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ORIGINAL RESEARCH

Prospective Observational Cohort Study to Describe the Use of Panitumumab in Combination with Chemotherapy in Real-World Clinical Practice for Patients with Wild-Type *RAS* mCRC

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ABSTRACT

Introduction: This study aimed to better understand panitumumab use in real-life clinical practice in first- and second-line treatment of metastatic colorectal cancer in five European countries.

Methods: This is a combined analysis of two observational, non-interventional prospective cohort studies, one of which was conducted in Germany and France, the other in Bulgaria, Czech Republic, and Hungary. The studies observed patients with wild-type [Kirsten] rat sarcoma viral oncogene homolog (*[K]RAS/RAS*) metastatic colorectal cancer (mCRC), who had been treated with panitumumab in combination with fluorouracil, leucovorin, and oxaliplatin (FOLFOX) in the first line or with panitumumab combined with fluorouracil, leucovorin, and irinotecan (FOLFIRI) in the second line following fluoropyrimidine-based chemotherapy. The planned duration of observation was 12 months from the first dose of panitumumab.

Results: A total of 332 patients treated with panitumumab + FOLFOX in the first line and 94 patients treated with panitumumab + FOLFIRI in the second line were analyzed. The median number of panitumumab

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infusions was 10.0 in first-line FOLFOX patients and 11.5 in second-line FOLFIRI patients; the median duration of panitumumab exposure was 5.7 and 6.9 months, respectively. The unadjusted overall response rate (complete or partial response) in patients with available post-baseline response assessment (n = 290) was 51.7% in first-line FOLFOX and 44.9% in second-line FOLFIRI patients. In the first-line setting, resectability was achieved in 9.3%. Reported hospitalizations were mostly cancer-related visits such as scheduled anticancer treatment administrations, tumor assessment visits, or interventions. The majority of adverse drug reactions were skin disorders, with 75.3% in first-line FOLFOX patients and 72.3% in second-line FOLFIRI patients.

Conclusion: Overall, the study results show that treatment patterns, clinical efficacy, and the safety profile of panitumumab in routine clinical practice were comparable to those in randomized controlled trials. The relatively low skin toxicity rate could be attributed to increasing experience in managing panitumumab-associated rash and some degree of underreporting.

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Keywords: Metastatic colorectal cancer; Observational study; Panitumumab; *RAS* wild-type; Real-world data; Tumor location

INTRODUCTION

According to the GLOBOCAN 2012 cancer statistics survey by the World Health Organization, colorectal cancer (CRC) is the third most common malignant tumor in men and the second in women, with 1.4 million new cases worldwide. Accounting for almost 700,000 deaths worldwide in 2012, it is the fourth leading cause of cancer deaths [1]. With some rare exceptions, the incidence of CRC is rising overall, notably more steeply in men than in women [1]. The 5-year survival rate in patients with metastatic disease varies by region [1], and is very low at approximately 8% [2, 3].

Systemic treatment for metastatic CRC (mCRC) is generally based on combinations of chemotherapy including 5-fluorouracil, oxaliplatin, and/or irinotecan and targeted agents [4]. Panitumumab, a fully human monoclonal antibody that binds specifically to epidermal growth factor receptor (EGFR) [5–7], was initially approved in the European Union in 2007 for metastatic carcinoma of the colon or rectum after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens [8]. Trials were initially conducted in patients with wild-type or mutant Kirsten rat sarcoma viral oncogene homolog (*KRAS*) tumors. A retrospective analysis from the first phase 3 trial analyzed by *KRAS* status showed the importance of the *KRAS* testing [9, 10]. The phase 3 PRIME (Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy) study investigated panitumumab combined with fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as initial treatment for mCRC. In the wild-type *KRAS* stratum, a longer median progression-free survival (PFS) was found in patients receiving panitumumab–FOLFOX4 compared with FOLFOX4 alone (9.6 versus 8.0 months, respectively; hazard ratio [HR] 0.80; 95% CI 0.66–0.97; P = 0.02) [11]. A phase 3 study investigating panitumumab combined with fluorouracil, leucovorin, and irinotecan (FOLFIRI) versus FOLFIRI alone in the second line showed that in the wild-type *KRAS* subpopulation a significant improvement in PFS was observed in the panitumumab–FOLFIRI group versus FOLFIRI alone (5.9 versus 3.9 months, respectively, HR 0.73; 95% CI 0.59–0.90; P = 0.004) [12]. In addition, three phase 2 studies supported the efficacy data for the use of panitumumab in combination with irinotecan-based chemotherapy as initial or second-line treatment for mCRC patients [13–15]. Results of the phase 2 studies for PFS, overall survival (OS), and objective response were generally consistent with the phase 3

