

Association of Prognostic Value of Primary Tumor Location in Stage III Colon Cancer With *RAS* and *BRAF* Mutational Status

Julien Taieb, MD, PhD; Hampig Raphael Kourie, MD; Jean-François Emile, MD, PhD; Karine Le Malicot, MS; Ralyath Balogoun, PhD; Josep Tabernero, MD, PhD; Enrico Mini, MD, PhD; Gunnar Folprecht, MD, PhD; Jean-Luc Van Laethem, MD, PhD; Claire Mulot, MS; Olivier Bouché, MD, PhD; Thomas Aparicio, MD, PhD; Pierre Michel, MD, PhD; Josef Thaler, MD, PhD; John Bridgewater, MD; Eric Van Cutsem, MD, PhD; Géraldine Perkins, MD, PhD; Come Lepage, MD, PhD; Ramon Salazar, MD, PhD; Pierre Laurent-Puig, MD, PhD; for the Pan-European Trials in Alimentary Tract Cancer (PETACC)-8 Investigators

+ Supplemental content

IMPORTANCE We know of no data on the prognostic value of primary tumor location (PTL) according to *BRAF*, *RAS*, and microsatellite instability (MSI) status in patients who have undergone resection for colon cancer (CC) and have been treated with current standard adjuvant chemotherapy.

OBJECTIVE To determine the prognostic and predictive value of PTL according to *BRAF*, *RAS*, and MSI status in patients with stage III CC receiving adjuvant treatment with FOLFOX (folinic acid [leucovorin calcium], fluorouracil, and oxaliplatin) with or without cetuximab.

DESIGN, SETTING, AND PARTICIPANTS This study included patients with available tumor blocks of resected stage III colon adenocarcinoma who participated in the Pan-European Trials in Alimentary Tract Cancer (PETACC)-8 phase 3 randomized trial. Among the 2559 patients who underwent randomization, 1900 were screened by next-generation sequencing, which showed that 1869 had full information concerning PTL. We categorized primary tumor site as located proximal (right) or distal (left) to the splenic flexure.

MAIN OUTCOMES AND MEASURES The associations between PTL (right- vs left-sided) and disease-free survival (DFS), survival after relapse (SAR), and overall survival (OS) were assessed by Cox models and adjusted for clinical and pathological features, treatment, and MSI, *BRAF*, and *RAS* status.

RESULTS Among the 1869 patients (1056 [57%] male; mean [SD] age, 59.4 [9.5] years) with full molecular data analyzed, 755 (40%) had a right-sided tumor, 164 (10%) had MSI, 942 (50%) had *RAS* mutations, and 212 (11%) had *BRAF* mutations. Right-sided tumor location was not prognostic for DFS in the whole population but was associated with a shorter SAR (hazard ratio [HR], 1.54; 95% CI, 1.23-1.93; $P = .001$) and OS (HR, 1.25; 95% CI, 1.02-1.54; $P = .03$). When looking at DFS in the different molecular subgroups, we found similar results for microsatellite-stable tumors and tumors with MSI; a better DFS in right-sided vs left-sided tumors in patients with *RAS* mutations (HR, 0.80; 95% CI, 0.64-1.00; $P = .046$); and a worse DFS in right-sided vs left-sided tumors in patients with *RAS* and *BRAF* double wild type (HR, 1.39; 95% CI, 1.01-1.92; $P = .04$). These results were found independently of the treatment received, and no beneficial effect of cetuximab on DFS or OS was observed in left-sided tumors.

CONCLUSIONS AND RELEVANCE Although right-sided tumor location is associated with poor survival in patients with metastatic CC as previously reported, the association with disease recurrence appears to vary for patients with stage III CC and *RAS* or *BRAF* mutations vs those with double wild type.

JAMA Oncol. 2018;4(6):1-8. doi:10.1001/jamaoncol.2017.3695
Published online November 22, 2017.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The PETACC-8 Investigators are listed at the end of the article.

Corresponding Author: Julien Taieb, MD, PhD, Pompidou European Hospital, Department of Hepatogastroenterology and GI Oncology, Sorbonne Paris Cité, Université Paris Descartes, 20 rue Leblanc, 75015 Paris, France (jtaieb75@gmail.com).

Biological and molecular factors such as microsatellite instability (MSI) and KRAS and BRAF mutational status have recently been proposed as prognostic factors in nonmetastatic colorectal cancers and may play a role as stratification factors in future adjuvant trials.¹

While the prognostic value of primary tumor location (PTL) for overall survival (OS) in metastatic colorectal cancer (mCRC) seems clear and consistent in reports in recent decades, the prognostic impact of PTL for stage III nonmetastatic colorectal cancer remains unclear. Moreover, as many recent publications on PTL deal with patients with mCRC treated with anti-epidermal growth factor receptors, very few data sets report results in patients with RAS mutations. Finally, greater effectiveness of anti-epidermal growth factor receptors in left-sided tumors has also been suggested in patients with mCRC.²

We therefore examined the relationship between PTL and disease-free survival (DFS), OS, and survival after recurrence (SAR) in patients with stage III colon cancer (CC) who received adjuvant FOLFOX (folinic acid [leucovorin calcium], fluorouracil, and oxaliplatin) alone or combined with cetuximab. These data were then assessed according to MSI, RAS, and BRAF status and treatment received.

Methods

Study Population and Patient Characteristics

All patients analyzed gave their informed consent for translational research projects in addition to the informed consent given for the therapeutic trial. Patients with histologically proven stage III resected colon adenocarcinoma for the previously reported Pan-European Trials in Alimentary Tract Cancer (PETACC)-8 trial were randomly assigned to receive 6 months of FOLFOX or FOLFOX plus cetuximab.³ We categorized PTL as on the right or the left of the splenic flexure.

Key Points

Question Is primary tumor location prognostic or predictive, according to BRAF, RAS, and microsatellite instability status, in patients with stage III colon cancer receiving adjuvant FOLFOX (folinic acid [leucovorin calcium], fluorouracil, and oxaliplatin) with or without cetuximab?

Findings For patients with RAS mutant or BRAF mutant genotype, disease-free survival was better with right-sided vs left-sided tumors. For patients who had RAS and BRAF double wild type, disease-free survival was worse in those with right-sided tumors. No predictive effect of sidedness for cetuximab efficacy was found.

Meaning The association between sidedness and disease recurrence varied between patients with RAS or BRAF wild type and those with a mutation; no beneficial effect of cetuximab on disease-free survival and overall survival in patients with left-sided tumors was seen in the adjuvant setting.

