approximately 9 months, 383 patients (77%) from the panitumumab group and 392 (78%) from the cetuximab group had died. Median overall survival (primary endpoint) was 10.4 months in the panitumumab group [9.4-11.6] versus 10.0 months in the cetuximab group [9.3-11.0], (HR = 0.97; [0.84-1.11]).
The statistical analysis plan provided that non-inferiority would be shown if the panitumumab treatment preserved at least 50% of the effect on overall survival obtained after treatment with cetuximab in the NCIC CTG CO.17 study[15] (HR cetuximab versus supportive care = 0.55; [0.41-0.74][16]). The primary non-inferiority endpoint was reached (p = 0.001) because the median overall survival in the panitumumab group preserved more than 50% of the overall survival benefit obtained after treatment with cetuximab in the NCIC CTG CO.17 study.
The median progression free survival (secondary endpoint) was similar in the two groups: 4.1 months for panitumumab versus 4.4 months for cetuximab (HR = 1.00; [0.88-1.14]).
Given the interim nature of this analysis and while waiting for the final analysis, the non-inferiority results for panitumumab compared with cetuximab should be interpreted with caution.

09.2 Adverse effects

According to the SPC, the most common adverse effects of VECTIBIX are skin reactions, observed in 93% of patients. These reactions are related to the pharmacologic effects of VECTIBIX, the majority are mild to moderate in nature with 25% being severe (grade 3 NCI-CTC), and less than 1% life threatening (grade 4 NCI-CTC). Other frequently reported adverse effects include gastrointestinal disorders [diarrhoea (50%), nausea (41%), vomiting (27%), constipation (23%) and abdominal pain (23%)], anaemia, general disorders [fatigue (37%), pyrexia (20%)], metabolism and nutrition disorders [anorexia (27%), hypomagnesaemia], paronychia (20%) and skin reactions [rash (45%), acneiform dermatitis (39%), pruritus (35%), rash (30%) and dry skin (22%)].

[14] Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol. 2014 May; 15(6): 569-79. doi: 10.1016/S1470-2045(14)70118-4.
[15] Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med*. 2008; 359: 1757-1765.
[16] HR cetuximab/supportive care = 0.55 CI 95% [0.41-0.74] is taken from a retrospective estimate in muted-type KRAS exon 2 patients (KRAS status determination rate of 69%) included in study NCIC CTG CO.17 (n = 215).

9.2.1 New safety data

9.2.1.1 20050203 – PRIME study

Summary of the data from the primary analysis by KRAS status, on 28 August 2009:

In the subgroup of patients whose tumours had wild-type KRAS in exon 2, treatment discontinuations due to adverse events affected 24% (78/322) of patients in the panitumumab + FOLFOX-4 group and 14% (46/327) of patients in the FOLFOX-4 alone group. The percentage of patients who had serious adverse events was 40% (130/322) in the panitumumab + FOLFOX-4 group and 36% (118/327) in the FOLFOX-4 group. The most common adverse event that led to discontinuation of panitumumab was rash (4%) and the most common one that led to discontinuation of FOLFOX-4 was parasthesia (3% in the panitumumab + FOLFOX-4 group versus 2% in the FOLFOX-4 alone group).

In the subgroup of patients with tumours expressing muted-type KRAS in exon 2, treatment discontinuations due to adverse events affected 19% (42/217) of patients in the panitumumab + FOLFOX-4 group and 14% (31/218) of patients in the FOLFOX-4 alone group. The percentage of patients who had serious adverse events was 47% (102/217) in the panitumumab + FOLFOX-4 group and 29% (63/218) in the FOLFOX-4 group. The most common adverse event that led to discontinuation of panitumumab was rash (5%) and the most common one that led to discontinuation of FOLFOX-4 was parasthesia (2% in the panitumumab + FOLFOX-4 group versus 1% in the FOLFOX-4 alone group).

Data from the retrospective analysis by RAS status, on 2 August 2010:

No new toxicities or worsening of previously recognised toxicities were observed during this analysis performed with additional follow-up data. The most common adverse effects (> 5% of patients) were identical to those observed in the primary analysis.

Regardless of the mutation status, the adverse effects known to be associated with panitumumab treatment, such as rashes, acneiform dermatitis and hypomagnesaemia were more commonly found in the panitumumab + FOLFOX-4 group than in the FOLFOX-4 alone group. Skin disorders were the most common adverse effects in patients receiving panitumumab in combination with chemotherapy (97% of patients in the panitumumab + FOLFOX-4 group had skin toxicity versus 44% in the FOLFOX-4 alone group).

