Efficacy and safety of panitumumab in a cohort of patients with metastatic colorectal cancer in France: PANI OUEST, a post–EMA-approval descriptive study with a geriatric oncology focus

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ABSTRACT

Background/Aims: The Bretagne-Pays de la Loire cancer observatory, an oncology network created by the French Ministry of Health, is specifically dedicated to assess the use of new targeted anticancer therapies in routine practice. In line with the French National Cancer III program, our cancer network set up a real-life cohort, which is independent of the pharmaceutical industry, for patients with colorectal cancer to monitor patient safety and quality of care and promote pharmacovigilance.

Materials and Methods: Panitumumab monotherapy was assessed in 243 patients with wild-type Kirsten rat sarcoma who were treated for metastatic colorectal cancer (mCRC) between July 2008 and December 2010 after prior chemotherapy using oxaliplatine and irinotecan. This was a post–European medicine agency marketing (EMA-M) study

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Results: *This study shed light on the best practices, strategic adaptations, clinical results (treatment objective responses, 13%; progression free survival, 2.99 months [2.73-3.15]; and overall survival, 6.8 months [5.49-8.38]) as well as expected or unexpected (grade 3 or 4: 11.5%) secondary effects in the phase IV panitumumab treatment of mCRC.*

Conclusion: *Our results are similar to those by Amado whose phase III study led to obtaining EMA-M for panitumumab and tend to confirm the antitumor activity of this antiepidermal growth factor receptor antibody in the treatment of mCRC. In addition, our results opened avenues to further assessment of panitumumab use as monotherapy as well as its benefit–risk ratio while taking into account the patients' general and clinical characteristics. In 2012, the French National Authority for Health appended these data to the panitumumab transparency committee report.*

Keywords: *Panitumumab, gastrointestinal neoplasm, neoplasm metastasis, survival, safety, aged*

INTRODUCTION

Epidermal growth factor receptor (EGFR) is identified as the clinically significant target for monoclonal antibodies, such as cetuximab and panitumumab. This targeted treatment has proven effective for all treatment lines of metastatic colorectal cancer (mCRC) (1-8). The ligands intended for EGFR activate the RAS/RAF/MAPK(genes encoding RAS and RAF proteins, STAT (Signal Transducers and Activators of Transcription), and P13K (Phosphatidyl Inositol 3-Kinase) /AKT (serine/threonine-specific protein kinase) signalization pathways in charge of cellular proliferation, adherence (cohesion and attachment), angiogenesis, migration, and survival (9, 10).

Panitumumab is a human antibody that targets the EGFR. Its first European medicine agency marketing authorization (EMA-MA) was obtained in 2007 because of a study by Van Custem et al. (7) who compared panitumumab to the best supportive care (BSC).The patients to be treated with panitumumab were selected according to their EGFR expression. Nevertheless, overexpression of EGFR shown by immunohistochemistry has not been a predictor of beneficial effect (8-14).

Retrospective studies have reported that the known Kristen rat sarcoma (KRAS) mutations that is, G12/G13 codons found in mCRC tumors, to be a negative predictor of panitumumab and cetuximab response rate (RR), progression free survival (PFS), and overall survival (OS) (15-22). Since the work by Amado et al. (23), screening for KRAS mutation has become a prerequisite for panitumumab therapy in patients with mCRC. Moreover, Amado's retrospective analysis of Van Cutsem's data with known KRAS status demonstrated that in the panitumumab group, median OS was longer (8.1 months vs. 4.9 months; HR (Hazard Ratio) 0.64; p=0.004) in 124 wild-type (Wt) KRAS than in the patients with 84 KRAS mutations. However, OS in patients with KRAS mutations was the same in both panitumumab and BSC groups. PFS was significantly longer in patients with Wt KRAS than in those with KRAS mutation (12.3 weeks vs. 7.4 weeks; p<0.0001). The treatment RR was also reported to be better in Wt KRAS: 17% partial response vs. 0% and 34% of stability vs. 12%. Treatment toxicity was reported in all patients. Grade III skin toxicity was shown in 25% of the patients with Wt KRAS and 13% of patients with KRAS mutations (grade IV: 0% vs. 1%). Since 2015, clinical practices have evolved, and evaluation of KRAS status has been replaced with that of RAS (KRAS and NRAS (Neuroblastoma RAS)). According to recent pathogenesis guidelines, among previous patients with Wt KRAS, <10% had RAS mutations (23).