Microsatellite Status Determination, DNA Extraction, and Mutation Analysis

Tumor samples were prospectively banked. Methods for MSI, KRAS, NRAS, and BRAF assessments were previously described.^{4,5}

Statistical Analysis

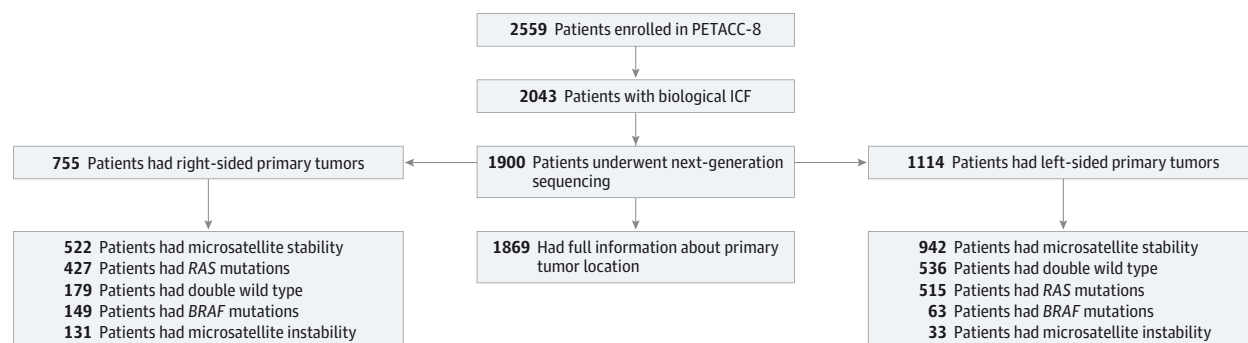
The DFS, OS, and SAR curves were estimated with the Kaplan-Meier method. Differences between groups of patients were analyzed using log-rank tests and Cox models with the SAS statistical software package version 9.4 (SAS Institute). A P value (1-sided) of less than .05 was considered significant.

Results

Study Population

Of 2559 patients who underwent randomization, 1900 were screened by next-generation sequencing, which showed that

Figure 1. Flow of Patients in PETACC-8 Trial Molecular Study



Of 2559 patients who underwent randomization, 1900 were screened by next-generation sequencing, which showed that 1869 had full information concerning PTL. Of those 1869 patients, 755 (40%) had right-sided tumors, 164

(10%) had microsatellite instability, 942 (50%) had RAS mutations, and 212 (11%) had BRAF mutations.

1869 patients had full information concerning PTL (Figure 1). Of those 1869 patients, 755 (40%) had right-sided tumors, 164 (10%) had MSI, 942 (50%) had *RAS* mutations, and 212 (11%) had *BRAF* mutations. Demographic and clinical characteristics of the patients in the molecular study ($n = 1869$) were not statistically different from those excluded from the molecular study ($n = 690$) (eTable 1 in the Supplement). All demographic and molecular characteristics according to sidedness are summarized in eTable 2 and eTable 3 in the Supplement.

Outcome in the Whole Population

No difference was noted in DFS when comparing right-sided with left-sided stage III CC in the whole study population (Figure 2A). However, SAR (hazard ratio [HR], 1.54; 95% CI, 1.23-1.93; $P = .001$) and OS (HR, 1.25; 95% CI, 1.02-1.54; $P = .03$) were significantly better for left-sided tumors, and 5-year SAR and OS rates were 31.1% vs 18.5% and 84.2% vs 78.6% for left-sided vs right-sided tumors, respectively (Figure 2B and C).

Multivariable Analysis

In multivariable analysis, the following were associated with shorter DFS: histopathology grades 3 and 4; TNM categories pT3, pT4, and pN2; *RAS* mutations; Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1 and 2; and bowel obstruction and/or perforation. Overall survival was also worse in patients with histopathology grades 3 and 4; TNM categories pT3, pT4, and pN2; *RAS* mutations; ECOG PS 1 and 2; and bowel obstruction and/or perforation. Moreover, patients with MSI tumors had better OS. Only right-sided, grade 3 or 4, pN2, and *BRAF*-mutated tumors were associated with shorter SAR (eTable 4 in the Supplement).

Outcome in Different Molecular Subgroups

All molecular subgroups' outcomes are summarized in eTable 5 in the Supplement.

No difference in DFS was reported for right-sided vs left-sided tumors in microsatellite-stable or MSI tumors (eFigure 1 in the Supplement).

In patients with double wild-type genome, those with right-sided primary tumors had a shorter DFS compared with those with left-sided tumors (HR, 1.39; 95% CI, 1.01-1.92; $P = .04$), with 3-year DFS rates of 75.7% and 81.9%, respectively (Figure 3A). However, these results were not significant (HR, 1.22; 95% CI, 0.86-1.72; $P = .26$) when adjusted for histopathological grade, pT, pN, ECOG PS, and bowel obstruction and/or perforation.

For *RAS*-mutated tumors, patients with right-sided primary tumors had a longer DFS compared with those with left-sided tumors (HR, 0.80; 95% CI, 0.64-1.00; $P = .046$), with 3-year DFS of 73.4% and 69.6%, respectively (Figure 3B). These results were still significant (HR, 0.75; 95% CI, 0.59-0.95; $P = .02$) when adjusted for histopathological grade, pT, pN, ECOG PS, and bowel obstruction and/or perforation in a multivariable model. The same trends were observed when looking at *BRAF*-mutated tumors (eTable 5 in the Supplement).

Treatment Outcomes in Right-Sided vs Left-Sided CC

When separately analyzing patients treated with FOLFOX alone or FOLFOX plus cetuximab, the association of PTL with DFS, OS, and SAR was comparable to that described in the general population (eFigure 2 in the Supplement).

In patients with double wild type, there was no statistical difference in DFS when comparing FOLFOX plus cetuximab vs FOLFOX alone in both right-sided tumors (HR, 0.89; 95% CI, 0.78-1.26; $P = .94$) and left-sided tumors (HR, 0.84; 95% CI, 0.59-1.21; $P = .34$) (eFigure 3 in the Supplement).

Discussion

These data describe the prognostic value of PTL in stage III CC treated with FOLFOX with full *RAS*, *BRAF*, and MSI assessment. We confirmed historical data that right-sided tumors were older and more likely to be poorly differentiated, exhibit vascular invasion or lymphatic infiltration, and have MSI and *BRAF* mutation.^{6,7} Similarly, at disease relapse, right-sided tumors had a worse prognosis. This result is similar in all molecular subgroups presently characterized and is in accordance with the currently published results of PTL prognostic value in the metastatic setting.²

However, when looking at disease recurrence, patients with *RAS*-mutated and/or *BRAF*-mutated right-sided tumors had a better DFS than left-sided tumors. Right-sided tumors remained of poor prognosis regarding DFS only in patients with double wild type.

Some recent studies demonstrated that PTL may be considered as a predictive factor in *RAS* wild-type mCRC treated with chemotherapy and cetuximab.^{2,8-11} In the present work, no benefit of adding cetuximab to FOLFOX was observed in our population of patients with stage III left-sided tumors; nor was any detrimental effect of adding cetuximab observed in right-sided tumors.

