doi: 10.1111/j.1472-8206.2011.00961.x

ORIGINAL ARTICLE

Chemotherapy and targeted agents for colorectal cancer in a real-life setting anticipate guidelines: the COLCHIC cohort study

Denis Smith[a], Eric Terrebonne[b], Magali Rouyer[c,d], Jean-Frédéric Blanc[a,c], Dominique Breilh[b,c], Stéphane Pedeboscq[a], Alise Le Monies[c,d], Coralie Lecomte[c,e], Régis Lassalle[c,d], Nicholas Moore[c,d,e,f], Annie Fourrier-Réglat[c,d,e,f,*]

[a]*CHU de Bordeaux, Hôpital Saint André, 1 rue Jean Burguet, F-33075 Bordeaux, France*
[b]*CHU de Bordeaux, Hôpital Haut-Léveque, 1, avenue Magellan, F-33604 Pessac, France*
[c]*Université de Bordeaux, 146 rue Léo Saignat, F-33076 Bordeaux, France*
[d]*INSERM CIC-P 0005, 146 rue Léo Saignat, F-33076 Bordeaux, France*
[e]*CHU de Bordeaux, Hôpital Pellegrin, Place Amélie Raba-Léon, F-33000 Bordeaux, France*
[f]*INSERM U657, 146 rue Léo Saignat, F-33076 Bordeaux, France*

Keywords
colorectal cancer,
chemotherapy,
targeted therapeutics,
recommendations,
guidelines,
cohort

Received 23 November 2010;
revised 9 May 2011;
accepted 20 May 2011

*Correspondence and reprints:
annie.fourrier@pharmaco.u-bordeaux2.fr

ABSTRACT

Introduction of new agents for the treatment for colorectal cancer (CRC) has been accompanied by the publication of guidelines. The COLCHIC cohort was set up to evaluate CRC treatment practices and the use of these innovative and expensive agents. Patients initiating CRC treatment at the Bordeaux teaching hospital between 1 March 2005 and 1 March 2006 were identified, and treatment courses from 1 March 2005 to 31 December 2006 were studied; 192 patients were included, 188 with analysable data: 43 patients initiated 51 courses for non-metastatic cancer, 153 initiated 366 courses for metastatic cancer, eight patients initiated courses for both non-metastatic and metastatic cancer. Most treatments were used for indications found in guidelines published during the study (83.9%). Of the others, nearly half were approved in guidelines published subsequently. In this teaching hospital, prescribing practice was generally in line with recommendations, with an anticipation of future guidelines. This mostly concerned monoclonal antibodies, which were new at the time of the study.

INTRODUCTION

Cancer is a public health priority in France. Cancer plans have been implemented since 2003; the French national cancer institute (*Institut National du Cancer*, INCa) was created with the objective of developing research, improving quality of care and facilitating access to innovative treatments [1].

Treatment for colorectal cancer (CRC) depends on tumour site (colon or rectum) and stage of disease. For many years, treatment strategies available were surgery, radiotherapy and conventional chemotherapy. For metastatic CRC (mCRC), chemotherapy was initially based on fluoropyrimidine [2], subsequently enriched by the introduction of irinotecan [3,4] and oxaliplatin [5]. Further improvement has more recently come from the introduction of targeted therapies using monoclonal antibodies, first cetuximab, targeting the epidermal growth factor receptor [6], and then bevacizumab, targeting vascular endothelial growth factor (VEGF) [7]. These therapeutic strategies increased life expectancy [8]. In parallel, the number of treatment lines has also increased [9–11], yet few studies have been conducted to describe the use of these targeted agents

in real life [12,13]. In France, off-label use is permitted if it can be documented that it may be beneficial, and this is often mentioned in the recommendations from the national gastroenterology society (*Société Nationale Française de Gastroentérologie*, SNFGE) and public health authorities. These guidelines, which may differ from the summary of product characteristics (SmPC), are a reference for reimbursement by the national health insurance system. In parallel, the national health authority (*Haute Autorité de Santé*, HAS) has initiated programmes to evaluate clinical practice to improve quality of care. Use of these drugs has been classified as normal (within the SmPC) or acceptable (within the national reference guidelines), but these may still be prescribed and reimbursed if there is at least low-level documented evidence that use is beneficial. Otherwise, or if the guidelines state it, prescription is considered not acceptable, and the drug will not be paid for by the healthcare insurance system.