MAIN POINTS

- *Our treatment response data confirm those by the gold standard study (Amado et al.) used for marketing authorization of panitumumab.*
- *Our survival data confirm those by the gold standard study (Amado et al.) used for marketing authorization of panitumumab.*
- *No statistical differences in treatment response, survival and toxicity were found for the geriatric population (> 75 years old) compared to those under 75 years old.*

The Bretagne-Pays de la Loire (BPL) cancer observatory, an oncology network created by the French Ministry of Health, is specifically dedicated to assess the use of new targeted anticancer therapies in routine practice. By gathering data from all the patients treated in 34 public hospitals and private institutions of the network, one of the major roles of BPL cancer observatory is to conduct large registry-based observational studies in various fields of oncology for the advancement of the current guidelines. PANI OUEST (study from western France on panitumumab) aimed to retrospectively evaluate the efficacy and safety of panitumumab (phase IV) in a cohort of patients with mCRC in the regions of Bretagne and Pays de la Loire (10% of the French national population). This was a post–EMA-MA study comparing the routine clinical practice with pre-marketing study conducted by Amado et al. (24).

Our study results were added to the postmarketing report by the French National Authority for Health (25).

MATERIALS AND METHODS

EMA-MA

The conditional EMA-M for panitumumab was obtained on December 3, 2007. The notice under the brand name Vectibix® gave indication for monotherapy in patients with mCRC, carrying the Wt KRAS and EGFR gene expression after failure of fluoropyrimidine-, oxaliplatine-, and irinotecan-based chemotherapy regimens. Panitumumab (Vectibix®) dosage was recommended at 6 mg/kg of body weight once every other week. In accordance with the consensus delivered by the cancer observatory general assembly (January 28, 2011), EGFR expression was regarded as a nonrelevant criterion in mCRC and will not be taken into account for panitumumab use (11, 26).

Patients

Panitumumab follow-up between July 1, 2008, and December 31, 2010, in the regions of Bretagne and Pays de la Loire allowed identifying 342 patients with mCRC (316 nontrial and 26 patients already included in clinical cancer research [mCRC and ear, nose and throat trials]). Eligible patients were 18 years or older with mCRC, carrying Wt KRAS, already treated with fluoropyrimidine-, oxaliplatine-, and irinotecan-based chemotherapy (except contraindication). EGFR gene expression was not an inclusion criterion.

This study was approved by the advisory committee for the treatment of information obtained from research in health matters (December 15, 2011) and the national committee on information confidentiality and privacy (CNIL, October 08, 2013). A letter of nonobjection describing the research objectives and the confidentiality of the patients' data was sent to all the surviving patients. A waiver to the right to information from the families of the deceased patients was approved by CNIL.

Data Collection

For each patient included in PANI OUEST, the following clinical and demographic data were collected and reported (regular follow-up was planned by the BPL cancer observatory): age, sex, primary tumor site, disease status (advanced or metastatic), adjuvant, neoadjuvant or metastatic treatment, KRAS status, any involved clinical trial inclusion, date of treatment onset and discontinuation, reason for discontinuation, treatment regimen (monotherapy, a combination chemotherapy, or adjuvant therapy) and dosage for each line of treatment.

Clinical characteristics of the patients' cohort treated in accordance with the marketing framework were completed by the following: possible comorbidities, date of diagnosis, context of disease detection, surgery, initial tumor histology, radiotherapy, metastasis resectability, pre- and postpanitumumab treatment regimens, KRAS status, grade III/IV toxicity (according to the United States national cancer institute common terminology criteria for adverse events version 4, 2010), side effects causing treatment discontinuation, best RR, presence of a secondary surgery, time to disease progression and OS, date of the end of the study, and the patient's status at the end of the study.