The major strengths of our study are that patients are coming from a randomized, prospective, registration-designed phase 3 trial; that all patients were treated with the current standard FOLFOX chemotherapy regimen (with or without cetuximab) in this setting; and that a full *RAS* and *BRAF* mutational profile using next-generation sequencing for all included patients (not limited to *KRAS* and *BRAFV600E*) was determined together with the MSI assessment.

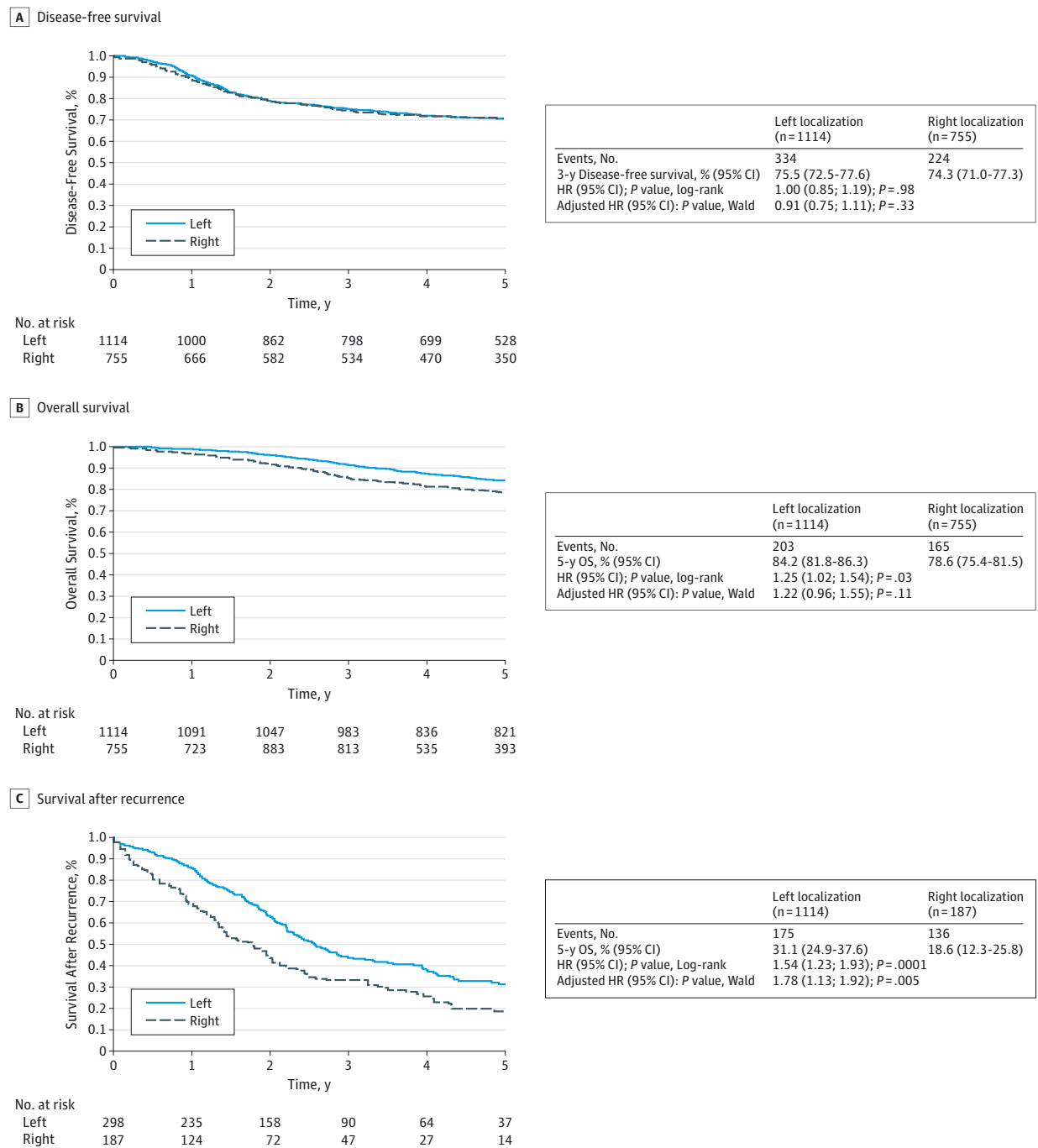
Limitations

Our work also has limitations. The post hoc design of the present analysis and the limited number of patients with *BRAF* mutations and MSI tumors led to small subgroups for some of the analyses performed.

Conclusions

Although PTL does not seem to be associated with DFS in the whole study population, opposite sidedness prognostic values are observed for *RAS* and *BRAF* wild-type and mutant tumors. A larger analysis that uses all currently available adju-

Figure 2. Disease-Free Survival, Overall Survival, and Survival After Recurrence in the Whole Population According to Primary Tumor Location