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studies. Additional activating mutations in *RAS* beyond *KRAS* exon 2 were predictive for outcomes with panitumumab treatment in the first-line setting in combination with FOLFOX [16, 17]. On the basis of these additional findings, the panitumumab indication for the treatment of adult patients with mCRC was changed from wild-type *KRAS* to wild-type *RAS* and extended to include first-line treatment in combination with FOLFIRI for patients with mCRC [18]. Routine clinical practice commonly involves an unselected patient population. Results and treatment practices may differ from the narrowly guided treatment schedules followed in the randomized clinical trials leading to initial approval of panitumumab and subsequent label changes. Real-life data on panitumumab use, especially from Europe with its diverse health care systems, are scarce.

The present report is a combined analysis of two studies that were conducted in two Western European and three Central and Eastern European countries to gain real-world evidence of panitumumab use in routine clinical practice for the treatment of mCRC patients with wild-type *KRAS* or *RAS* status within the approved indication in Europe at the time of study, which bridged both changes in indication described above [7].

METHODS

This observational study was not registered as this was not required in any of the participating countries.

Patient Eligibility Criteria

Eligible patients were at least 18 years old at the date of enrollment, had histologically or cytologically confirmed metastatic colon or rectum cancer and confirmed wild-type *KRAS* or *RAS* status, depending on the approved indication at the time of enrollment. Tumor assessment [i.e., computed tomography (CT) or magnetic resonance imaging (MRI)] must have been conducted within 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 the study. Patients with concurrent participation in any clinical study involving a non-approved investigational product or where the dosing of panitumumab was determined by the protocol were excluded.

Study Design

This is a combined analysis of two multicenter, observational, non-interventional, prospective cohort studies conducted in Germany and France (study number, 20120100; study period, 2012–2016) and Bulgaria, Czech Republic, and Hungary (study number, 20120271; study period, 2013–2016). The studies were similarly designed in order to enable a prespecified combined analysis. The planned duration of observation was 12 months following the first dose of panitumumab.

Study Objectives

The studies were conducted to anticipate expected reimbursement agency requirements in the participating countries. The primary objective was 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 (1L FOLFOX) or second-line treatment in combination with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan; 2L FOLFIRI). Secondary objectives were to describe demographics, disease characteristics, individual treatment goals, co-morbidities and prior treatment history, treatment response in routine clinical practice, hospitalizations, and safety. Adverse drug reactions were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.0. Information on tumor-sidedness was also collected. When these studies were carried out, the generally accepted definition by the oncologists for right-sided tumors was primary tumors originating in the appendix, cecum, ascending colon, hepatic flexure, and transverse colon;

left-sided tumors were primary tumors originating in the splenic flexure, descending colon, and sigmoid colon. Rectum cancers were counted separately, but combined with left-sided colon cancer to accommodate recent methodology reported in the literature [19].

Ethics Compliance

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Where required per local regulations, the study protocols were approved by independent ethics committees. Informed consent was obtained from all individual participants or their legally acceptable representatives.

Statistical Analysis

The combined analysis of these studies was descriptive in nature. For continuous variables, the mean, standard deviation, median, interquartile range (IQR), and range were provided. If not denoted otherwise, descriptive results are expressed as median (IQR). For categorical variables, the frequency and percentage, with two-sided 95% confidence interval (CI; calculated using Wilson's method), were displayed. The data were summarized for the two analysis sets 1L FOLFOX and 2L FOLFIRI as described above. Centers within each country were pooled and the data was summarized by country to fulfil local post reimbursement requirements.

