Title	Prospective Observational Cohort Study to Describe the Use of Vectibix® in Combination With Chemotherapy in Routine Clinical Practice for Patients With Wild-type *RAS* Metastatic Colorectal Cancer
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Active Substance	Panitumumab; ATC code: L01XC08
Medicinal Product	Vectibix® (Panitumumab)
Product Reference	EMEA/H/C/000741
Marketing Authorization Holder	Amgen Europe B.V. Minervum 7061 NL-4817 ZK Breda The Netherlands
Research Question and Objectives	*Primary objective:* • To describe the pattern of use of panitumumab in combination with chemotherapy in patients with wild-type (*KRAS/*)*RAS* metastatic colorectal cancer (mCRC): as first-line treatment in combination with FOLFOX or FOLFIRI or second-line treatment in combination with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). *Secondary objectives:* • To describe key healthcare resource utilization indicators attributed to treatment and clinical management of mCRC; • to describe key clinical indicators (demographics, disease characteristics, individual treatment goals, co-morbidities and prior treatment history); • to describe the response to panitumumab in routine clinical practice (including best response and conversion to resectability if available and by individual treatment goals if applicable); • to provide an overview of planned anti-cancer treatments initiated post panitumumab discontinuation.
Countries of Study	Germany, France

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1. ABSTRACT

- **Title**

Prospective Observational Cohort Study to Describe the Use of Vectibix® in Combination With Chemotherapy in Routine Clinical Practice for Patients With Wild-type *RAS* Metastatic Colorectal Cancer

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- **Keywords**

Panitumumab, metastatic colorectal cancer, *RAS* wild-type, *KRAS* wild-type, observational study

- **Rationale and Background**

The collected data was intended to anticipate expected reimbursement agency requirements in Germany and France. The requirements focused on gaining a clear understanding of the real-life use of panitumumab in accordance with the label. The objectives of this study were defined to meet such requirements. This study was therefore conducted to gain an understanding of panitumumab use for the treatment of patients with wild-type rat sarcoma viral oncogene homolog (*RAS*) metastatic colorectal cancer (mCRC), in first-line in combination with FOLFOX or FOLFIRI or second-line in combination with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

- **Research Question and Objectives**

Primary objective:

To describe the pattern of use of panitumumab in combination with chemotherapy in patients with wild-type (*KRAS*/)*RAS* mCRC: as first-line treatment in combination with FOLFOX or FOLFIRI or second-line treatment in combination with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

Secondary objectives:

To describe key healthcare resource utilization indicators attributed to treatment and clinical management of mCRC, describe key clinical indicators (demographics, disease characteristics, individual treatment goals, co-morbidities and prior treatment history), describe the response to panitumumab in routine clinical practice (including best response and conversion to resectability if available and by individual treatment goals if applicable), and to provide an overview of planned anti-cancer treatments initiated post panitumumab discontinuation.

- **Study Design**

This was a multicentre, observational, non-interventional prospective cohort study in France and Germany.

- **Setting**

The study was conducted in France and Germany between 10 December 2012 and 30 November 2016. Sites were selected to include a variety of hospital types,

including large specialist referral centres as well as smaller general hospitals. Each country was required to include a representative sample of different types of hospitals (academic, specialist, general hospitals, private practices, etc). In Germany the outpatient oncology clinic setting was also represented. The database was locked on 11 April 2017.

- **Patients and Study Size, Including Dropouts**

Patients or patients' legally acceptable representatives must have provided informed consent (for countries where required per local regulations).

Eligible patients were ≥18 years of age at date of enrolment, had histologically or cytologically confirmed metastatic carcinoma of colon or rectum and confirmed wild-type (*KRAS*/)*RAS* status of tumour. Tumour assessment (i.e., CT/MRI) must have been conducted within 12 weeks (84 days) prior to the first panitumumab infusion. Patients must have received at least one infusion of panitumumab in combination with chemotherapy a maximum of 84 days before entering study: first-line in combination with FOLFOX or FOLFIRI or second-line in combination with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) for treatment of wild-type (*KRAS*/)*RAS* mCRC per approved prescribing information.

Initially wild-type *KRAS* (exon 2) patients were recruited. Following a panitumumab label change, wild-type *RAS* (exons 2,3,4 of *KRAS* and *NRAS*) patients were recruited after the subsequent protocol amendment (23-Sep-2013). Moreover, patients receiving panitumumab first-line in combination with FOLFIRI were enroled following an extension of the panitumumab license and subsequent protocol amendment (9-Apr-2015).