Study Design

This was an observational retrospective multicenter post–EMA-MA panitumumab study. Intention-to-treat (ITT) analysis was used to analyze the patients' results. Study treatment was continued until progressive disease (PD), panitumumab toxicity, secondary surgery, patient's decision, medical decision, or death.

Objectives

The aim of the PANI OUEST study was to evaluate the efficacy and toxicity of panitumumab monotherapy after disease progression following fluoropyrimidine, oxaliplatine, and irinotecan containing chemotherapy regimens for treatment of unresectable mCRC. The primary end point was OS. The secondary end points were objective response rate (ORR), PFS, surgery for metastasis (e.g. liver), or other surgery and safety. A subgroup of patients ≥75 years was described. OS was defined as the time between treatment onset and the patient's death. ORR was defined as either total or partial response observed on imaging according to the Response evaluation Criteria in Solid Tumors 1.0 criteria and regarded as the best panitumumab-related response. The latter was evaluated by the multidisciplinary team in charge of the patient and was recorded in our database. PFS was defined as the time between treatment onset and event onset (e.g. recurrence, PD, and death).

Statistical Analysis

All qualitative variables were presented in percentages. All quantitative variables were presented in means and standard deviation, median, and min/max. Survival data were presented as survival curves and calculated using the Kaplan-Meier method and presented with 95% confidence interval. The baseline date was set at the inclusion date, that is, panitumumab therapy onset.

The log-rank test was used to compute the time to death and disease progression. X^2 or the Fisher exact test was used to analyze any association between the qualitative variables, for example, toxicity and response to different treatments. All the tests were bilateral and regarded as significant at 5% threshold.

PANI OUEST hypothesized that clinical practice results are consistent with those reported in the literature. A total of 243 descriptive analyses from our large and representative sample of patients were compared with those by Amado et al. (24).

RESULTS

Patient Description

Between July 2008 and December 2010, 32 healthcare structures participated in this study.

Table 1. Data on patient exclusion criteria.

No. of patients	Reasons	Details
4	Other cancer than mCRC	2 small intestine, 1 duodenum, 1 ileum
13	KRAS gene status undetermined or uninterpretable	- Extraction defect - Insufficient tissue - Difficult access to the tumor site
3	KRAS mutant gene	- Clinician's faulty assessment - Absence of data in the patient's medical file - KRAS mutant patient treated with first-line therapy and retreated for progression disease with third-line therapy
44	Combination with chemotherapy (without EMA approval)	- 17 combination with chemotherapy using irinotecan in second-line therapy (Peeters et al., 2010), - 10 combination with the chemotherapy in second- or third-line therapy because of contraindication to cetuximab (Resch et al., 2011; Brugger et al., 2010, Kim et al., 2009; Nielsen et al., 2009; Cartwright et al., 2008; Langerak et al., 2009; Heun et al., 2007; Helbling et al., 2007). - 3 combination with chemotherapy using oxaliplatine in first-line therapy (Douillard et al., 2010), - 3 combination with chemotherapy using irinotecan in first-line therapy (Kohne et al., 2010), - 7 combination prescriptions because of the good responses to prior anti-HER1 treatments - 4 other combination prescriptions according to patient specific customized strategies.
7	Dosage (without EMA approval)	- 4 patients at 9 mg/m2 at day 1 and day 21 (Carrato et al., 2013; Stephenson et al., 2009). - 3 patients at 4.5 or 5 mg/m2 at day 1 and day 14 initially owing to physiopathological criteria
2	No prior chemotherapy using oxaliplatine or irinotecan	Incomplete clinical data not allowing the validation of this inclusion criterion

KRAS: Kirsten rat sarcoma; EMA: European medicine agency; mCRC: metastatic colorectal cancer; HER-1: human epidermal growth factor receptor-1.

Only 243 patients (77%) of the entire sample (n=342) who reported to the BPL cancer observatory fulfilled the inclusion criteria (Table 1 displays the exclusion reasons). These patients were followed up until September 25, 2012. Table 2 displays PANI OUEST characteristics of patients, for example, sex ratio of 1.96, 67 (±11) years mean age and 68 years (36–89) median age. The age distribution of patients treated with panitumumab was as follows: 81% patients were 51 to 80 years, 46% were 70 years and older, and 28% were older than 75 years.