We therefore identified a cohort of patients treated for CRC to describe the clinical practice for the treatment of CRC in our hospital. Because we thought that prescribing patterns in a teaching hospital might precede official guidelines, the indications of these new and expensive targeted treatments were compared with treatment guidelines, both at the time of the treatment initiation and later on.

MATERIALS AND METHODS

Study design

The COLCHIC study is a cohort of patients whose chemotherapy for CRC was initiated between the 1 March 2005 and the 1 March 2006 in the Bordeaux University Hospitals (France). They were identified through electronic hospital registries (*Programme de Médicalisation des Systèmes d'Information,* PMSI) using the following ICD 10 codes: C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.9, C19, C20, C21.8, D37.4, D37.5. Inclusion criteria were verified manually using medical files. For each such identified patient, the inclusion date was the first date of treatment (*Figure 1*). The protocol of the study was submitted and received approval from the French data protection agencies (*Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé,* CCTIRS and *Commission Nationale de l'Informatique et des Libertés*, CNIL). Ethics committee approval was not required, in line with French regulations for observational studies. Not being a randomized trial, this study was not reported to the clinical trial registries.

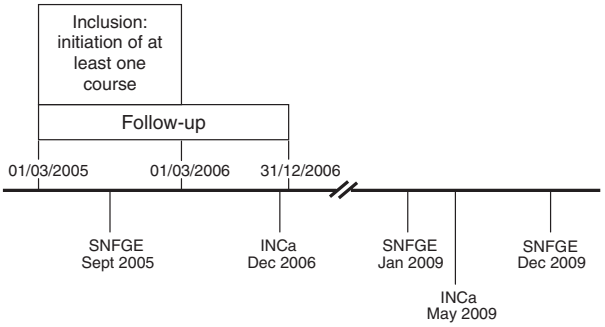

Figure 1 Study timeline. Patients included in the study were identified through their initiation of a treatment course between 1 March 2005 and 1 March 2006. All treatment courses initiated by these patients between 1 March 2005 and 31 December 2006 were considered in the analysis. The guidelines published by the Société Nationale Française de Gastroentérologie and the Institut National du Cancer are also indicated.

Patients and data collection

Patients were informed of the data collection in writing, by a letter given to them by their physician. They had the opportunity to indicate their wish not to participate; though, none did so. Eligible patients were those who initiated chemotherapy for CRC during the inclusion period (from 1 March 2005 to 1 March 2006), with long-term care management in the centre and who did not decline to participate to the study. For these patients, treatment courses that were initiated from 1 March 2005 to 31 December 2006 (the study period) were considered in the analysis.

For all eligible patients, clinical and treatment data were extracted from medical records and from the prescription databases of the hospital pharmacy (using CHIMIO, Computer Engineering, or DXCARE, Medasys). All data were collected on case report forms (CRFs). In cases where there were inconsistent or missing data, discrepancies were resolved with the physicians in charge of the patient. At inclusion, data collected included age, gender, tumour location (colon, rectum) and stage of the disease with Tumour, Node, Metastasis classification and grading at the date of diagnosis. For each treatment course (series of treatment cycles), data collected included the name of the drugs, indications of treatment, number of cycles, whether or not the course was part of a clinical trial, date of initiation and termination.

Concordance with summary of product characteristics (SmPC) and guidelines

Treatment courses initiated during the study period were compared with the SmPCs of the products involved and

in place during the study period to identify off-label use [14]. These were also compared to the guidelines of the French National Gastroenterology Society (SNFGE) that included the labelled indications of the SmPC for the anticancer drugs and unlabelled but recommended uses. These guidelines were first available in September 2005 (*Thesaurus de cancérologie digestive,* SNFGE Sept 2005) and thereafter published in the journal *Gastroentérologie Clinique et Biologique* in September 2006 [15–17].