RESULTS

Patient Disposition

A total of 509 patients was screened for both studies. Of these, 31 were ineligible, 29 (5.7% of screened patients) because of screening failures, 2 (0.4%) because of missing data. Of 478 eligible patients, 40 patients (8.4%) did not start panitumumab treatment. An additional 12 patients (2.5%) from study 20120100 received panitumumab first-line in combination with FOLFIRI; these were excluded from this combined analysis, because the respective treatment combination was not part of study 20120271. Patient and disease characteristics as well as results for this group are shown in Table S3 of the online supplemental material. Of eligible patients, 426 (89.1%) were analyzed (full analysis set, FAS), 332 patients (69.5%) received panitumumab first-line treatment in combination with FOLFOX and 94 patients (19.7%) second-line treatment in combination with FOLFIRI (Table 1). Overall, study 20120100 contributed 201 patients (47.2%), with 179 from Germany and 22 from France. Study 20120271 contributed 225 patients (52.8%), with 123 from Czech Republic, 78 from Hungary, and 24 from Bulgaria.

Patient Demographics and Disease Characteristics

The majority of patients (64.3%, $n = 274$) were male. The median age was 64.0 years (58.0, 70.0). Slightly over half of patients (54.7%, $n = 233$) were less than 65 years old. The proportion of patients aged 75 years or older was 9.4% ($n = 40$; Table 2). The median age and number of patients aged 75 years or older was lower in the 20120271 study compared to the 20120100 study (Supplemental Table S1).

Tumor location was assessed in all patients. Of those patients with known treatment location, left-sided colon cancer (including rectal cancer) was detected in 73.0% ($n = 311$) and right-sided colon was diagnosed in 20.0% ($n = 85$). There were 30 patients with unspecified location of colon cancer (Table 3). The vast majority had synchronous metastases. Liver metastases were present in 73.7% of patients ($n = 314$) and 26.1% of patients had more than five metastatic hepatic lesions. For patients with lung metastases or other metastatic sites, the number of lesions was not recorded. Overall, 14.8% of 1L FOLFOX patients ($n = 49$) and 8.5% of 2L FOFIRI patients ($n = 8$) received prior radiotherapy; 28.3% ($n = 94$) of 1L FOLFOX and

Table 1 Patient disposition, *n* (%)

	1L FOLFOX (*N* = 332)	2L FOLFIRI (*N* = 94)
Completed study[a,b]	63 (19.0)	15 (16.0)
Discontinued study	266 (80.1)	77 (81.9)
Reasons for study discontinuation		
Discontinuation of panitumumab	219 (66.0)	63 (67.0)
Death	15 (4.5)	4 (4.3)
Loss to follow-up	12 (3.6)	3 (3.2)
Administrative decision	8 (2.4)	2 (2.1)
Consent withdrawal	3 (0.9)	0 (0)
Other	9 (2.7)	5 (5.3)
Reasons for discontinuation of panitumumab		
Disease progression	99 (29.8)	36 (38.3)
Physician decision	31 (9.3)	10 (10.6)
Planned surgical resection	30 (9.0)	1 (1.1)
Adverse drug reaction	19 (5.7)	6 (6.4)
Patient request to end all treatment	16 (4.8)	3 (3.2)
Adverse event	10 (3.0)	2 (2.1)
Patient request to end panitumumab	7 (2.1)	3 (3.2)
Death	1 (0.3)	0 (0)
Other	6 (1.8)	2 (2.1)

1L first-line, *2L* second-line, *FOLFOX* folinic acid, fluorouracil, oxaliplatin, *FOLFIRI* folinic acid, fluorouracil, irinotecan

[a] 12 months of observation

[b] 5 patients in the 20120271 study (3 1L FOLFOX, 2 2L FOLFIRI) have missing data for "end of panitumumab" and "end of study". The duration of exposure to panitumumab is less than 12 months for all 5 patients as per last non-zero visit date of panitumumab, if the last dose date is missing

all 2L FOLFIRI patients received prior anticancer therapies. Co-morbidities not related to the primary tumor are shown in the Supplementary Table S2.

RAS/Rapidly Accelerated Fibrosarcoma (BRAF) Biomarker Status

As per inclusion criteria, all patients were confirmed as either wild-type *KRAS* or *RAS*, depending on the approved indication at the time of enrollment. Wild-type *RAS* status (all exons) was confirmed in 96.0% of patients ($n = 409$). The remaining patients (11 1L FOLFOX and 6 2L FOLFIRI patients) had confirmed wild-type *KRAS* status. *BRAF* status was determined in 58 patients (13.6%) and was found to be mutant in 7 patients (12.1% of tested). For *RAS* testing, polymerase chain reaction (PCR) was used in 57.5% of patients ($n = 245$) followed by Sanger sequencing (20.4%; $n = 87$). For *KRAS* testing, PCR was used in 58.7% of patients ($n = 250$) followed by Sanger sequencing (21.8%; $n = 93$). *BRAF* status was determined using PCR in 3.3% of patients ($n = 14$; i.e., 24.1% of tested) or by Sanger sequencing in