Table 2. Demographics and tumor characteristics of total population, onco-geriatric population, and the EMA-approval population (24).

	Total population (n=243)	<75 years (n=175)	≥75 years (n=68)	Amado et al., 2008 (n=124)
Demographics				
Woman/man	82 W/161 M	59 W/116 M	23 W/45 M	41 W/83 M
Sex ratio	1.96	1.97	1.96	2.02
Median age (years)	68 (36-89)			62.5 (29-82)
Mean age (years)	67 (+/-11)			UK
Age distribution		72%	28% (80-85 14%	
>85 years: 3%)				
Tumor type				
Colon	157 (65%)	108 (62%)	49 (72%)	86 (69%)
Rectum	75 (31%)	60 (34%)	15 (22%)	68 (31%)
Rectosigmoid junction	8 (3%)	6 (3%)	2 (3%)	0
Colon and rectum	3 (1%)	1 (1%)	2 (3%)	0

UK: unknown.

Table 3. Study population treatment data at disease onset and panitumumab therapy lines.

	Total population (n=243)	<75 years (n=175)	≥75 years (n=68)	p
Treatment				
Synchronous metastases	138 (57%)	101 (58%)	37(54%)	0.667
Primary tumor resection	200 (82%)	141 (81%)	59 (86%)	0.349
Combination CT	68 (28%)	54 (31%)	14 (20%)	0.115
Neoadjuvant CT	2 (1%)	1 (0.5%)	1 (1.5%)	0.482
Neoadjuvant RT	4 (2%)	3 (1.5%)	1 (1.5%)	0.999
Neoadjuvant RT-CT	18 (7%)	17(10)	1 (1.5%)	0.028
Line of metastatic therapy using panitumumab				
First line	3 (1%)	1 (0.5%)	2(3%)	
Second line	50 (20%)	27 (15%)	23 (34%)	
Third line	71 (29%)	51 (29%)	20 (29.5%)	
Fourth line	66 (27%)	48 (27%)	18 (26.5%)	
Fifth line	35 (14%)	32 (18%)	3 (4%)	
Sixth line	10 (4%)	10 (6%)	0	
Seven-ninth lines	11 (5%)	9 (4.5%)	2 (3%)	
2 lines of treatment	3 (1%)	3 (2%)	0	
Median	3	4	3	
Mean	3.63	3.84	3.10	

CT: chemotherapy; RT: radiotherapy.

Table 4. Comparison of results of this study population and those of study by Amado et al.: best response to panitumumab, causes of panitumumab discontinuation.

	Total population (n=243)	<75 years (n=175)	≥75 years (n=68)	p
Best response to panitumumab				
Total response	0	0	0	0%
Partial response	31 (13%)	23 (13%)	8 (12%)	10%
Stable disease	46 (19%)	35 (20%)	11 (16%)	25%
Progressive disease	117 (48%)	86 (49%)	31 (46%)	50%
Toxicity	5 (2%)	2 (1%)	3 (4%)	2%
NA	44 (18%)	29 (17%)	15 (22%)	13%
Causes of panitumumab discontinuation				
Death	29 (12%)	23 (13%)	6 (9%)	
Medical decision	62(26%)	40 (23%)	22 (32%)	
End of treatment	6 (2%)	3 (2%)	3 (4%)	
Progressive disease	125 (51%)	92 (52.5%)	33 (49%)	
Toxicity	10 (4%)	8 (4.5%)	2 (3%)	
Patient's decision	10 (4%)	9 (5%)	1 (1.5%)	
Lost to follow-up	1	(0.4%)	0	1 (1.5%)

NA: Not assessable.

Primary tumor site distributions were mostly the colon (65%) and rectum (31%) (Table 2). Metastatic tumor was reported in 138 (57%) of our patients (Table 3). Primary tumor resection was performed during hospitalization in 200 patients (82%). Treatment regimens were prior adjuvant chemotherapy (for local advanced cancer) in 68 patients (30%), neoadjuvant chemotherapy in 2 patients, neoadjuvant radiotherapy in 4 patients, and neoadjuvant radiochemotherapy in 18 patients.