In a second step, courses not found in these guidelines were compared with the recommendations of the French National Cancer Institute (INCa) published in December 2006 (INCa Dec 2006) [17]. Those that were not found in either SNFGE Sept 2005 or INCa Dec 2006 were then compared with updated guidelines published by the SNFGE in January (SNFGE Jan 2009) [18] and in December 2009 (SNFGE Dec 2009) [16] or by the INCa in May 2009 (INCa May 2009) [19].

The SNFGE Sept 2005 guidelines only gave positive recommendations. However, in all the INCa guidelines and the SNFGE guidelines from January 2009, the notion of 'unacceptable situation' was introduced, and these were also identified in the present study. Treatment courses that were found to deviate from the SNFGE Sept 2005 guidelines but that were part of a clinical trial (not listed in these guidelines) were identified and considered not to be a deviation. All the analyses were descriptive and performed using SAS® (SAS Institute, version 9.1, Cary, NC, USA).

RESULTS

There were 192 patients included in the study, representing all patients initiating treatment for CRC in our hospital over 1 year; 41.7% were women, and the mean (SD) age was 65.4 (11.1) years. At inclusion, 50 patients (26.0%) had non-metastatic, 61 (31.8%) metachronous metastatic and 81 (42.2%) synchronous mCRC. Of those with non-metastatic cancer at inclusion, disease stage was not known for four patients (having received six courses of treatment), and these were excluded from the description of treatment courses. The resulting 188 patients had a total of 417 treatment courses (corresponding to 2942 treatment cycles) initiated during the period of interest: 43 patients initiated 51 treatment courses for non-metastatic cancer, 153 initiated 366 treatment courses for metastatic cancer, and eight patients initiated courses for both non-metastatic and metastatic cancer. With regard to the SmPCs of anticancer medicines used and in place during the study period, 333 (79.9%) of courses were for labelled indications, and with regard to the SNFGE Sept 2005 guidelines, 350 (83.9%) courses were for recommended indications.

Treatment courses in non-metastatic colorectal cancer

For four patients who received six courses of treatment, disease stage was not given, and these were excluded from analysis. One-third of treatment courses in non-mCRC were for colon cancers (n = 16, 31.4%). There was no treatment course for stage I, six for stage II and ten for stage III. All courses were indicated as adjuvant chemotherapy, and with regard to the SmPCs in place during the study period, there was no off-label indication for non-metastatic CRC. According to guidelines for stage II colon cancer, only one course with fluoropyrimidine-based chemotherapy was considered an unacceptable situation (INCa Dec 2006 May 2009; and SNFGE Jan and Dec 2009 guidelines). In this case, treatment was initiated at the request of the patient as indicated in the medical record in spite of an absence of recognized poor prognosis factors (poorly differentiated tumour, T4, presence of venous, perineural and lymphatic embolism, analysis of <12 lymph nodes, perforation and, for some, revealing occlusion); others had at least one of these.

Two-thirds of treatment courses were for rectal cancer (n = 35, 68.6%). The indications for all of these were recommended in the SNFGE Sept 2005 guidelines. There were two treatment courses for stage I: neoadjuvant and adjuvant treatments (for the same patient in a clinical trial); eight for stage II: neoadjuvant treatment (five courses), adjuvant treatment (two courses), and palliative treatment (one course for inoperable primary tumour); and 25 for stage III: neoadjuvant treatment (13 courses) and adjuvant treatment (12 courses).

Whatever the localization and the stage of the disease, neither targeted therapy nor irinotecan-based chemotherapy was used for the treatment for non-metastatic cancer.

Treatment courses in metastatic colorectal cancer (mCRC)

Among the 366 treatment courses identified in mCRC, 84 (23.0%) in 62 patients were for off-label indications according to the SmPCs in place during study period (95.2% of these for the use of targeted therapy). According to guidelines, there were 66 courses (18.0%)

Table I Treatment courses for metastatic cancer.