Patients with an ongoing or planned concurrent participation in any clinical study involving an investigational product that has not been approved by the European Medicines Agency for any indication or with an ongoing or planned concurrent participation in any clinical study where the dosing of panitumumab was determined by the protocol were excluded (participation in clinical trials on an approved drug and observational trials are permitted but these could not mandate how mCRC should be treated).

A total of 273 patients was screened; 213 received panitumumab (22 from France, 191 from Germany; primary analysis set). 29 patients (12.0%) did not get treatment allocation, 2 (0.7%) were ineligible due to key data missing, and 29 (10.6%) patients did not meet eligibility criteria (screening failures, percentage based on screened patients). 98 patients (46.0%) completed the study and 115 (54.0%) discontinued.

- **Variables and Data Sources**

At baseline, site characteristics, patient characteristics and demographics, medical history and treatment specifications were collected. During the observation period, panitumumab treatment patterns, concomitant anticancer therapies, tumour response and tumour status, healthcare resource utilization (HRU), and panitumumab safety data were collected. At end of study, the date and reason for ending study, planned further treatments, and panitumumab safety data were documented. Source data included but were not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

- **Results**

This study collected data of 213 patients from France (n=22) and Germany (n=191) receiving panitumumab as first-line treatment in combination with FOLFOX (77.0%

[n=164]) or as first- or second-line treatment in combination with FOLFIRI (5.6% [n=12] and 17.4% [n=37], respectively). The study mainly aimed at understanding panitumumab treatment patterns, healthcare resource utilization, and response to panitumumab treatment in these patients, as well as documenting safety findings. All respectively tested patients had *KRAS* or *RAS* wild type tumour status. *BRAF* results were available for a minority of patients only (n=34), and 8.8% of samples had *BRAF* mutant status.

The median of time between initial primary CRC diagnosis and diagnosis of metastatic disease was 0.0 for first line FOLFOX plus panitumumab treatment (FLFAS), 0.5 months for second line FOLFIRI plus panitumumab treatment (SLFAS), and 6.7 months in the subject group receiving first line panitumumab in combination with FOLFIRI (FLFFAS). After metastatic disease diagnosis the first dose of panitumumab was administered in the median after 1.6 months for FLFAS and 2.3 months for FLFFAS.

As per approved indication, the recommended dose of panitumumab is 6 mg per kilogram body weight given once every two weeks. In the present study, patients received a median number of 10 infusions when panitumumab was combined with FOLFOX in the first-line setting, 8 and 10 infusions when combined with FOLFIRI in the first- and second-line setting, respectively. The median duration of panitumumab exposure was 5 months for FLFAS, 6 months for SLFAS, and 5 months for FLFFAS, resulting in a median cumulative dose of 4262.5 mg in FLFAS patients, 4000.0 mg in SLFAS patients, and 3782.5 mg FLFFAS patients. The preferred administration interval was >14 to 21 days in the FLFAS and SLFAS groups and >21 to 28 days in the FLFFAS group. Note: FLFFAS is based on 12 patients only.

The unadjusted overall response rate of complete or partial response was 47.6% in FLFAS patients, 33.3% in SLFAS patients, and 50.0% in FLFFAS patients; resectability was achieved in 12.2% of FLFAS, 8.1% of SLFAS, and 8.3% of FLFFAS patients. Adverse drug reactions were reported for 73.2% of FLFAS patients, 67.6% of SLFAS patients, and 66.7% of FLFFAS patients; 6.1% of FLFAS patients and no SLFAS or FLFFAS patients experienced serious adverse events and no patients experienced fatal adverse events. Rash was the most frequently reported adverse drug reaction, mostly of grade 2. Hospitalizations were reported for 99.4% FLFAS patients and all SLFAS and FLFFAS patients, with 96.3%, 94.6%, and 100.0%, respectively, reporting outpatient visits and 46.0%, 32.4%, and 50.0%, respectively, reporting inpatient visits. The median duration of hospital stays was 40.0 days for FLFAS, 28.0 days for SLFAS, and 24.5 days for FLFFAS.

- **Discussion**

Overall, the study results of this observational study show that clinical efficacy in the routine practice setting was comparable to randomised controlled studies. Hospitalizations were reported for almost all patients participating in the study, about one-third to half of patients required inpatient care. The safety findings reported do not alter the known safety profile of panitumumab and no new safety signal emerged.

- **Marketing Authorization Holder**

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