Treatments

Most of our patients received panitumumab as the second-line (50/243, 20%), third-line (71/243, 29%), and fourth-line (66/243, 27%) treatment (Table 3). The following contraindications to prior recommended chemotherapy were reported in 51 patients: irinotecan in 17, oxaliplatine in 23, oxaliplatine and irinotecan in 10, and fluoropyrimidine in 1. The median and mean number of panitumumab cycles were 6 (1–35) and 6.8 (±4.8), respectively. Our study's mean and median of treatment duration was 94 days ±84 and 71 days [1–535], respectively.

Efficacy

Response Rate

Table 4 displays the study populations and population results of the study by Amado et al.: best response to panitumumab and causes of panitumumab discontinuation based on ITT (i.e., the entire sample of patients) and age. Causes for treatment discontinuation in our study were PD (51%), toxicity (4%), patient's choice (4%), medical decision (26%), and death (12%). These data were not reported in the study by Amado et al.

Panitumumab-related response was evaluated using imaging every 2 or 3 months according to each center's routine practice. Our results represent 80% of patients who were eligible for this follow-up after 2 or 3 months of treatment. During this time, 18% of the patients showed clinical PD (before 2 months), deterioration of general state unsuitable for treatment continuation, or died prematurely. Because of acute toxicity, 2% of the patients discontinued treatment prematurely.

Imaging-derived computed results were as follows: PR (Partial Response), 13%; SD (Stable Disease), 19%; and PD (Progressive Disease), 48%. The median time of 15 days (5–58) (mean: 19 days, σ: 12.6) between treatment discontinuation and death was reported in 29 patients who died prematurely.

OS and PFS

The median of OS and PFS was 6.8 months (95% confidence interval [CI]: 5.49-8.38) and 2.99 months (95% CI: 2.73-3.15), respectively (Figures 1a, b).