In the subgroup of "RAS wild-type status" patients (Marketing Authorisation population)

Treatment discontinuations due to adverse events affected 26% (66/256) of the patients in the panitumumab + FOLFOX-4 group and 16% (39/250) of the patients in the FOLFOX-4 alone group. The percentage of patients who had serious adverse events was 43% (111/256) in the panitumumab + FOLFOX-4 group and 37% (92/250) in the FOLFOX-4 group. Events graded ≥ 3 affected 85% (217/256) of the patients in the panitumumab + FOLFOX-4 group and 70% (175/250) of the patients in the FOLFOX-4 group. As expected, the most commonly reported adverse effects in both treatment groups were diarrhoea, neutropenia, asthaenia, nausea. The adverse effects reported more frequently in the panitumumab + FOLFOX-4 group than in the FOLFOX-4 alone group were: diarrhoea (65% versus 52%), rash (55% versus 8%), acneiform dermatitis (34% versus 0%), hypomagnesaemia (32% versus 7%) and stomatitis/oral mucositis (49% versus 30%).

In the subgroup of "RAS muted-type status" patients:

The safety profile (incidence and type of adverse events) in patients whose tumours have a RAS mutation was similar to that observed in patients with tumours expressing a KRAS exon 2 mutation during the primary analysis.

Treatment discontinuations due to adverse events affected 23% (62/266) of the patients in the panitumumab + FOLFOX-4 group and 15% (40/273) of the patients in the FOLFOX-4 alone group. The percentage of patients who had serious adverse events was 45% (121/266) in the panitumumab + FOLFOX-4 group and 31% (84/273) in the FOLFOX-4 group. Events graded ≥ 3 affected 81% (216/266) of patients in the panitumumab + FOLFOX-4 group and 73% (201/273) of patients in the FOLFOX-4 group. The serious adverse effect more commonly reported in the panitumumab + FOLFOX-4 than in the FOLFOX-4 alone group was: diarrhoea (10% versus 3%).

9.2.1.2 20070509 – PEAK study

The safety profile of panitumumab observed in the *post hoc* analysis according to the RAS gene mutation status was similar to that observed in this same analysis of the PRIME study.

In the "wild-type RAS" subgroup, serious adverse events were reported for a larger number of patients in the panitumumab + FOLFOX-6 group than in the bevacizumab + FOLFOX-6 group (43% versus 39%). This difference was found for grade 3 adverse events (70% versus 54%). In total, 98% of wild-type RAS patients presented with one adverse event in this study: 100% in the panitumumab + FOLFOX-6 group versus 96% in the bevacizumab + FOLFOX-6 group.

9.2.1.3 PSUR data

The analysis of the last periodic pharmacovigilance report provided by the company (PSUR covering the period from 01/10/2011 to 30/09/2012) did not reveal any new pharmacovigilance signal for this proprietary medicinal product.

9.2.1.4 RMP data

Within the scope of the European Risk Management plan (updated on 26 April 2013), a newsletter was distributed to healthcare professionals in August 2013 so as to notify them of the importance of determining the RAS status of the colorectal tumour before initiating treatment with VECTIBIX.

09.3 Usage data

It should be noted that a monitoring study on management of skin toxicities occurring during treatment with VECTIBIX was implemented in October 2010 (POPEC monitoring study). The results, initially expected at the end of 2013, were not provided by the laboratory (study report expected in June 2014).

09.4 Summary & discussion

Monitoring of the development of new biomarkers imposed by the EMA under the conditional marketing authorization for VECTIBIX, led to the performance of a *post hoc* analysis of the PRIME study assessing panitumumab as the first-line treatment based on the RAS and BRAF subgroups.

The primary analysis of this study which was performed based on the KRAS status (mutations in exon 2) for 1096 of the 1183 randomized patients, showed that the addition of panitumumab to FOLFOX-4 alone was associated with a modest gain of 1.6 months for median progression-free survival (primary endpoint, 9.6 months versus 8 months, HR = 0.80 [0.66; 0.97]; p = 0.02) with no impact on the overall survival (23.9 months versus 19.7 months, HR = 0.83; [0.67-1.02]; NS) in the subgroup of 656 patients with a wild-type KRAS gene. In this subgroup of patients an increase in treatment discontinuations due to adverse effects (24% versus 14%) and events graded ≥ 3 (89% versus 76%) was also observed.

During the *post hoc* retrospective analysis, the RAS gene (exons 2, 3 and 4 of the KRAS and NRAS genes) mutation status was determined in the subgroup of 656 patients with muted-type KRAS status in exon 2. New mutations were identified in 108 of the 641 patients for whom the RAS gene status could be determined: 51 in the panitumumab + FOLFOX-4 group and 57 in the FOLFOX-4 group.
In the subgroup of 512 patients with wild-type RAS, the addition of panitumumab to FOLFOX-4 alone was associated with:
- an absolute gain of 2.2 months in median progression-free survival in favour of the panitumumab + FOLFOX-4 combination (10.1 months versus 7.9 months, HR = 0.72; [0.58-0.90]; p = 0.004);

- an extension in median progression-free survival (26 months versus 20.2 months, HR = 0.78; [0.62-0.99]; p = 0.043);
- an increase in treatment discontinuations due to adverse effects (26% versus 16%) and events graded ≥ 3 (89% versus 70%).

