Rationale and Design of the IROCAS Study: Multicenter, International, Randomized Phase 3 Trial Comparing Adjuvant Modified (m) FOLFIRINOX to mFOLFOX6 in Patients With High-Risk Stage III (pT4 and/or N2) Colon Cancer—A UNICANCER GI-PRODIGE Trial

Jaafar Bennouna,[1,2] Thierry André,[3,4] Loïc Campion,[5,6] Sandrine Hiret,[7] Laurent Miglianico,[8] Laurent Mineur,[9] Yann Touchefeu,[1] Pascal Artru,[10] Timothy Asmis,[11] Olivier Bouché,[12] Florence Borde,[13] Petr Kavan,[14] You-Heng Lam,[15] Laetitia-Shana Rajpar,[16] Jean-François Emile,[17] Claire Jouffroy,[18] Sharlene Gill,[19,20] Julien Taïeb[21,22]

Abstract

Background: According to the IDEA trial, 6-month adjuvant chemotherapy should remain the treatment standard in stage III T4 or N2 colon cancer. The relatively poor survival in this high-risk subgroup—a 3-year disease-free survival (DFS) rate of 65%—and the potential synergistic efficacy of 5-fluorouracil (5-FU), oxaliplatin, and irinotecan suggest that FOLFIRINOX may be a regimen of particular interest in this setting. **Patients and Methods:** This multicenter international phase 3 trial (ClinicalTrials.gov NCT02967289) being conducted in 49 centers in France and Canada plans to randomize (1:1; minimization method) 640 patients aged 18 to 70 years with Eastern Cooperative Oncology Group performance status ≤ 1. Randomization occurs within 42 days (with treatment initiated within 56 days) after curative-intent R0 surgical resection of a pT4N1 or pT1-4N2 colon adenocarcinoma. Patients will be randomized to receive adjuvant modified FOLFIRINOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 180 mg/m^2, and 5-FU 2.4 g/m^2 over 46 hours) or modified FOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, 5-FU bolus 400 mg/m^2, then 2.4 g/m^2 over 46 hours) every 2 weeks for 24 weeks (12 cycles). Patients will be followed for 5 years after the end of adjuvant chemotherapy. A gain of 9% in 3-year DFS (primary end point) is expected (74% in the experimental arm vs. 65% in the control arm; α, 5% [2-sided log-rank test]; 1-β, 80%). Secondary end points of this study include 2-year DFS, overall survival, and toxicity.

Clinical Colorectal Cancer, Vol. 18, No. 1, e69-73

Keywords: 5-FU, Adjuvant, Colon cancer, Irinotecan, oxaliplatin

[1]Digestive Oncology, University Hospital of Nantes, Nantes, France
[2]University of Nantes, Nantes, France
[3]Hôpital Saint-Antoine, Assistance Publique-Hôpitaux de Paris, Paris, France
[4]Sorbonne Universités, UMPC Paris 06, Paris, France
[5]Biometrics, ICO Cancer Center, Nantes, France
[6]CRCINA, University of Nantes, INSERM UMR1232, CNRS-ERL6001, Nantes, France
[7]Department of Medical Oncology, ICO Cancer Center, Nantes, France
[8]Centre Hospitalier Privé St Grégoire, Saint Grégoire, France
[9]Institut Sainte Catherine, Avignon, France
[10]Hôpital Privé Jean Mermoz, Lyon, France
[11]Division of Oncology, Allan Blair Cancer Centre, Regina, Saskatchewan, Canada
[12]Service Hépatogastroentérologie et Cancérologie Digestive, CHU Robert Debré, Reims, France
[13]Centre Hospitalier de Saintonges, Saintes, France
[14]Jewish General Hospital-McGill University, Montreal, Canada
[15]Centre Hospitalier de Cholet, Cholet, France
[16]CH Chartres Louis Pasteur-Coudray, Chartres, France
[17]Pathology Department, Ambroise Paré Hospital, Boulogne-Billancourt, France
[18]UNICANCER, Paris, France
[19]Division of Medical Oncology, British Columbia Cancer Agency
[20]University of British Columbia, Vancouver, British Columbia, Canada
[21]Sorbonne Paris Cité, Paris Decartes University
[22]Hôpital Européen Georges-Pompidou, Paris, France