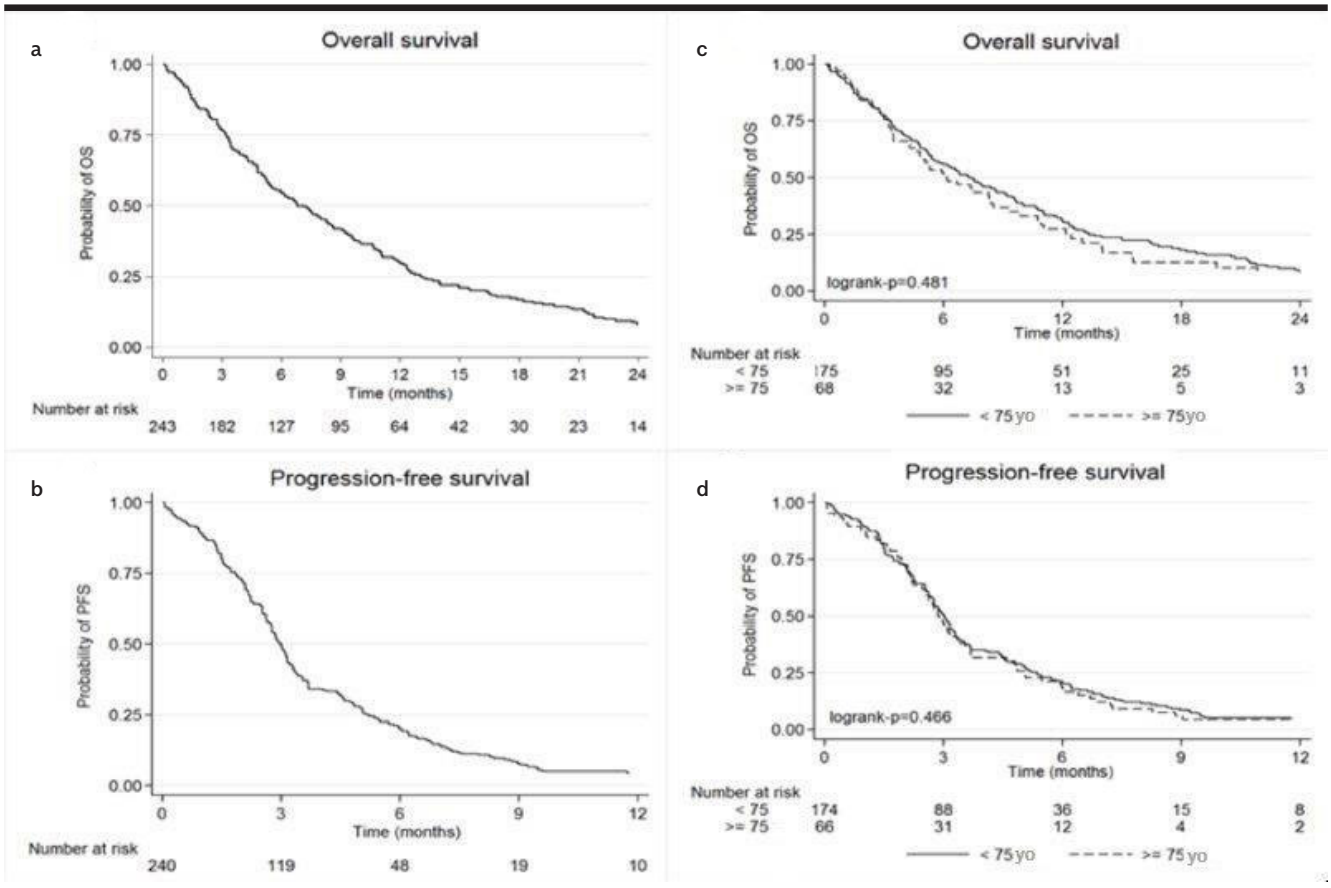

Figure 1. a, b. Kaplan-Meier overall survival and progression free survival–analysis for total population and according to age.

Toxicity

Grade III/IV toxicity was reported in 28 patients (11.5%) with 22 skin toxicities, 2 hematological toxicities, 1 femoral thrombosis, 1 allergy, 1 severe sepsis, and 1 hemorrhagic necrosis of the upper limb with purpura on the abdomen and the chest. Moreover, 1 patient presented with Charcot disease symptoms. On September 25, 2012, 217 patients were dead, 17 were alive, and 9 were lost to follow-up.

Onco-geriatric Subgroup

Patient characteristics of this subgroup (28%) are displayed in Table 2. Similar sex ratio (1.96) was reported here. In comparison with the younger population of our study (<75 years), a nonsignificant increase in the colon cancer incidence and a decrease in that of the rectal cancer was observed in this older subgroup (≥75 years). Of note, both groups of patients were managed in a similar manner (Table 3). Those ≥ 75 years received panitumumab earlier than the younger patients (median treatment line 3 vs. line 4) (p<0.0001). There was no significant difference in the number of therapies received by patients according to age (p=0.228). There was no significant difference in the median treatment duration (p=0.204).

Median OS in patients ≥75 years was 6.18 months (95% CI: 4.30-8.54) vs. 7.29 months (95% CI: 5.49-9.20) in patients <75 years. There was no significant difference in OS between the 2 groups (Figure 1c).

The following rates were reported in patients ≥75 years: PR, 12%; SD, 16%; PD, 46%; and premature toxicity, 4% (Table 4). RR was not computed for 22% of the patients owing to either disease progression or premature death. There was no significant difference between the 2 patient groups (p=0.415).

There was no significant difference in the time duration between treatment discontinuation and death between the 2 patient groups (p=0.212). No significant difference was reported in median PFS between patients ≥75 years and those <75 years (2.86 months, 95% CI: 2.46-3.42 vs.

3.02 months, 95% CI: 2.73-3.29) (Figure 1d). The following toxicities (grade III/IV) were recorded for 8 patients (≥75 years): 5 skin toxicities, 2 hematologic toxicities, and 1 allergy. Moreover, 1 patient ≥75 years presented with Charcot disease.

In the group of patients <75 years, 20 patients (11.4%) presented with grade III/IV toxicities as follows: 17 skin toxicities, 1 femoral thrombosis, 1 severe sepsis, and 1 hemorrhagic necrosis of the upper limb with purpura on the abdomen and chest.