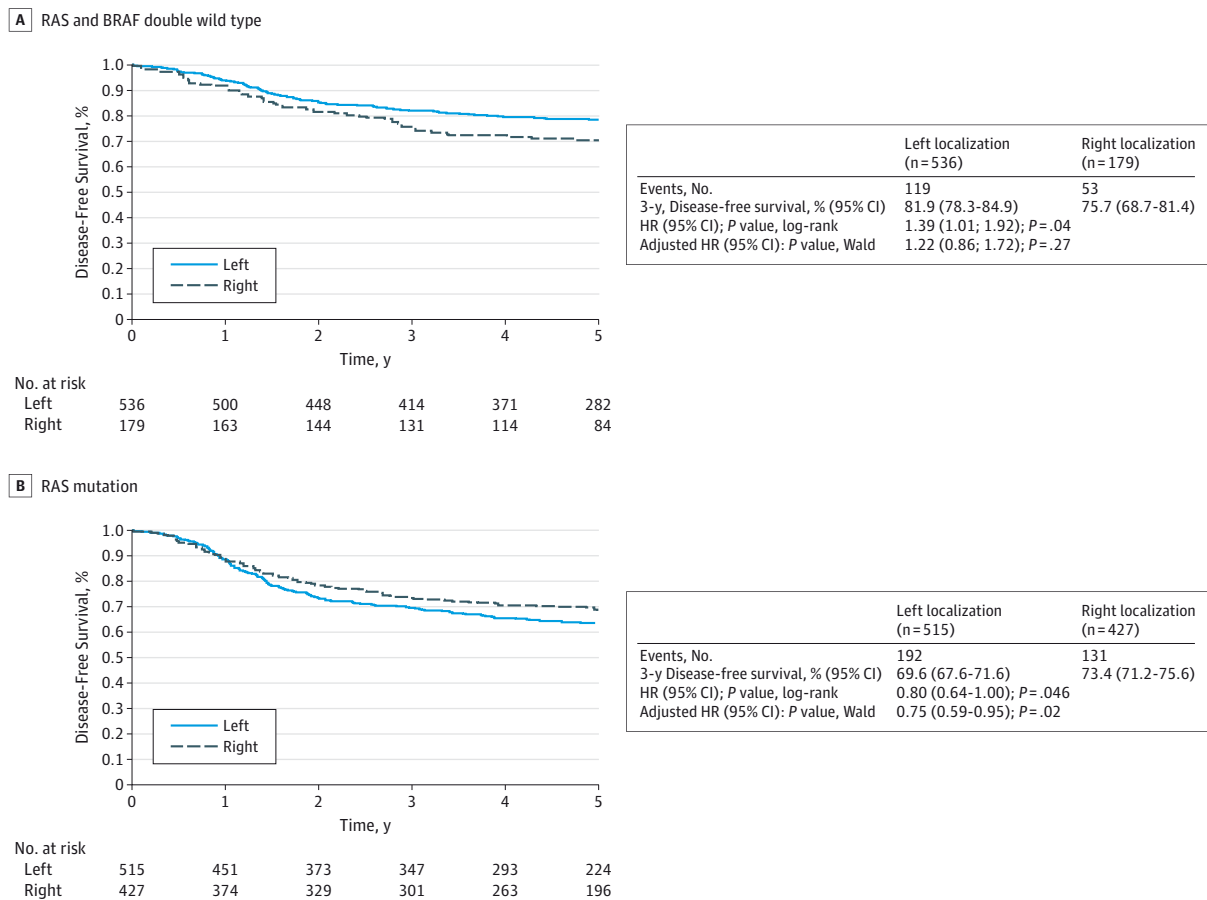


A, No difference was noted in disease-free survival when comparing right-sided with left-sided stage III colon cancer in the whole study population. B, Overall survival was significantly better for left-sided tumors. C, Survival after

recurrence was significantly better for left-sided tumors. HR indicates hazard ratio.

vant trials with complete molecular analysis and takes into account other prognostic molecular data from the consensus molecular subtypes¹² is needed to confirm these first results and to better determine the molecular differences explaining them.

Figure 3. Disease-Free Survival in Patients With RAS and BRAF Double Wild Type and RAS Mutations According to the Primary Tumor Location



A, In patients with RAS and BRAF double wild type, those with right-sided primary tumors had a shorter disease-free survival compared with those with left-sided tumors. B, For RAS-mutated tumors, patients with right-sided primary

tumors had a longer disease-free survival compared with those with left-sided tumors.

ARTICLE INFORMATION

Accepted for Publication: August 18, 2017.

Published Online: November 22, 2017.

doi:10.1001/jamaoncol.2017.3695

Author Affiliations: Sorbonne Paris Cité, Université Paris Descartes, Department of Hepatogastroenterology and GI Oncology, Hôpital Européen Georges Pompidou, Paris, France (Taieb, Kourie); Pathology Department, Ambroise Paré Hospital, Boulogne-Billancourt, France (Emile); Fédération Francophone de Cancérologie Digestive (FFCD), Dijon, France (Le Malicot, Lepage); Université Paris Descartes, Sorbonne Paris Cité, France (Balogoun, Mulot, Laurent-Puig); Assistance Publique-Hôpitaux de Paris, Department of Biology, Hôpital Européen Georges Pompidou, INSERM UMR-S1147, Paris, France (Balogoun, Mulot, Laurent-Puig); Medical Oncology Department, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), CIBERONC, Universitat Autònoma de Barcelona, Spanish Gastrointestinal Tumours TTD Group, Barcelona, Spain (Taberbero); Section of Internal Medicine, Department of Experimental and Clinical Medicine, University of

Florence, Florence, Italy (Mini); Medical Department I, University Hospital Carl Gustav Carus, Dresden, Germany (Folprecht); Department of Gastroenterology, Hôpital Universitaire Erasme, Brussels, Belgium (Van Laethem); Department of Hepato-Gastroenterology, Reims University Hospital, Reims, France (Bouché); Gastroenterology Department, CHU Saint Louis, Assistance Publique-Hôpitaux de Paris and Université Paris 7, Sorbonne Paris Cité, Paris, France (Aparicio); Department of Gastroenterology, Rouen University Hospital, University of Rouen, Rouen, France (Michel); Department of Internal Medicine IV, Klinikum Wels-Grieskirchen, Wels, Austria (Thaler); UCL Cancer Institute, University College London, London, England (Bridgewater); Digestive Oncology, University Hospitals Leuven and KU Leuven, Leuven, Belgium (Van Cutsem, Perkins); Hepato-Gastroenterology Department, Dijon University Hospital and INSERM U 866, Dijon, France (Lepage); Catalan Institute of Oncology (IDIBELL), Universitat de Barcelona, CIBERONC, Spanish Gastrointestinal Tumours TTD Group, Barcelona, Spain (Salazar).

Author Contributions: Drs Taieb and Le Malicot had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Taieb, Le Malicot, Taberbero, Mini, Folprecht, Van Laethem, Mulot, Bouché, Aparicio, Michel, Thaler, Bridgewater, Perkins, Lepage, Laurent-Puig. *Acquisition, analysis, or interpretation of data:* Taieb, Kourie, Emile, Le Malicot, Balogoun, Taberbero, Mini, Folprecht, Van Laethem, Mulot, Bouché, Aparicio, Michel, Thaler, Bridgewater, Perkins, Lepage, Laurent-Puig. *Drafting of the manuscript:* Taieb, Kourie, Le Malicot, Taberbero, Laurent-Puig. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Taieb, Le Malicot, Laurent-Puig. *Obtained funding:* Taieb. *Administrative, technical, or material support:* Emile, Balogoun, Taberbero, Folprecht, Van Laethem, Mulot, Bouché, Thaler, Bridgewater, Lepage. *Study supervision:* Taieb, Thaler, Bridgewater, Salazar, Laurent-Puig.

Conflict of Interest Disclosures: Dr Taieb has participated in consulting and/or advisory boards for Merck KGaA, Sanofi, Roche/Genentech, Pfizer, and Amgen; Dr Tabernero for Amgen, ImClone Systems, Lilly, Millennium, Novartis, Roche/Genentech, Sanofi, Celgene, Chugai Pharma, Taiho Pharmaceutical, Boehringer Ingelheim, and Merck KGaA; Dr Folprecht for Merck KGaA, Roche/Genentech, Sanofi-Aventis, Bayer, Lilly, Servier, and Bristol-Myers Squibb; Dr Salazar for Merck KGaA, Amgen, Novartis, and Lilly; and Dr Laurent-Puig for Sanofi, Merck KGaA, Amgen, Roche, Genomic Health, Myriad Genetics, and Pfizer. Dr Bridgewater received honoraria from Merck KGaA; Dr Emile from Amgen and Merck KGaA. Dr Folprecht has received research funding from Merck KGaA. Dr Van Cutsem received research funding from Amgen, Bayer, Boehringer Ingelheim, Celgene, Ipsen, Merck KGaA, Novartis, Roche, and Sanofi. No other disclosures are reported.