	Oxaliplatin-based *n* = 105	Irinotecan-based *n* = 176	Oxaliplatin- and irinotecan-based *n* = 10	5FU alone *n* = 62	No chemotherapy *n* = 13
Neoadjuvant chemotherapy, *n* (%)	15 (14.3)	15 (8.5)	6 (60.0)	0 (0.0)	0 (0.0)
Bevacizumab	1 (0.9)*	1 (0.6)	0 (0.0)		
Cetuximab	1 (1.0)*	2 (1.1)*	0 (0.0)		
No targeted therapy	13 (12.4)	12 (6.8)	6 (60.0)*		
Adjuvant chemotherapy, *n* (%)	10 (9.5)	8 (4.5)	0 (0.0)	3 (4.8)	0 (0.0)
Bevacizumab	0 (0.0)	0 (0.0)		0 (0.0)	
Cetuximab	0 (0.0)	0 (0.0)		0 (0.0)	
No targeted therapy	10 (9.5)	8 (4.5)		3 (4.8)	
Palliative treatment					
First-line, *n* (%)	27 (25.7)	62 (35.2)	3 (30.0)	24 (38.7)	8 (61.5)
Bevacizumab	7 (6.7)*	36 (20.4)	1 (10.0)*	7 (11.3)	8 (61.5)*
Cetuximab	0 (0.0)	1 (0.6)* 1 (0.6)[a]	0 (0.0)	0 (0.0)	0 (0.0)
No targeted therapy	20 (19.0)	24 (13.6)	1 (10.0)* 1 (10.0)[b]*	17 (27.4)	0 (0.0)
Second-line, *n* (%)	29 (27.6)	54 (30.7)	0 (0.0)	14 (24.2)	3 (23.1)
Bevacizumab	13 (12.4)*	13 (7.4)* 2 (1.1)*		5 (8.1)*	2 (15.4)*
Cetuximab	1 (0.9)*	19 (10.8)		1 (1.6)*	1 (7.7)*
No targeted therapy	15 (14.3)	20 (11.4)		8 (12.9)	0 (0.0)
Third-line, *n* (%)	15 (14.3)	28 (15.9)	0 (0.0)	11 (17.7)	1 (7.7)
Bevacizumab	3 (2.9)*	1 (0.6)*		0 (0.0)	0 (0.0)
Cetuximab	3 (2.9)*	24 (13.6)		3 (4.8)*	1 (7.7)*
No targeted therapy	9 (8.5)	3 (1.7)		8 (12.9)	0 (0.0)
Fourth-line and above, *n* (%)	9 (8.6)	9 (5.1)	1 (10.0)	10 (16.1)	1 (7.7)
Bevacizumab	1 (0.9)* 1 (1.0)*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cetuximab	1 (1.0)*	9 (5.1)	1 (10.0)*	1 (1.6)*	1 (7.7)*
No targeted therapy	6 (5.7)	0 (0.0)	0 (0.0)	9 (14.5)	0 (0.0)

[a]Treatment course included in a clinical trial not listed in the SNFGE 2005 guideline.

[b]Treatment course of IRINOX, possible alternative if contraindication to fluoropyrimidines.

*Off-label indications.

SNFGE, Société Nationale Française de Gastroentérologie; INCa, Institut National du Cancer.

Discrepancies with SNFGE 2005 guidelines:

▨, Situation found in INCa Dec 2006 guidelines.

▒, Situation found in SNFGE Jan 2009 guideline or INCa May 2009 guidelines.

▓, Situation not found in any guideline.

■, Situation considered as not acceptable in INCa Dec 2006 or May 2009 guidelines and in SNFGE Jan and Dec 2009 guidelines.

in 58 patients for indications not recommended in the SNFGE Sept 2005 guidelines (*Table I*). For 29 (43.9%) of these 66 courses, however, the indications were recommended in subsequent guidelines (SFNGE and/or INCa). For 21 (31.8%), indications were not found in any guideline, and for 16 (24.2%), indications were described as unacceptable. Of these discrepancies, 89.4% concerned the use of targeted therapy.

Courses using bevacizumab for metastatic colorectal cancer

For bevacizumab, in 46 treatment courses, the indications were not in the SNFGE Sept 2005 guidelines, but for 16 (34.8%), the indications later became recommended: in neoadjuvant situation, bevacizumab associated with oxaliplatin- or with irinotecan-based regimens (SNFGE Jan and Dec 2009); in palliative first-line treatment, bevacizumab associated with oxaliplatin-based chemotherapy (SNFGE Jan and Dec 2009, INCa May 2009); in palliative second-line treatment, reintroduction of bevacizumab after its use in first-line treatment (SNFGE Jan and Dec 2009 guidelines).