DISCUSSION

Our study was designed and deployed in line with post–EMA-M requirements set forth by several national governmental cancer plans and in accordance with the American society of clinical oncology guidelines (2014). Our institutional cohort of patients with mCRC was treated with panitumumab monotherapy as part of the care center's clinical routine. The patient data and outcomes were recorded to assess the efficacy and safety of panitumumab in cohorts of patients with mCRC, including the older adults.

Our study included 243 patients with mCRC with similar demographics, except for our older median age (68 years [36-89] vs. 62.5 years [29-82]) and different baseline clinical characteristics compared with phase III prospective study by Amado et al. (i.e., the panitumumab marketing study) (24). Prior adjuvant chemotherapy (for local advanced cancer) was administered in 30% patients in PANI OUEST vs. 40% of patients in the EMA-MA study by Amado et al. Panitumumab was given as second- (50/243, 20%), third- (71/243, 29%), and fourth- (66/243, 27%) line treatment to most of our patients compared with second- and third-line treatment given to most of the patients in the study by Amado et al. It is worth mentioning that 21% of our patients had not received prior chemotherapy using irinotecan and oxaliplatine. Median and mean numbers of panitumumab cycles were lower in our study than those reported in the EMA-MA study (6 [1-35] and 6.8 [±4.8] vs. 8 and 10).

Per our main objective, we aimed to assess the efficacy and toxicity outcomes. Clinical efficacy outcome can be assessed by measuring the ORR after first- and second-line chemotherapy. We believe that the clinical efficacy outcome encompassing both disease stability and ORR seems to be the most appropriate efficacy outcome beyond first- and second-line therapies. Of note, the EMA-marketing for panitumumab use had initially required Wt KRAS and, in particular, had set forth ORR as the efficacy outcome irrespective of disease stability status (19).

Imaging-derived computed results were PR, 13%; SD, 19%; PD, 48%; and premature toxicity, 2%. Similar clinical benefits and premature toxicity were reported in our study compared with the study by Amado et al. (33% vs. 35%). It must be noted that 20% of our patients compared with 13% in the study by Amado et al. did not continue the treatment until imaging.

The median OS was 6.8 months (95% CI: 5.49-8.38) and 8.1 months ([HR]: 0.67; 95% CI: 0.55-0.82) in our study and the EMA-approval study, respectively (Figure 1a).

The median PFS was 2.99 months (95% CI: 2.73-3.15) (Figure 1c) compared with 12.3 weeks (3.08 months) (HR 0.45; 95% CI: 0.34-0.59) in the EMA-approval study (24). In our study, PFS was reported at 3 months. The PFS data must be carefully interpreted because our study is retrospective compared with the phase III prospective study, which requires mandatory monitoring (at regular time intervals) of PFS over the study duration. Nevertheless, our reported 3-month PFS was very close to that reported by Amado et al. OS results of first- or second- or any-line of therapy were consistent with those reported by Amado et al. For the best evaluation of OS as the efficacy outcome, in addition to the line of therapy, clinicians should also take into account several criteria, such as drug composition of each chemotherapy regimen after panitumumab treatment, the patient's general state, comorbidities, and age.

Using additional lines of therapy seems of great importance in the treatment of patients with mCRC. The "CORRECT trial" comparing regorafenib regimen with BSC showed a significant difference in disease stability rate and PFS (27). According to this trial, major toxicities and dose adjustments not only during treatment but also at treatment onset should warn the oncologist on the pertinence of regorafenib use as first- or second- or any-line of treatment. To date, there is no prognostic predictor of the best treatment response based on treatment risk–benefit ratio according to other criteria than the patient's ECOG (Eastern Cooperative Oncology Group) performance status and nutritional status. Grade III/IV toxicity of 11.5% and 44% was reported in the PANI OUEST and the study by Amado et al., respectively. In terms of grade III/IV toxicities, our study confirmed the expected toxicity related to panitumumab use, that is, skin toxicity and the absence of allergies. Moreover, given the

absence of aberrant toxicities in our study, we suggest panitumumab use in patients with mCRC, taking into account its induced skin toxicity, in accordance with ECOG scale of performance status. According to Lacouture et al., (28) the toxicities can be prevented using prophylaxis to panitumumab without any impact on the RR. Furthermore, our study highlighted similar toxicity outcomes in patients ≥75 years (28% of our cohort) and those <75 years. Thus, the absence of aberrant toxicities in those ≥75 years suggests use of panitumumab in this mCRC subgroup.