Table 2 Patient demographics, *n* (%)

	All patients (*N* = 426)
Male gender	274 (64.3)
Age	
Mean (SD)	63.0 (9.7)
Median (IQR)	64.0 (58.0, 70.0)
Age group	
< 65 years	233 (54.7)
≥ 65 to < 75 years	153 (35.9)
≥ 75 years	40 (9.4)
ECOG performance score	
0	177 (41.5)
1	121 (28.4)
2	11 (2.6)
Missing	117 (27.5)

ECOG Eastern Cooperative Oncology Group

Table 3 Disease characteristics, *n* (%)

	All patients (*N* = 426)
Primary cancer location[a]	
Colon, not specified	30 (7.0)
Colon, left-sided	135 (31.7)
Colon, right-sided	85 (20.0)
Rectum[b]	176 (41.3)
Metastatic colorectal cancer status	
Metachronous	120 (28.2)
Missing	11 (2.6)
Synchronous	293 (68.8)
Unknown	2 (0.5)
Metastatic disease lesion sites	
Liver	314 (73.7)
Lung	94 (22.1)
Other	143 (33.6)
Number of lesions in liver[c]	
1–2	100 (23.5)
3–5	46 (10.8)
> 5	111 (26.1)
Number unknown	112 (26.3)
Data missing	57 (13.4)

[a] The study collected tumor location as colon or rectum. When this study was carried out, the generally accepted definition by the oncologist for right-sided tumors was primary tumors originating in the appendix, cecum, ascending colon, hepatic flexure, and transverse colon; left-sided tumors were primary tumors originating in the splenic flexure, descending colon, and sigmoid colon. Rectum cancers were collected separately

[b] In clinical trials, rectum cancer is commonly added to left-sided tumors

[c] The data field for the number of lesions was mostly empty for other sites, i.e., data entry missing

1.5% (*n* = 5, i.e., 8.6% of tested). Other methodologies to determine biomarker status used less frequently were pyrosequencing, next-generation sequencing, or a surveyor wave-based system (transgenomics).

Panitumumab Exposure

Per inclusion criteria, all patients received panitumumab. The median time between diagnosis of metastatic disease and initiation of panitumumab was 1.9 months (1.3, 2.9) in the first-line setting. The median number of panitumumab infusions was 10.0 (6.0, 17.0) in the 1L FOLFOX and 11.5 (6.0, 17.0) in the 2L FOLFIRI group. The median duration of exposure to panitumumab was 5.7 months (2.79, 9.96) in 1L FOLFOX patients and 6.9 months (2.46, 9.17) in the 2L FOLFIRI group. The median cumulative doses were 4472 mg (2475.0, 7087.5) in 1L FOLFOX and 4384 mg (2400.0, 7200.0) in 2L FOLFIRI patients. For number of infusions, duration of exposure and cumulative dose, the censored regression mean, i.e. the value that would have been observed had patients been followed for longer than the 12 months observation period, is shown in Table S4. The most frequent panitumumab administration interval was > 14–21 days (Table 4). Panitumumab was discontinued before the end of the planned