There were 14 courses (30.4%) that included bevacizumab for which indications were not recommended in SNFGE Sept 2005 or in any of the subsequent guidelines: in palliative first-line treatment, bevacizumab associated with fluoropyrimidine, oxaliplatin and irinotecan (a situation that was recommended in the SNFGE Jan 2009 but not in SNFGE Dec 2009 update); in

palliative second-line treatment, bevacizumab associated with irinotecan-based chemotherapy.

The indications of 16 courses (34.8%) with bevacizumab were considered unacceptable situations (INCa Dec 2006 or May 2009): use as monotherapy (INCa Dec 2006); use beyond second-line treatment after failure of irinotecan and oxaliplatin (INCa Dec 2006); association with cetuximab (INCa May 2009, SNFGE Jan 2009 and Dec 2009).

Courses using cetuximab for metastatic colorectal cancer treatment

The indications of 14 treatment courses including cetuximab were not found in the SNFGE Sept 2005 guidelines. Of these, 12 (85.7%) were subsequently recommended: for neoadjuvant use, cetuximab associated with oxaliplatin- or irinotecan-based regimens (SNFGE Jan and Dec 2009); in palliative first-line treatment, cetuximab associated with irinotecan-based chemotherapy; cetuximab in monotherapy (INCa May 2009, SNFGE Jan and Dec 2009); cetuximab associated with oxaliplatin-based regimen (INCa May 2009, SNFGE Dec 2009).

There was one course that included cetuximab that was not indicated either in SNFGE Sept 2005 or in the subsequent guidelines: for palliative treatment beyond the fourth-line treatment, cetuximab associated with oxaliplatin- and irinotecan-based chemotherapy.

Finally, the indication in one course was described as unacceptable in subsequent guidelines: cetuximab associated with bevacizumab (also reported above concerning bevacizumab).

Courses using chemotherapy alone for metastatic colorectal cancer treatment

Concerning chemotherapy without targeted agents, seven treatment courses were not within the SNFGE Sept 2005 guidelines; all concerned the association of irinotecan, oxaliplatin and fluoropyrimidine (FOLFIRINOX). Among these, one course was subsequently recommended: palliative first-line treatment (INCa Dec 2006 and May 2009). The remaining six courses were not recommended in either SNFGE Sept 2005 or the subsequent guidelines; all were FOLFIRINOX in neoadjuvant treatment.

DISCUSSION

This study of CRC pharmacotherapy in the Bordeaux University Hospitals found that the majority of treatment courses were for labelled indications (79.9%). This may be considered to be low, but it is important to highlight once more that in France off-label use is permitted and reimbursed if this can be documented to be beneficial. Such a situation gives additional importance to guidelines formulated by learned societies and national institutes. When considering the first such guidelines applicable (SNFGE Sept 2005 [15–17]), 83.9% of indications were recommended. For 67 courses (16.1%), however, this was not the case, but in 29 (43.3%) of these, the indications were found in later guidelines, and in 17 (25.4%) the use was deemed unacceptable in subsequent guidelines; in 21 cases (31.3%), treatment options were not described in any of the guidelines considered. The subsequent inclusion in later recommendations for nearly half of these initially not recommended or unacceptable indications may be explained by the prescribers having access to the literature on which guidelines would later be based or even participation in clinical trials that may be used to document benefit and therefore reimbursement, or from the retrospective nature of guidelines. The latter point is illustrated by the timing of the study that considered a period when monoclonal antibodies for CRC were new therapies still being actively explored in clinical trials that were at that time yet to be published. More importantly, the September 2005 SNFGE guidelines chosen for the purposes of the study were the first to incorporate these therapies [15–17]. Because the guidelines were published in September whereas the study presented started in March 2005, there was an initial period of approximately 7 months without guidelines other than the approved SmPC of bevacizumab and cetuximab [20,21]. This point may be considered a limitation, but marketing authorizations are the initial and officially approved regulatory guidelines, and almost all off-label uses were not indications in the SNFGE Sept 2005 guidelines. However, when considering course options for mCRC, which represent the overwhelming majority of deviating courses, the proportion of courses deviating from the SNFGE Sept 2005 guidelines was similar in the periods before and after their publication (17.4% in the period preceding September 2005 and 20.5% thereafter; data not shown).