Funding/Support: The PETACC-8 study was sponsored by the Fédération Francophone de Cancérologie Digestive (FFCD). Merck KGaA provided the study cetuximab and financial support for study management. Sanofi-Aventis provided financial support for the provision of oxaliplatin to Belgian sites when necessary.

Role of Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The FFCD was responsible for study management, and Merck KGaA provided financial support for study management.

PETACC-8 Investigators:

Country

Group(s), Coordinator(s)

Principle investigator(s) (Centre)

Austria

Austrian Breast and Colorectal cancer Study Group (ABCSCG), Joseph Thaler

Josef Thaler (Klinikum Kreuzschwern Wels, Wels); Richard Greil (LKH Salzburg); Johannes Gaenzler (BKH Hall in Tirol, Hall in Tirol); Wolfgang Eisterer (University Klinik Innsbruck, Innsbruck); Joerg Tschmelitsch (KH Barmherzige Brüder St. Veit / Glan); Felix Keil (LKH Leoben, Leoben); Hellmut Samonigg (Landeskrankenhaus Graz Medizinische Universitätsklinik, Graz); August Zabernigg (BKH Kufstein, Kufstein); Franz Schmid (LKH Bregenz, Bregenz); Günther Steger (Universitätsklinik für Innere Medizin I, Wein); Robert Steinacher (LKH Wolfsberg, LKH); Johannes Andel (LKH Steyr, Steyr); Björn Jagdt, (a.ö. Krankenhaus d. Barmherz. Schwest. Ried, Ried); Alois Lang (LKH Rankweil, Rankweil); Michael Fridrik (AKH Linz, Linz); Reinhold Függer (A.ö. Krankenhaus d. Elisabethinen Linz); Friedrich Hofbauer (LKH Oberpullendorf, Oberpullendorf); Ewald Woell (KH St. Vinzenz Zams, Zams); Dietmar Geissler (LKH Klagenfurt, Klagenfurt); Alfred Lenauer (KH Wiener Neustadt, Wiener Neustadt); Manfred Prager (A.ö. KH Oberwart, Oberwart)

Belgium

Belgian Group of Digestive Oncology (BGDO),

Jean-Luc Van Laethem and Eric Van Cutsem

Geert D'Haens (Imelda Ziekenhuis, Bonheiden); Gauthier Demolin (Clinique St-Joseph, Liège); Joseph Kerger (Cliniques Universitaires de Mont-

Godinne U.C.L. Yvoir); Guido Deboever (A. Z. St-Jozef, Oostende); Gilbert Ghillebert (Heilig Hart Ziekenhuis, Roeselare); Marc Polus (C. H. U. Sart-Tilman, Liège); Eric Van Cutsem (University Hospitals, Leuven); Hassan Rezaie Kalantari (C. H. Peltzer-La Tourelle, Verviers); Thierry Delaunoy (Centre Hospitalier de Jolimont-Lobbès, La Louvière); Jean Charles Goeminne (Clinique et Maternité Sainte-Elisabeth, Namur); Marc Peeters (Universitair Ziekenhuis Gent, Gent); Philippe Vergauwe (AZ Groeninge-Campus Kennedylaan, Kortrijk); Ghislain Houbiers (Centre médical de L'Avenue, Liège); Yves Humblet (Cliniques Universitaires Saint-Luc, Brussels); Jos Janssens (St-Elisabeth Ziekenhuis, Turnhout); Dirk Schrijvers (ZNA Middelheim, Antwerpen); Erik Vanderstraeten (AZ Maria Middelaere, Gent); Jean-Luc Van Laethem (ULB Hôpital Erasme, Brussels); Jan Vermorken (UZ Antwerpen, Edegem); Daniel Van Daele (Clinique Notre-Dame de Grâce, Gosselies); Michel Ferrante (AZ Sint-Maarten, Mechelen); Frederic Forget (Centre Hospitalier de l'Ardenne, Libramont); Alain Hendlisz (Jules Bordetinstituut, Brussels)

Denmark

Lone Nørgård Petersen

Mette Yilmaz (Aalborg Sygehus-Afsnit Syd, Aalborg); Svend Erik Nielsen (Hillerød Hospital, Hillerød); Lene Vestermarck (Odense Universitets Hospital, Odense); Jim Larsen (Roskilde Amtssygehus, Roskilde)

France Fédération Francophone de Cancérologie Digestive (FFCD), Jean François Seitz; Fédération Nationale des Centres de Lutte Contre le Cancer (UNICANCER), Marc Ychou; Fédération Nationale des Centres de Lutte Contre le Cancer Association Européenne de Recherche en Oncologie (AERO), Ayman Zawadi

Mohamed-Ayman Zawadi (Centre Hospitalier Les Oudairies, La Roche sur Yon); Olivier Bouche (CHU de Reims, Hôpital Robert Debre, Reims); Laurent Mineur (Institut Sainte Catherine, Avignon); Jaafar Bennouna-Louridi (CRLCC René Gauducheau, St Herblain); Louis Marie Dourthe, (Clinique Sainte Anne, Strasbourg); Marc Ychou (Centre Regional Val d'Aurelle Paul Lamarque, Montpellier); Eveline Boucher (CRLC Eugène Marquis, Rennes); Julien Taieb (Hôpital Européen Georges Pompidou, Paris); Denis Pezet (CHU Estaing, Clermond Ferrand); Françoise Desseigne (Centre Leon Berard, Lyon); Michel Ducreux (Institut Gustave Roussy Villejuif); Patrick Texereau (Hopital Layne, Mont-de-Marsan); Laurent Miglianico (Centre Hospitalier Privé Saint-Grégoire (Rennes), Saint-Grégoire); Philippe Rougier (Hôpital Européen Georges Pompidou, Paris); Serge Fratte (Centre Hospitalier de Belfort-Montbeliard, Belfort); Charles-Briac Levasche (Polyclinique Francheville, Perigueux); Yacine Merrouche, (Institut de Cancérologie de la Loire, Saint-Priest-En-Jarez); Stephen Ellis (Clinique Saint Pierre, Perpignan); Christophe Locher (CH Meaux, Meaux); Jean-Francois Ramee (Centre Catherine de Sienne, Nantes); Claire Garnier (UMGEC-Institut Daniel HOLLARD, Grenoble); Frederic Viret (Institut Paoli Calmettes, Marseille); Bruno Chauftert (Centre Georges François Leclerc, Dijon); Isabelle Cojean-Zelek (Hopital Croix Saint Simon, Paris); Pierre Michel (Hopital Charles Nicolle, Rouen); Cedric Lecaille (Polyclinique Bordeaux Nord Aquitaine, Bordeaux); Christian Borel (CLCC Paul Straus, Strasbourg); Jean-Francois Seitz (CHU de la Timone, Marseille); Denis Smith (Groupe