Table 4 Panitumumab exposure and dose changes

	1L FOLFOX (*N* = 332)	2L FOLFIRI (*N* = 94)
Total number of infusions		
Mean (SD)	11.9 (7.0)	11.9 (6.8)
Median (IQR)	10.0 (6.0, 17.0)	11.5 (6.0, 17.0)
Cumulative dose (mg)		
Mean (SD)	5221.2 (3660.7)	5245.7 (3345.6)
Median (IQR)	4472.0 (2475.0, 7087.5)	4384.0 (2400.0, 7200.0)
Duration of exposure (months)[a]		
Mean (SD)	6.3 (4.0)	6.5 (4.1)
Median (IQR)	5.7 (2.8, 10.0)	6.9 (2.5, 9.2)
Mean interval between infusions (days)		
Mean (SD)	17.7 (4.4)	17.9 (3.5)
Median (IQR)	16.5 (14.7, 19.0)	17.0 (15.0, 19.9)
Mean interval between infusions (days), *n* (%)		
> 0–7	0 (0.0)	0 (0.0)
> 7–14	57 (17.2)	12 (12.8)
> 14–21	224 (67.5)	64 (68.1)
> 21–28	40 (12.0)	16 (17.0)
> 28	9 (2.7)	1 (1.1)
Number of patients with at least one panitumumab dose reduction (95% CI)	101 (30.4) (25.7, 35.6)	26 (27.7) (19.6, 37.4)
Reasons for dose reduction		
Adverse event	79 (23.8)	23 (24.5)
Dose administration error	12 (3.6)	3 (3.2)
Noncompliance	3 (0.9)	0 (0.0)
Other	16 (4.8)	4 (4.3)
Number of patients with at least one panitumumab dose delay (95% CI)	206 (62) (56.7, 67.1)	54 (57.4) (47.4, 67.0)
Reasons for dose delay		
Adverse event	70 (21.1)	22 (23.4)
Dose administration error	5 (1.5)	2 (2.1)
Noncompliance	23 (6.9)	8 (8.5)
Other	156 (47)	40 (42.6)
Surgical resection	6 (1.8)	0 (0.0)

Table 4 continued

	1L FOLFOX (N = 332)	2L FOLFIRI (N = 94)
Number of patients with at least one panitumumab dose increase (95% CI)	31 (9.3) (6.7, 12.9)	9 (9.6) (5.1, 17.2)
Reasons for dose increase		
Adverse event	4 (1.2)	0 (0.0)
Dose administration error	6 (1.8)	4 (4.3)
Noncompliance	3 (0.9)	1 (1.1)
Other	22 (6.6)	4 (4.3)
Number of patients with at least one panitumumab dose earlier than planned (95% CI)	1 (0.3) (0.1, 1.7)	1 (1.1) (0.2, 5.8)
Reasons for dose earlier than planned		
Other	1 (0.3)	1 (1.1)

1L first-line, *2L* second-line, *CI* confidence interval, *FOLFOX* folinic acid, fluorouracil, oxaliplatin, *FOLFIRI* folinic acid, fluorouracil, irinotecan, *IQR* interquartile range, *SD* standard deviation

[a] The duration of exposure is the time from the first to the last panitumumab infusion

12-months observation period, in 66.0% of 1L FOLFOX patients (n = 219) and 67.0% of 2L FOLFIRI patients (n = 63), mainly due to disease progression, physician decision, or planned surgical resection (Table 1). Fifty-three 1L FOLFOX patients (16.0%) and 10 2L FOLFIRI patients (10.6%) completed the study-related observation after 12 months of observation without a date of last panitumumab dose.

At least one panitumumab dose reduction was reported in 30.4% of 1L FOLFOX patients (n = 101) and 27.7% of 2L FOLFIRI patients (n = 26). Dose reductions were mainly due to adverse events in 23.8% of 1L FOLFOX patients (n = 79) and 24.5% of 2L FOLFIRI patients (n = 23). At least one panitumumab dose delay was reported for 62.0% of 1L FOLFOX patients (n = 206) and 57.4% of 2L FOLFIRI patients (n = 54). Reasons for dose delay were mainly reasons classified as "other" in 47.0% of 1L FOLFOX patients (n = 156) and 42.6% of 2L FOLFIRI patients (n = 40) and adverse events in 21.1% of 1L FOLFOX patients (n = 70) and 23.4% of 2L FOLFIRI patients (n = 22). At least one panitumumab dose increase was reported for 9.3% of 1L FOLFOX patients (n = 31) and 9.6% of 2L FOLFIRI patients (n = 9), mainly due to "other" reasons in 6.6% of 1L FOLFOX patients (n = 22) and 4.3% of 2L FOLFIRI patients (n = 4). Details are presented in Table 4.

Concomitant Therapies

Concomitant chemotherapy was administered to 99.7% of 1L FOLFOX patients (n = 331) and all 2L FOLFIRI patients. In one 1L FOLFOX patient information on concomitant chemotherapy was missing. Chemotherapy dose was reduced at least once in 43.4% of 1L FOLFOX patients (n = 144) and 40.4% of 2L FOLFIRI patients (n = 38), mainly due to adverse events in both groups, with 33.7% of 1L FOLFOX patients (n = 112) and 35.1% of 2L FOLFIRI patients (n = 33). At least one chemotherapy dose delay was reported for 56.3% of 1L FOLFOX patients (n = 187) and 57.4% of 2L FOLFIRI patients (n = 54), mainly for reasons classified as "other", with 35.2% of 1L FOLFOX patients (n = 117) and 40.4% of 2L FOLFIRI patients (n = 38) or due to adverse events, with 28.0% of 1L FOLFOX patients

(n = 93) and 26.6% of 2L FOLFIRI patients (n = 25).