In the subgroup of 548 with mutant RAS genes, the addition of panitumumab to FOLFOX-4 alone was associated with a decrease in progression-free survival (7.3 months versus 8.7 months, HR = 1.31; [1.07-1.60]; p = 0.008) and an increase in treatment discontinuations due to adverse effects (23% versus 15%) and events graded ≥ 3 (81% versus 73%). The safety profile of patients with mutant RAS genes was comparable with that of patients with a mutation in exon 2 of the KRAS gene.

Despite the low level of evidence of this analysis, the results favour the hypothesis that was put forward following the retrospective analysis of study 20020408 (monotherapy) which states that mutations in exons 2, 3 or 4 of the NRAS and KRAS genes are negative predictive biomarkers of response to VECTIBIX treatment. The analysis also suggests that although the BRAF mutation status is a prognostic factor (regardless of treatment), the BRAF mutation status is not a predictive factor of response to treatment with panitumumab. The results of the retrospective analysis of the phase II study, PEAK, also support these conclusions.

In the absence of demonstrated superiority and due to the safety profile in the subgroup of patients with metastatic colorectal cancer with at least one RAS gene mutation, the Marketing Authorisation indication was limited to tumours with wild-type RAS genes.

In addition, the inclusion of panitumumab to chemotherapy including oxaliplatin for tumours with the RAS gene mutations (or whose RAS gene status is not determined) is contraindicated due to the reduced efficacy and increased toxicity.

In summary, in the subgroup of patients with wild-type RAS metastatic colorectal cancer, the level of effect for panitumumab as a first-line treatment, in combination with FOLFOX-4, compared with chemotherapy alone is modest.

In light of the current data, the role of panitumumab compared with the other two biotherapies indicated in mCRC (cetuximab and bevacizumab) is still poorly evaluated.

09.5 Planned studies

20080763 - ASPECCT study:

The final results of the comparative phase III study versus ERBITUX in patients with wild-type KRAS metastatic colorectal cancer in whom prior therapy has failed are pending.

NCT00655499 - PIMABI study:

This is a phase II study, carried out by the cooperative group GERCOR evaluating the efficacy and safety of the panitumumab and irinotecan combination in pretreated patients with wild-type KRAS exon 2 status.

Studies 20101120 and 20101121:

These European surveys including France are currently being carried out within the scope of the RMP so as to assess the use (20101120) and understanding (20101121) of the KRAS test by doctors.

010 THERAPEUTIC USE

Three biotherapies are currently indicated in the first-line treatment or beyond of mCRC: VECTIBIX (panitumumab) and ERBITUX (cetuximab) in patients with tumours with a wild-type RAS status (exons 2, 3 and 4 of KRAS and 2, 3 and 4 of NRAS) and AVASTIN (bevacizumab) regardless of the RAS gene mutation status.
According to current recommendations8[,17], the optimal therapeutic strategy as a first-line treatment or beyond is not established. Determination of the RAS gene status of the tumour (and optionally the BRAF gene status) is useful in selecting the therapeutic strategy.

According to available data, VECTIBIX should not be used in combination with:
- a regimen other than FOLFOX in first-line treatment and other than FOLFIRI in second-line treatment in patients with mCRC with RAS wild-type status;
- chemotherapy in patients treated in the first-line with anti-EGFR antibodies (absence of data in the PEETERS study);
- polychemotherapy including oxaliplatin in patients with mCRC with a RAS muted-type status or for whom the RAS mutation status is unknown;
- chemotherapy including AVASTIN, as the risk/benefit ratio is unfavourable, regardless of the RAS gene mutation status.

The exact therapeutic use of VECTIBIX is difficult to establish, particularly while waiting:
- for the final results of studies comparing VECTIBIX with another monoclonal antibody, in particular ERBITUX, in combination with chemotherapy;
- for studies evaluating VECTIBIX in second-line treatment after failure with another biotherapy.

In the treatment of wild-type RAS metastatic colorectal cancer, VECTIBIX represents an alternative to ERBITUX when patients are eligible for:
- first-line FOLFOX chemotherapy or
- a second-line FOLFIRI regimen and on the condition of having received chemotherapy as a first-line treatment that included fluoropyrimidine, but neither irinotecan nor an anti-EGFR antibody.