Of the 21 courses with indications not found in any guideline, the majority were for second-line palliative treatment associating irinotecan-based chemotherapy and bevacizumab. This suggests that such use increases in more desperate cases, potentially at the expense of high-grade toxicity and increased cost to society: i.e.

unacceptable use. However, it is of note that they are undocumented. A literature search for articles relating to this situation found only one recently published retrospective study of such treatments following previous treatment with oxaliplatin-based regimens that found positive results [22]. Such a situation concerned five of the 13 courses reported here, but more importantly, this underlines the lack of information available for certain indications and treatment combinations that are in effect excluded from guidelines. Presuming relative short time from communication of abstracts in meetings to publication of an article, this suggests that treatments were prescribed in the absence of any positive or negative information, with presumption of action based on clinical impressions, or by analogy with other indications.

Unacceptable situations were first described by the INCa in December 2006 [17]. However, this term covers both deleterious and ineffective treatments. Interestingly, only the combination of bevacizumab and cetuximab was thought unacceptable because of a deleterious effect (INCa May 2009, SNFGE Jan and Dec 2009 [16,18,19]), while others that were initially considered unacceptable in the INCa Dec 2006 guidelines were no longer considered so in subsequent updates of one or the other of these guidelines. This highlights an inherent difference in the guidelines used to evaluate practice in the current study: the INCa is an institutional organization that is officially mandated to provide opposable guidelines, provides guidelines by product, cannot go against the SmPC and more readily gives negative recommendations, whereas the SNFGE is a learned society that provides guidelines for therapeutic strategies based on disease and more readily gives positive recommendations. The difference in approach transpires in the data presented here, as the SNFGE recommended strategies in neoadjuvant situations and after disease progression which were not considered in the INCa guidelines [16,19]: cetuximab associated with oxaliplatin- or irinotecan-based regimens in neoadjuvant situations (SNFGE Jan and Dec 2009 [16,18]); bevacizumab associated with fluoropyrimidine, oxaliplatin and irinotecan for first-line palliative treatment (SNFGE Jan 2009 but not in SNFGE Dec 2009 update [16,18]); for palliative second-line treatment, reintroduction of bevacizumab after its use in first-line treatment (SNFGE Jan and Dec 2009 guidelines [16,18]). An interesting point is that, by definition, unacceptable situations also cover the non-treatment of patients that would benefit from this. Although potentially as damaging as unacceptable use, investigation into such non-use was beyond the scope of the current study and is probably limited by the current conditions for healthcare reimbursement in France.

Taken together, this tends to limit the impact of prescription outside recommendations, considering that in fact prescribing in a teaching hospital often precedes later recommendations. However, it may still be considered worrisome that such practice was possible in nearly one-fifth of courses. There are two aspects that may go some way to explain this: firstly, non-recommended prescriptions mainly concerned monoclonal antibodies that were the most recent therapies available at the time of the study. They may have been prescribed outside approved indication in cases with few other options, even without evidence, in the hope that they might improve the patient. If later results confirmed these hopes, then this use might be considered as retrospectively appropriate. On the other hand, if later knowledge confirmed the lack of efficacy or danger of such indications, then their inappropriateness was confirmed. Secondly, these newly available medications were still being investigated and results reported, and prescribers were free to adjust their practice before guidelines were rewritten to incorporate new knowledge. This is facilitated in France as relatively low level of evidence is required to justify prescription that can then be reimbursed. These indications would naturally be included in later editions of the recommendations and guidelines.

Over time, as the body of evidence becomes more complete and the guidelines more stable, there will, mechanically, be a decrease in non-recommended prescriptions. Such a situation may not be found in other countries. For instance, in the UK, as the NICE has not recommended either bevacizumab or cetuximab for NHS use, patients must petition their primary care trust for access to these drugs which may lead to much more tightly controlled use and certainly require a much higher level of evidence than that permitted in France. The generalization of results to non-specialized hospitals within France may also be limited as this study only considered the teaching hospitals of Bordeaux that is a centre of excellence in the treatment for cancer to which more complex, severe or advanced cases may be referred. To obtain a representative sample of cancer treatment in France, this study should be extended to the different healthcare systems available to include the diversity of cancer patients treated.