Other concomitant procedures were performed in 7.2% of 1L FOLFOX patients (n = 24) and 6.4% of 2L FOLFIRI patients (n = 6). Overall, 53.3% of patients receiving such procedures (n = 16) received surgery, 23.3% (n = 7) received radiofrequency ablation, 6.7% (n = 2) received a biopsy, 6.7% (n = 2) underwent chemoembolization, and 33.3% (n = 10) underwent other procedures. The intent of such procedures was curative or palliative in equal proportions with 50.0% (n = 15) each.

Tumor Response

Tumor response to treatment was assessed by the treating physician with no predefined timepoints, mainly by CT scan (Table 5). Respective post-baseline response assessment data was available for 87.3% of 1L FOLFOX patients (n = 290) and 94.7% of 2L FOLFIRI patients (n = 89). The unadjusted objective response rate of complete or partial response was 51.7% (based on patients with available response assessment) in 1L FOLFOX patients (n = 150, 95% CI 46.0–57.5) and 44.9% in 2L

Table 5 Tumor response assessment, n (%)

	1L FOLFOX (N = 332)	**2L FOLFIRI (N = 94)**
Number of patients with tumor response data post-baseline	290 (87.3)	89 (94.7)
Best tumor response[a]		
Complete response	38 (13.1)	9 (10.1)
Disease progression	47 (16.2)	20 (22.5)
Partial response	112 (38.6)	31 (34.8)
Stable disease	88 (30.3)	29 (32.6)
Unknown	5 (1.7)	0 (0)
Number of patients with response of ORR (CR or PR)[a]	150 (51.7)	40 (44.9)
95% CI of response rate or ORR	46.0, 57.5	34.6, 55.3
Method of assessment[a]		
CT scan	191 (65.6)	67 (75.3)
MRI	24 (8.3)	5 (5.6)
Other	16 (5.5)	4 (4.5)
PET/CT	20 (6.9)	8 (9)
Physical examination	16 (5.5)	4 (4.5)
Spiral CT scan	72 (24.8)	17 (19.1)
Ultrasound	24 (8.3)	8 (9)
X-ray	14 (4.8)	9 (10.1)

1L first-line, *2L* second-line, *CT* computed tomography, *1L FOLFOX* first-line full analysis set, *PET* positron emission tomography, *FOLFOX* folinic acid, fluorouracil, oxaliplatin, *FOLFIRI* folinic acid, fluorouracil, irinotecan, *ORR* objective response rate, *PD* progressive disease, *PR* partial response, *SD* stable disease

[a] Percentages are based on the number of patients with tumor response data post-baseline. The subcategories for methods of tumor response assessment are not mutually exclusive. Patients are only included once within each subcategory

FOLFIRI patients (n = 40, 95% CI 34.6–55.3). A complete response was achieved in 13.1% of 1L FOLFOX patients (n = 38) and 10.1% of 2L FOLFIRI patients (n = 9). Partial responses were achieved in 38.6% of 1L FOLFOX patients (n = 112) and 34.8% of 2L FOLFIRI patients (n = 31; Table 5). In the 1L FOLFOX group, resectability was achieved in 9.3% (n = 31), not achieved in 42.5% (n = 141), and resectability status was unknown in 48.2% (n = 160).

Health Care Resource Utilization

Overall, 99.5% of patients (n = 424) had at least one outpatient or inpatient hospitalization. Most patients had mCRC-related visits such as scheduled anticancer treatment (chemotherapy or panitumumab administrations), tumor assessment visits, or other interventions. Emergency room visits were infrequent with 6.0% of patients from study 20120100 (n = 12) and 0.4% of patients from study 20120271 (n = 1). Adverse drug reactions that resulted in hospitalizations were reported for 8 patients with a total of 14 hospitalizations in study 20120100 (this information was not collected for study 20120271).