Hospitalier Saint-Andre, Bordeaux); Catherine Lombard-Bohas (Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon); Thierry Andre (Groupe Hospitalier PitieSalpêtrière, Paris); Jean-Marc Gornet, (Hopital Saint Louis, Paris); Francine Fein (CHU de Besancon, Hopital Jean Minjot, Besançon); Marie-Aude Coulonsfairs (Centre Hospitalier du Mans, Le Mans); Marie-Christine Kaminsky (Centre Alexis Vautrin Brabois, Vandoeuvre les Nancy); Jean-Paul Lagasse (CHR d'Orléans La Source, Orléans); Dominique Luet (CRLCC Paul Papin, Angiers); Pierre-Luc Etienne (Clinique Armoricaine de Radiologie, Saint-Brieux); Mohamed Gasmî (Hopital Nord de Marseille, Marseille); Andre Vanoli (Clinique Ste-Marie, Chalonsur Saone); Suzanne Nguyen (Centre Hospitalier de Beauvais, Beauvais); Thomas Aparicio (Hôpital Bichat, Paris); Hervé Perrier (Hopital Saint Joseph, Marseille); Noel Stremmsdoerfer (Hopital Pierre Oudot, BourgoinJallieu); Philippe Laplaige (Clinique Saint Côme, La Chaussée St Victor); Dominique Arsene (CHU de Caen, Caen); Dominique Auby (Hôpital Robert Boulin, Libourne); Laurent Bedenne (Hopital du Bocage, Dijon); Romain Coriat (Hopital Cochin, Paris); Bernard Denis (Hopital Pasteur, Colmar); Patrick Geoffroy (Clinique Saint-Vincent, Eprenay); Gilles Piot (Clinique des Ormeaux, Le Havre); Yves Becouarn (CHU de Bordeaux, Bordeaux); Gilbert Bordes (Centre Hospitalier de Digne Les Bains, Digne Les Bains); Gael Deplanque (Hopital Saint Joseph, Paris); Olivier Dupuis (Clinique Victor Hugo, Le Mans); Frederic Fruge (CHU Poitiers-Hôpital la Milétrie, Poitiers); Rosine Guimbaud (Hopital Purpan,Toulouse); Thierry Locmte (Hopital Trousseau - CHU de Tours, Tours); Gérard Lledo (Hopital Prive Jean Mermoz, Lyon); Iradej Sobhani (Hôpital Henri Mondor (GastroEntérologie), Créteil); Amani Asnacios (Hopital Antoine Beclere, Clamart); Ahmed Azzedine (Boulat, Michel, Avignon); Christophe Desauv (Hopital Saint Vincent de Paul-GHICL Lille, Lille); Marie-Pierre Galais (Centre François Baclesse, Caen); Dany Gargot (Centre Hospitalier de Blois, Blois); You-Heng Lam (Hopital de Cholet, Cholet); Abakar Abakar-Mahamat (Hopital l'Arche II, Nice); Jean-Francois Berdad (Clinique Sainte Marguerite, Hyères); Sylviane Catteau (Hopital Duchenne, Boulogne sur Mer); MarieChristine Clavero-Fabri (Clinique Hartman, Levallois Perret); Jean-Francois Codoul (Hopital de Draguignan, Draguignan); Jean-Louis Legoux (Hôpital Haut Levêque, Pessac); Denis Goldfain (Centre Hospitalier General de Dreux, Dreux); Pierre Guichard (Clinique des quatre Pavillons, Lormont); Denis Pere Verge (Hôpital de la Croix Rousse (Gastroentérologie), Lyon); Jocelyne Provencal (Centre Hospitalier d'Annecy, Pringy); Bruno Vedrenne (Hopital E. Muller, Mulhouse); Catherine Brezault-Bonnet (Hopital de Rambouillet, Rambouillet); Denis Cleau (Centre Hospitalier Intercommunal de Vesoul, Vesoul); Jean-Paul Desir (Clinique Pole Sante Republique, Clermont-Ferrand); David Fallik (Polyclinic Jeanne d'Arc Gien); Bruno Garcia (Clinique de Courlancy, Reims); MarieHélène Gaspard (Clinique Claude Bernard, Albi); Dominique Genet (Centre de Cancérologie Chenuieux, Limoges); Johannes Hartwig (Infirmierie Protestante de Lyon, Caluire et Cuire.); Yves Krummel (Centre Hospitalier Selestat, Selestat); Tamara Matysiak Budnik (CH de Nantes Hotel Dieu, Nantes); Vanessa Palascak-Juif (Hopital de HautePierre, Strasbourg); Harizo Randrianarivelo (Centre Frederic Joliot, Rouen);

Yves Rinaldi (Clinique Clairval, Marseille); Albert Aleba (Centre Hospitalier de Niort, Hôpital Georges Renon, Niort); Ariane Darut-Jouve (Centre d'oncologie et Radiothérapie, Dijon); Aimerie de Gramont (Hôpital Saint Antoine, Paris); Herve Hamon (Centre Hospitalier de Valence, Valence); Frederic Wendehenne (Clinique Charcot, Sainte-Foy-les-Lyon)