CONCLUSION

The results of this study indicate that prescribing practice was generally in line with recommendations either existing at the time of prescription or by anticipation. This anticipation of guidelines must be taken into account in drug use studies, especially when newly marketed drugs are investigated.

ACKNOWLEDGEMENTS

The authors wish to thank all the participants in this study, Prof Alain Ravaud, CHU de Bordeaux, Université de Bordeaux, and Dr. Philip Robinson, PhD, Département de Pharmacologie, Université de Bordeaux, for his help in writing this paper.

DISCLOSURE OF CONFLICT OF INTEREST

This study was entirely funded by the Bordeaux University Department of Pharmacology and the Bordeaux University Hospital. The authors are all employed by the Bordeaux University or the Bordeaux University Hospital and declare no conflict of interest in this study.

REFERENCES

1 Chevreul K. Colorectal cancer in France. Eur. J. Health Econ. (2010) **10**(Suppl 1) S15–S20.
2 de Gramont A., Bosset J.F., Milan C. et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J. Clin. Oncol. (1997) **15** 808–815.
3 Cunningham D., Pyrhonen S., James R.D. et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet (1998) **352** 1413–1418.
4 Rougier P., Van Cutsem E., Bajetta E. et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet (1998) **352** 1407–1412.
5 de Gramont A., Figer A., Seymour M. et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J. Clin. Oncol. (2000) **18** 2938–2947.
6 Cunningham D., Humblet Y., Siena S. et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N. Engl. J. Med. (2004) **351** 337–345.
7 Hurwitz H., Fehrenbacher L., Novotny W. et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N. Engl. J. Med. (2004) **350** 2335–2342.
8 Tournigand C., Andre T., Achille E. et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J. Clin. Oncol. (2004) **22** 229–237.
9 Grothey A. Is there a third-line therapy for metastatic colorectal cancer? Semin. Oncol. (2006) **33** S36–S38.
10 Guglielmi A.P., Sobrero A.F. Second-line therapy for advanced colorectal cancer. Gastrointest Cancer Res. (2007) **1** 57–63.
11 Kohne C.H., Lenz H.J. Chemotherapy with targeted agents for the treatment of metastatic colorectal cancer. Oncologist (2009) **14** 478–488.
12 Grothey A., Sugrue M.M., Purdie D.M. et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J. Clin. Oncol. (2008) **26** 5326–5334.
13 Kozloff M., Yood M.U., Berlin J. et al. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. Oncologist (2009) **14** 862–870.
14 VIDAL. Le dictionnaire VIDAL, VIDAL, Paris, 2005.
15 Bouche O., Conroy T., Michel P., Penna C., Tournigand C. Metastatic colorectal cancer. Gastroenterol. Clin. Biol. (2006) **30** (Spec No 2) 2S30–2S42.
16 Legoux J.L., Lehur P.A., Penna C., Calais G., Roseau G., Calan L.D. Rectal cancer. Gastroenterol. Clin. Biol. (2006) **30** (Spec No 2), 2S43–2S51.
17 Rougier P., Andre T., Panis Y., Colin P., Stremsdoerfer N., Laurent-Puig P. Colon cancer. Gastroenterol. Clin. Biol. (2006) **30** (Spec No 2), 2S24–2S29.
18 Société Nationale Française de Gastroentérologie. Thésaurus National de Cancérologie digestive. January 2009.
19 Institut National du Cancer. Référentiels de bon usage hor GHS. Cancer digestifs. Décembre 2006.
20 Société Nationale Française de Gastroentérologie. Thésaurus National de Cancérologie digestive. Décembre 2009.
21 Société Nationale Française de Gastroentérologie. Thésaurus National de Cancérologie digestive. Janvier 2009.
22 Yildiz R., Buyukberber S., Uner A. et al. Bevacizumab plus irinotecan-based therapy in metastatic colorectal cancer patients previously treated with oxaliplatin-based regimens. Cancer Invest. (2010) **28** 33–37.