Safety

Adverse drug reactions were reported for 80.1% of 1L FOLFOX patients (n = 266) and 74.5% of 2L FOLFIRI patients (n = 70). The majority of adverse drug reactions were skin disorders (75.3% [n = 250] and 72.3% [n = 68]). In 0.2% of patients (n = 1) non-serious infusion-related reactions were reported. Serious adverse drug reactions were reported for 5.1% of 1L FOLFOX patients (n = 17) and 2.1% of 2L FOLFIRI patients (n = 2), mainly gastrointestinal disorders (2.1% of 1L FOLFOX patients [n = 7] and no 2L FOLFIRI patient) or skin disorders (1.8% of 1L FOLFOX patients [n = 6] and no 2L FOLFIRI patients). No fatal adverse drug reactions were reported. Table 6 shows reported adverse drug reactions.

Table 6 Adverse drug reactions by system organ class in at least 5% of patients, n (%)

	1L FOLFOX (N = 332)	2L FOLFIRI (N = 94)
Any ADR	266 (80.1)	70 (74.5)
Skin and subcutaneous tissue disorders	250 (75.3)	68 (72.3)
Rash[a]	134 (40.4)	46 (48.9)
Dermatitis acneiform[a]	52 (15.7)	11 (11.7)
Gastrointestinal disorders	26 (7.8)	5 (5.3)
General disorders and administration site conditions	22 (6.6)	3 (3.2)
Infections and infestations	18 (5.4)	6 (6.4)
Any serious ADR	17 (5.1)	2 (2.1)

1L first-line, *2L* second-line, *ADR* adverse drug reaction, *FOLFOX* folinic acid, fluorouracil, oxaliplatin, *FOLFIRI* folinic acid, fluorouracil, irinotecan

Coded using MedDRA version 18.0

The subcategories are not mutually exclusive. Patients are only included once within each subcategory

[a] Subcategories are shown, if they occurred in at least 10% of patients

Treatments Planned After Panitumumab Discontinuation

After discontinuing panitumumab, 50.6% of 1L FOLFOX patients (n = 168) and 52.1% of 2L FOLFIRI patients (n = 49) were assigned to receive further lines of anticancer treatment. In the 1L FOLFOX group, the most frequent planned follow-on regimens were chemotherapy (52.4%, n = 88) or chemotherapy in combination with bevacizumab (22.6%; n = 38). In the 2L FOLFIRI group, patients were most frequently assigned to receive chemotherapy (38.8%; n = 19) or regorafenib monotherapy (18.4%; n = 9).

DISCUSSION

The two studies presented investigated the real-life use patterns of panitumumab in

combination with 1L FOLFOX and 2L FOLFIRI, as well as aspects of efficacy and safety in a real-world patient population. No other similarly designed observational studies investigating the routine clinical practice use of first- or second-line panitumumab treatment in combination with chemotherapy in mCRC have been published to date. The results of this study are important as they describe panitumumab use and treatment patterns in clinical reality.

In the randomized controlled setting, the 1L FOLFOX group in this study can be put in context with the phase 2 PEAK (Panitumumab Efficacy in combination with mFOLFOX6 Against bevacizumab plus mFOLFOX6 in metastatic colorectal cancer subjects with wild-type KRAS tumors) and the phase 3 PRIME studies; the 2L FOLFIRI setting corresponds to study 20050181 [20–23]. In PEAK, 170 patients underwent extended *RAS* analysis, with 88 of the wild-type *RAS* population receiving panitumumab + mFOLFOX6 and 82 receiving bevacizumab + mFOLFOX6 in 1L. In PRIME, 505 wild-type *RAS* patients received either panitumumab + FOLFOX4 ($n = 253$) or FOLFOX4 alone ($n = 252$) in 1L. In study 20050181, of wild-type *RAS* patients, 208 received panitumumab + FOLFIRI and 213 received FOLFIRI alone in 2L. In the routine clinical practice setting, two observational studies evaluated the use of panitumumab monotherapy in patients with confirmed *KRAS* wild-type mCRC, who had failed prior chemotherapy with 5-fluorouracil, oxaliplatin, and irinotecan. VECTIS (VECTIbix® monotherapy in patients with recurrent or progressive colorectal cancer) included 632 patients from Czech Republic, Poland, Hungary, Slovenia, Bulgaria, and Slovakia [24]. The VECTOR study included 428 patients from Germany [25]. The study setting of both these clinical practice studies implies a more heavily pretreated patient population compared with the present study.