[17] Schmoll HJ, van Cutsem E, Stein A et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Annals of Oncology 2012; 23: 2479-2516.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

- Metastatic colorectal cancer is a serious and life-threatening disease.
- VECTIBIX is intended as curative therapy specifically for metastatic colorectal cancer.
- The efficacy/adverse effects ratio is modest.
- Alternative medicinal products exist.
- It is a first-line therapy or beyond.

- Public health benefit: Colorectal cancer is a serious and common clinical situation which is a major public health burden. The burden of metastatic colorectal cancer is substantial. The burden represented by the population of patients likely to benefit from this proprietary medicinal product (presenting with wild-type RAS genes) can also considered as substantial.
  Improved treatment of this disease is a public health need which is an established priority (Cancer Plan 2014-2019).
  In view of the available data (*post hoc* analysis of clinical studies showing an improvement in progression-free survival versus chemotherapy alone, which is only modest), this proprietary medicinal product is not expected to have an impact on morbidity or mortality and quality of life in this population.
  Therefore, it would not be expected that the proprietary medicinal product VECTIBIX would provide any additional response to the identified public health need.
  Consequently, in the current state of knowledge, it is not expected that VECTIBIX will have an impact on public health in this new indication.

Taking account of these points, the Committee considers that the actual benefit of VECTIBIX is substantial in the Marketing Authorisation indications.

The Committee recommends continued inclusion on the list of medicines approved for hospital use in the indications and at the dosage in the Marketing Authorisation.

- **Proposed reimbursement rate: 100%**

011.2 Improvement in actual benefit (IAB)

The modification of indication for VECTIBIX, restricting its use to patients with wild-type RAS (KRAS and NRAS) metastatic colorectal cancer within the scope of a stratified strategy, does not change the Transparency Committee's previous assessments in the absence of comparative data versus the other biotherapies indicated in these patients in the various lines of treatment.

Consequently, and given the current state of the data, VECTIBIX does not provide any improvement in actual benefit (level V, non-existent) in the treatment of wild-type RAS metastatic colorectal cancer:

- **in first-line therapy in combination with FOLFOX**
- **in second-line therapy in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan)**
- **in monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.**

011.3 Target population

The target population of VECTIBIX is represented by patients with wild-type RAS metastatic colorectal cancer:

- not previously treated and eligible for FOLFOX chemotherapy or
- previously treated with chemotherapy:
    - o in second-line after failure of a fluoropyrimidine-based regimen which did not contain irinotecan or anti-EGFR antibodies.
    - o in monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens.

In 2012, the incidence of colorectal cancer was 42,152 new cases of cancer per year in France.[18]
The metastatic stages are observed in about 20 to 25% of cases on diagnosis of the disease and in total almost 50% of patients will have metastases5 (i.e. 21,076 patients).
Among the patients with metastatic colorectal cancer, it is thought that 64.5% will have chemotherapy (i.e. 13,595 patients), according to a National Health Insurance study[19] using data from 4273 incident cases of metastatic colorectal cancer diagnosed between April and September 2009 in France.

The incidence of RAS gene mutations is estimated to be around 50%-60%5[,20,21].

The target population of VECTIBIX in first-line treatment can be estimated to be a maximum of 5438-6798 patients.
According to experts, approximately 80% of patients treated in first-line relapse and go on to receive second-line treatment. The target population can be estimated as between 4350 and 5438 patients in second-line treatment.
It is not possible to estimate the number of patients receiving a third-line chemotherapy, after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.

The Committee notes that the calculation results in a maximum estimation being given, as the following populations should not be counted:

- patients who are not eligible for first-line FOLFOX chemotherapy or second-line FOLFIRI chemotherapy;
- in the second-line: the proportion of patients treated in the first-line with irinotecan or with a chemotherapy regimen containing an anti-EGFR antibody, in the absence of efficacy data for VECTIBIX in these circumstances.

These proportions of patients are difficult to quantify.

In summary, the target population for VECTIBIX can be estimated to be a maximum of 6800 patients in first-line and 5450 patients in second-line per year.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.

[18] National estimate of the incidence and mortality of cancer in France from 1980 to 2012. Study from the Francim network of cancer registers, July 2013 - Health Monitoring Institute
[19] Study directed by Prof. Guillemot and Prof. Mitry using data from the National Salaried Workers' Health Insurance Fund (CNAMTS) with its support in the context of the RISE (Research Innovation Health Environment) research federation, INSERM unit U657, at the University of Versailles-St-Quentin.
[20] Douillard JY, Oliner KS et al. Panitumumab–FOLFOX4 Treatment and RAS Mutations in Colorectal Cancer. N Engl J Med 2013; 369: 1023-34.
[21] Study 200204108