Germany

Arbeitsgemeinschaft Internistische Onkologie (AIO), Gunnar Folprecht

Axel Matzdorff (Caritasklinik St. Theresia, Saarbruecken); Michael Konrad Stahl (Kliniken EssenMitte-PS, Essen); Wolfgang Schepp (KKH Muenchen Bogenhausen, Muenchen); Martin Burk (Klinikum der Stadt Hanau, Hanau); Lothar Mueller (Onkologische Schwerpunktpraxis, Leer); Gunnar Folprecht (Universitaetsklinikum Carl Gustav Carus, Dresden); Michael Geissler (Staedtische Kliniken Esslingen, Esslingen); Luisa Mantovani-Loeffler (Staedtisches Klinikum St. Georg Leipzig, Leipzig); Thomas Hoehler (Prosper-Hospital, Recklinghausen); Walter Asperger (Krankenhaus St. Elisabeth und St. Barbara, Halle); Hendrik Kroening (Gemeinschaftspraxis, Magdeburg); Ludwig Fischer von Weikersthal (MVZ Gesundheitszentrum St. Marien GmbH, Amberg); Stefan Fuxius (Onkologische Praxis, Heidelberg); Matthias Groschek (Haematologisch-Onkologische Praxis Wuerselen, Wuerselen); Johannes Meiler, Tanja Trarbach (Universitaetsklinikum Essen, Essen); Jacqueline Rauh (Gemeinschaftspraxis Ardeystrasse, Witten); Nicolas Ziegenhagen, Albrecht Kretzschmar (HeliosKliniken Berlin, Berlin); Ullrich Graeven (Kliniken Maria Hilf GmbH, Moenchengladbach); Arnd Nusch (Onkologische Praxis, Velbert); Goetz von Wichert (Universitaetsklinikum, Ulm); Ralf-Dieter Hofheinz (Klinikum der Stadt Mannheim, Mannheim); Gerhard Kleber (Ostalb-Klinikum Aalen, Aalen); Karl-Heinz Schmidt (Johanniter-Krankenhaus Rheinhausen, Duisburg); Ursula Vehling-Kaiser (Gemeinschaftspraxis, Landslut); Claudia Baum, Jochen Schuette (Marien Hospital Duesseldorf GmbH, Duesseldorf); Georg Martin Haag (Universitaetsklinikum Heidelberg, Heidelberg); Wilhelm Holtkamp (Ammerland-Klinik GmbH, Westerstede); Jochen Potenberg (Evangelisches Waldkrankenhaus, Berlin); Tobias Reiber (Praxis fuer Haematologie/Onkologie, Freiberg); Georg Schliesser (Praxis fuer Haematologie und Onkologie, Giessen); Hans-Joachim Schmoll (Martin-Luther-Universitaet Halle-Wittenberg, Halle); Wolfgang Schneider-Kappus (Arztpraxis, Ulm); Wolfgang Abenhardt (Onkologie Praxis im Elisenhof, Muenchen); Claudio Denzlinger (Marienhospital Stuttgart, Stuttgart); Jan Henning, Bartscht Marxsen (Universitaetsklinikum Schleswig-Holstein, Luebeck); Hans Guenter Derigs (Staedtische Kliniken Frankfurt-Hoechst, Frankfurt); Helmut Lambertz (Klinikum Garmisch-Partenkirchen, Garmisch-Partenkirchen); Ingulf Becker-Boost (MVZ Duisburg Sued GmbH, Duisburg); Karel Caca (Klinikum Ludwigsburg, Ludwigsburg); Christian Constantin (Kliniken Lippe-Lemgo GmbH, Lemgo); Thomas Decker (Gemeinschaftspraxis, Ravensburg); Henning Eschenburg (Internistische Gemeinschaftspraxis, Guestraw); Sigrun Gabius (Gemeinschaftspraxis, Rosenheim); Holger Hebart (Klinikum Schwaebisch Gmuend-Stauferklinik, Mutlangen); Albrecht Hoffmeister (Universitaetsklinikum Leipzig, Leipzig); Heinz-August Horst

(Universitaetsklinikum Schleswig-Holstein-Campus Kiel, Kiel); Stephan Kremers (Caritas-Krankenhaus, Lebach); Malte Leithaeuser (Universitaetsmedizin Rostock, Rostock); Sebastian Mueller (Ambulantes Onkologie Zentrum, Ansbach); Siegfried Wagner (Klinikum Deggendorf, Deggendorf); Severin Daum (Charité Universitaetsmedizin Berlin-Campus Charité Mitte, Berlin); Frank Schlegel (St. Antonius-Hospital, Eschweiler); Martina Stauch (Onkologische Schwerpunktpraxis, Kronach); Volker Heinemann (Klinikum der Ludwig-Maximilians-Universitaet, Muenchen)

Italy

Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD), Roberto Labianca; Gruppo Oncologico dell'Italia Meridionale (GOIM), Giuseppe Colucci; Istituto Oncologico Romagnolo (IOR), Dino Amadori; Gruppo Cooperativo Chirurgico Italiano (GOCCI), Enrico Mini; Gruppo Oncologico Nord Ovest (GONO), Alfredo Falcone; Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC), Corrado Boni Evaristo Maiello (IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo); Luciano Latini (Ospedale di Macerata, Macerata); Alberto Zaniboni (Fondazione Poliambulanza Istituto Ospedaliero, Brescia); Dino Amadori (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola); Giuseppe Aprile (Az. Policlinico Universitario di Udine, Udine); Sandro Barni (Azienda Ospedaliera Treviglio-Caravaggio, Treviglio); Rodolfo Mattioli (Ospedale Santa Croce ASUR 3, Fano); Andrea Martoni, Francesca di Fabio (Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Ma, Bologna); Rodolfo Passalacqua (Azienda Ospedaliera Istituti Ospitalieri di Cremona, Cremona); Mario Nicolini, Enzo Pasquini (Ospedale Cervesi, Cattolica); Carla Rabbi, Enrico Aitini (Azienda Ospedaliera Carlo Poma, Mantova); Alberto Ravaoli, Emiliano Tamburini (Ospedale degli Infermi, Rimini); Carlo Barone (Policlinico Universitario Agostino Gemelli, Roma); Guido Biasco (Ospedale Marcello Malpighi Policlinico Sant'Orsola, Bologna); Stefano Tamberi, Angelo Gambi (Ospedale Degli Infermi, Faenza); Claudio Verusio (Ospedale di Saronno, Saronno); Marina Marzola, Giorgio Lelli (Azienda Ospedaliera Universitaria Arcispedale Sant'Anna, Cona (Ferrara)); Corrado Boni (A.O. Arcispedale Santa Maria Nuova, Reggio Emilia); Stefano Cascinu (Azienda Ospedaliera Universitaria Ospedali Riuniti, Ancona); Paolo Bidoli, Massimo Vaghi (Azienda Ospedaliera San Gerardo, Monza); Giorgio Cruciani (Ospedale Umberto I, Luggo); Francesco Di Costanzo (Azienda Ospedaliera Universitaria Careggi, Firenze); Alberto Sobrero (Azienda Ospedaliera San Martino, Genova); Enrico Mini, Stefania Nobili (A.O. Universitaria Careggi, Firenze); Roberto Petrioli (A.O.U. Senese Policlinico Santa Maria alle Scotte, Siena); Massimo Aglietta (Istituto per la Ricerca e la Cura del Cancro, Candiolo); Oscar Alabiso (Ospedale Maggiore della Carità, Novara); Federico Capuzzo, Alfredo Falcone (Presidio Ospedaliero di Livorno, Livorno); Domenico Cristì Corsi (Ospedale "S. Giov. Calibita" Fatebenefratelli, Roma); Roberto Labianca (Ospedali Riuniti di Bergamo, Bergamo); Stefania Salvagni (Azienda Ospedaliera di Parma, Parma); Silvana Chiara (Istituto nazionale per la ricerca sul cancro, Genova) Libero Ciuffreda (A.O. San Giovanni Battista, Torino); Francesco Ferrai (Azienda Ospedaliera San Vincenzo, Taormina); Francesco Giuliani (Istituto Oncologico Giovanni Paolo II IRCCS, Bari); Sara

Lonardi (IOV-Istituto Oncologico Veneto IRCCS, Padova); Nicola Gebbia, Antonio Russo (Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone, Palermo); Giovanni Mantovani, Elena Massa (Università di Cagliari-Presidio Policlinico Monserrato, Monserrato)