Furthermore, the causes for treatment discontinuation were disease progression (51% in our study), toxicity (4%), patient's decision (4%), medical decision (26%), and death (12%). The latter outcome is paramount to the conduct of studies on palliative care as well as toxicity and efficacy of any additional new line of chemotherapy in patients with cancer often treated with multiple chemotherapies. The choice of cancer therapy can put public health at stake. The study by Bourgeois et al. (29) puts forward the patient outcome criteria, such as ECOG performance status, number of metastatic sites, lactate dehydrogenase, and albuminemia level, to be accounted for when choosing the best therapeutic strategy (active treatment vs. BSC) to achieve optimal treatment benefit. Clinicians and healthcare providers need objective patient outcome scoring tools to help and guide them in choosing the most appropriate treatment and its best use. A multidisciplinary assessment and management of patients with cancer, including all support cares, as early as possible seems to be the most beneficial for better OS (30-34).

The patient's decision (owing to treatment-related debilitating lassitude and skin toxicities) to stop the treatment (although low, 4% in our study) should be taken into account in the studies evaluating the efficacy and toxicity of new chemotherapy regimens.

Since the set up and deployment of our study, EMA indications for panitumumab use have evolved. This evolution is based on the study by Douillard et al. (35) who reported optimal RR, PFS, and OS in patients with Wt RAS and KRAS mutations treated with panitumumab.

Wt RAS and KRAS statuses are now mandatory before starting panitumumab therapy.

This change by EMA has opened the avenue to recent studies on cetuximab use (36). The results of recent studies demonstrating continuous effect of anti-EGFR beyond the first-line panitumumab treatment has prompted healthcare professionals to favor panitumumab monotherapy after oxaliplatine and irinotecan chemotherapy failures.

Several novel treatment regimens are emerging. Given the lack of optimal treatment for patients with BRAF mutation, panitumumab-based regimen (FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan)+/-panitumumab) is being used without relevant phase III trial and quality clinical evidence. Moreover, the use of panitumumab-based regimen (FOLFOXIRI+/-panitumumab) was studied in patients with BRAF mutations (Wt RAS t) ("VOLFI" phase II trial) (37). The use of FOLFIRINOX bevacizumab-based regimen has been suggested as the first-line therapy (38, 39). The option to use ramucirumab-based regimen was very recently suggested by Yoshino et al. (40) in a retrospective analysis of "RAISE" phase III trial. This treatment option is not used in France. Other treatment options on the basis of a BRAF inhibitor (vemurafenib in 1 case report) or a combination of targeted therapies (Beacon mCRC trial) have been suggested recently (41, 42).

Our findings suggested a new treatment strategy, that is, the use of an anti–EGFR-based regimen (cetuximab or panitumumab) as the second-line therapy when the patient's general health is good. Novel therapeutic agents and treatment strategies are being evaluated to overcome RAS-mediated resistance. Accordingly, further studies are warranted to identify the predictors of response to these novel therapeutic agents. Systematic BRAF status analysis is being evaluated by our cancer network to provide helpful data on potential predictors of response to novel therapeutic agents.

This was the first postmarketing study using panitumumab in patients with mCRC in clinical practice by an institutional regional cancer expertise network. This study evaluated the effectiveness of panitumumab in patients with mCRC through assessment of clinical efficacy outcomes as well as clinical safety outcomes, that is, expected and unexpected, in clinical routine independent of pharmaceutical industry. Our results were paramount to panitumumab use in clinical practice in France and were compared to those by Amado et al. (EMA-MA study). In addition, this study led to further discussion on panitumumab use as a monotherapy in the treatment of mCRC and to the advancement of the guidelines. Indeed, panitumumab should be used after considering the patient's general state and preferences.

Ethics Committee Approval: This study was approved by the advisory committee on the processing of information in the field of health research.

Informed Consent: Informed consent was obtained from the patients who participated in this study (file number: 11-718; approved 2011/12/15).

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