In the present study with a 12-month observation period, patients received a median of 10.0 and 11.5 infusions in the 1L FOLFOX and 2L FOLFIRI groups, respectively, with a wide range of treatment intervals, but mostly more than 14 to 21 days. In VECTIS, where the observation period was limited to 18 cycles, panitumumab was administered over a mean of 9.6 biweekly cycles (median 9.0 [5.0, 13.0]; unpublished data) [24]. In VECTOR, the median number of administered panitumumab cycles was 8 (range 2–45) [25]. In the phase 3 PRIME study, the median number of panitumumab cycles received was 11 [26]. In the phase 2 PEAK study, the median exposure to panitumumab was 14 cycles [21]. In phase 3 study 20050181, the median duration of exposure for the wild-type *RAS* stratum was not provided in the literature, but was 9 cycles for the wild-type *KRAS* stratum [12]. Overall, the number of panitumumab cycles administered in the 1L FOLFOX group of the present study was in line with previous randomized controlled trials (RCTs) conducted in this setting. In the 2L FOLFIRI group, the number of administered panitumumab cycles was slightly higher than seen in previous RCTs in the second-line setting.

In the present study, the unadjusted overall response rate of complete or partial response was 51.7% in 1L FOLFOX and 44.9% in 2L FOLFIRI patients amongst the 290 patients who had tumor response data post baseline. The disease control rate, defined as complete response, partial response, or stable disease, was 82.1% in 1L FOLFOX and 77.5% in 2L FOLFIRI. In VECTIS, an overall disease control rate of 58.9% was observed [24]. In VECTOR, the disease control rate was 60% and the overall response rate was 20% [25]. The phase 3 PRIME study found an objective response rate (complete response or partial response) of 60% [26]. The phase 2 PEAK study found an objective response rate of 65% [21]. In the second-line panitumumab + FOLFIRI setting, the objective response rate was 41% in the panitumumab + FOLFIRI group [12, 23].

In the present study, skin toxicities were reported for 75.3% of 1L FOLFOX patients and 72.3% of 2L FOLFIRI patients. In VECTIS, skin toxicities of any type occurred in 84.3% of patients. [24] In VECTOR, skin reactions occurred in 67% of patients [25]. Most patients experienced some type of rash. In the two RCTs that reported skin toxicities of all grades, 96% were reported in PRIME [11] and 97% in PEAK [20]. In study 20050181, rash of any grade was reported in 54% of patients [23]. Considering

the fact that VECTIS focused explicitly on skin toxicity as a marker of response, the incidence of skin toxicity was found to be higher than in the present study and in VECTOR, but lower in the observational studies than the RCTs. This may be an indication that lower grade skin toxicity is not always recorded well in clinical practice. Underreporting of known and thus expected adverse drug reactions is a known bias in observational research. Additionally, evidence from clinical studies [27] as well as the availability of respective guidelines suggests that physicians' experience with managing EGFR inhibitor-related skin reactions is increasing. It can be assumed that patients are now treated more proactively with skin ointments, sun protection, skin moisturizers, and other measures to prevent skin reactions, compared with the earlier years of use of panitumumab in daily clinical routine. VECTIS also described health care resource use including *KRAS* testing procedures, which was not covered by this study nor by VECTOR.

In the studies presented there may be a selection bias due to inclusion criteria that patients had to be on treatment and alive at the time of inclusion. Patients dying, e.g., from disease progression, between the first dose of panitumumab and enrollment into this study were not captured. This bias cannot be quantified as a result of lack of data before enrollment.

CONCLUSIONS

In this study of panitumumab use in the routine practice setting, median length of treatment with panitumumab was 10 cycles in 1L in combination with FOLFOX and 11.5 cycles in 2L in combination with FOLFIRI. Overall response rate of complete and partial response was 52% in the 1L and 45% in the 2L setting. The skin toxicity rate was 75% and 72%, respectively. Overall, these results are consistent with the literature, taking into consideration differences in study design, treatment setting, and physicians' increasing routine over time with using panitumumab. This is especially important in the context of managing panitumumab-related skin toxicity. However, underreporting of very mild cases of skin toxicity in the setting of observational research may not be ruled out.

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Where required per local regulations that the study protocols were approved by independent ethics committees. Informed consent was obtained from all individual participants or their legally acceptable representatives.

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