Portugal

Grupo Cooperativo do Cancro Digestivo da Associação Portuguesa de Investigação Oncológica (GCCD, APIO), Evaristo Sanches Evaristo Sanches (Instituto Português de Oncologia do Porto Francisco Gentil, Porto); Juan Carlos Mellidez (Hospital Distrital de Aveiro, Aveiro); Pedro Santos (Hospital São Sebastião, EPE, Santa Maria da Feira); Joao Freire (Instituto Portugues de Oncologia, Lison); Cristina Sarmento (Hospital de Sao Joao, Porto); Luis Costa (Hospital de Santa Maria, Lisbon); Antonio Moreira Pinto (Hospital Geral de Santo Antonio, Porto); Sergio Barroso (Hospital Distrital de Beja, Beja); Jorge Espírito Santo (Hospital do Barreiro, Barreiro); Fátima Guedes (Hospital Distrital Figueira da Foz, EPE, Figueira da Foz); Amélia Monteiro (Hospital São Teotónio, EPE, Viseu); Anabela Sa (Hospitais da Universidade de Coimbra, Coimbra); Irene Furtado (Hospital Distrital de Faro, Faro)

Spain

Grupo Español para el Tratamiento de los Tumores Digestivos (TTD), Josep Taberner Ramon Salazar (ICO ÍHospitalet Hospital Duran i Reynals, Barcelona); Enrique Aranda Aguilar (Hospital Reina Sofia, Cordoba); Fernando Rivera Herrero (Hospital Universitario Marques de Valdecilla, Santander); Josep Taberner (Hospital Vall d'Hebron, Barcelona); Javier Sastre Valera (Hospital Clinico San Carlos, Madrid); Manuel Valladares Ayerbes (Complejo Hospitalario Universitario A Coruña, A Coruña); Jaime Feliu Batlle (Hospital Universitario La Paz, Madrid); Silvia Gil (Hospital Carlos Haya, Malaga); Albert Abad Esteve (ICO Badalona-Hospital Germans Trias i Pujol, Barcelona); Carlos Garcia-Giron (Hospital Universitario de Burgos, Burgos); Guillermo Lopez Vivanco (Hospital de Cruces, Vizcaya); Antonia Salud Salvia (Hospital Universitario de Lleida Arnau de Vilanova, Lleida); Vicente Alonso Orduña (Hospital Miguel Servet, Zaragoza); Ruth Vera Garcia (Complejo Hospitalario de Navarra, Pamplona); Javier Gallego (HGU de Elche, Elche-Alicante); Bartomeu Massuti Sureda (Hospital General Universitario de Alicante, Alicante); Jordi Remon (Hospital de Mataro, Barcelona); Maria Jose Safont Aguilera (Hospital General Universitario de Valencia, Valencia); Luis Cirera Noguera (Hospital Mutua de Terrassa, Barcelona); Bernardo Queralt Merino (Hospital Universitari de Girona Dr Josep Trueta, Girona); Cristina Gravalos Castro (Hospital 12 de Octubre, Madrid); Purificación Martínez de Prado (Hospital de Basurto, Bilbao); Carlos Pijaume Pericay (Consorti Hospitalari Parc Tauli, Barcelona); Manuel Constenla Figueiras (Hospital Universitario de Pontevedra, Pontevedra); Inmaculada Guasch Jordan (Hospital Sant Joan de Deu de Manresa, Manresa); Maria Jose Gome Reina (Hospital del Mar, Cadiz); Amelia Lopez-Ladron Garcia (Hospital El Tomillar-Ntra Sra de Valme, Sevilla); Antonio Arrivi Garcia-Ramos (Fundacion Hospital Son Llatzer, Palma Mallorca); Andres Cervantes (Hospital Clinico Universitario de Valencia, Valencia); Carlos Fernandez Martos (Instituto Valenciano de Oncologia, Valencia); Eugenio Marcuello Gaspar (Hospital de la Santa Creu i Sant

Pau, Barcelona); Ines Cabezas Montero (Hospital Universitario Sant Joan de Reus, Tarragona); Pilar Escudero Emperador (Hospital Clinico Universitario Lozano Blesa, Zaragoza); Ana Leon Carbonero (Fundacion Jimenez Diaz, Madrid); Manuel Gallen Castillo (Hospital del Mar, Barcelona); Teresa Garcia Garcia (Hospital Morales Meseguer, Murcia); Jose Garcia Lopez (Hospital Universitario Ramón y Cajal, Madrid); Encarnacion Gonzalez Flores (Hospital Virgen de las Nieves Ruiz de Alda, Granada); Monica Guillot Morales (Hospital Son Espases, Palma de Mallorca); Marta Llanos Muñoz (Hospital Universitario de Canarias, Santa Cruz de Tenerife); Ana López Martín (Hospital Severo Ochoa); Joan Maurel (Hospital Clinic i Provincial, Barcelona); Juan Carlos Camara (Fundacion Hospital Alcorcon, Madrid); Rosario Dueñas Garcia (Hospital Ciudad de Jaen, Jaen); Mercedes Salgado (Complejo Hospitalario Ourense, Ourense); Isabel Hernandez Busquier (Hospital Provincial Castellon, Castellon); Teresa Checa Ruiz (Instituto de Oncologia Corachan, Barcelona); Adelaida Lacasta Muñoz (Hospital. de Donostia, San Sebastian); Miquel Nogue Aliguer (Hospital General de Vic, Vic); Amalia Velasco Ortiz de Taranco (Hospital Universitario de La Princesa, Madrid); Miguel Mendez Ureña (Hospital General de Mostoles, Mostoles); Ferran Losa Gaspa (Consorci Sanitari Creu Roja, Barcelona); Jose Juan Ponce (Hospital Virgen de los Lirios, Alicante); Carlos Bosch Roig (Hospital Universitario. Dr. Peset, Valencia); Pedro Valero Jimenez (Clínica Infanta Luisa, Sevilla); Antonio Galan Brotons (Hospital Sagunto, Sagunto); Santiago Albiol Rodriguez (Hospital Espiritu Santo, Barcelona); Jose Ales Martinez (Hospital Ruber Internacional de Madrid, Madrid); Liliانا Canosa Ruiz (Hospital Torrecardenas, Almeria); Margarita Centelles Ruiz (Hospital Sagrat Cor, Barcelona)

United Kingdom

John Allen Bridgewater

John Bridgewater (North Middlesex University Hospital NHS Trust, London); Rob Glynn-Jones (Centre for Cancer Treatment, Mount Vernon Hospital, Northwood, London); Saad Tahir

(Broomfield Hospital, Chelmsford); Tamas Hickish (Poole Hospital NHS Trust, Poole and Bournemouth Hospital, Bournemouth); Jim Cassidy (Beatson West of Scotland Cancer Centre, Glasgow); Leslie Samuel (Aberdeen Royal Infirmary, Aberdeen)

Disclaimer: Merck KGaA reviewed the manuscript for medical accuracy only before journal submission. The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors.

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