Submitted: May 29, 2018; Revised: Sep 25, 2018; Accepted: Sep 26, 2018; Epub: Oct 19, 2018

Address for correspondence: Jaafar Bennouna, MD, PhD, CHU Nantes, Digestive Oncology, 1 place Alexis-Ricordeau, 44000 Nantes, France
E-mail contact: Jaafar.bennouna@univ-nantes.fr

1533-0028/$ - see frontmatter
https://doi.org/10.1016/j.clcc.2018.09.011

Rationale and Design of IROCAS Study

Introduction

In 1990, Moertel et al[1] validated the use of 5-fluorouracil (5-FU) combined with levamisole (LEV), an antihelmintic drug with immunomodulatory properties, as adjuvant treatment in patients with resected colon cancer classified as stage C (lymph node involvement) according to the former Dukes staging system. With this regimen, the disease-free survival (DFS) rate at $3^1/_2$ years was 63%, versus 47% in the observation arm with surgery alone ($P <$ .0001).

Over the past 28 years, the adjuvant treatment for colon cancer has evolved by successive steps, most often slowly, driven by the results of large randomized pivotal phase 3 trials. Initially studies focused on different administration schedules of 5-FU. In 2004, the NASBP C-04 randomized phase 3 trial suggested abandoning LEV for leucovorin (LV) combined with bolus 5-FU.[2] The Intergroup 0089 study reinforced these data but also added that 6- to 8-month duration of treatment was sufficient and could replace the 12-month previous standard treatment with 5-FU + LEV.[3] Finally, the GERCOR group performed a randomized phase 3 trial challenging the semimonthly regimen for 2 consecutive days (with bolus 5-FU and continuous infusion) against the monthly regimen for 5 consecutive days with bolus 5-FU. DFS was similar between the LV5FU2 and FULV groups (hazard ratio [HR] = 1.04; $P = .74$) and between 24 and 36 weeks (HR = 0.94; $P = .63$).[4] Toxicities were significantly lower in the LV5FU2 group ($P < .01$), thus promoting this schedule as a new standard.

In 2004, a significant breakthrough greatly modified the adjuvant treatment of stage III resected colon cancer by introducing oxaliplatin in the therapeutic schedule.[5] In the MOSAIC trial, for stage III colon cancer, the DFS rate at 3 years was 65.3% and 72.2% (HR = 0.76; 95% confidence interval [CI], 0.62-0.92) in the LV5FU2 and FOLFOX4 arms, respectively. Two other trials, NSABPC-07 and NO16968 (with capecitabine and oxaliplatin), clearly confirmed the gain provided by oxaliplatin in the adjuvant setting.[6,7] Conversely, irinotecan is not an approved drug in the adjuvant setting. The PETAC-3 and the Accord 02/FFCD9802 trials, with LV5FU2 as the standard-therapy arm, failed to demonstrate a statistically significant superiority in the 3-year DFS rate with irinotecan plus LV5FU2, even if the HR was 0.90 (95% CI, 0.79-1.02) in favor of the experimental arm in PETAC-3.[8,9]

Further studies failed to demonstrate an advantage of adding targeted therapy with cetuximab or bevacizumab to the chemotherapy backbone.[10-13] Consequently, 6 months of folinic acid, fluorouracil, and oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin remained the standard treatment regimens for stage III colon cancer until the presentation of the IDEA trial.[14] Three months of capecitabine plus oxaliplatin is now the new recommendation for stage T1, T2, T3, and N1 (low-risk group) disease, while 6 months' duration of adjuvant chemotherapy is still indicated for stage T4 and or/N2 (high-risk group) disease. For this high-risk group, 6 months is superior to 3 months, with a 3-year DFS rate at 64.4% versus 62.7% (HR = 1.12; 95% CI, 1.03-1.23; $P = .01$ for superiority). The French part of the study (IDEA France) reported a similar conclusion for stage T4 and/or N2 disease, with a 3-year DFS rate of 65% in the 6-month arm (vs. 59% in the 3-month arm; HR, 1.38; 95% CI, 1.10-1.73), thus emphasizing the need to improve adjuvant treatment for high-risk stage III colon cancer (T4 and/or N2).[15]

The present randomized phase 3 study evaluates the role of modified (m) FOLFIRINOX in the adjuvant setting compared to the standard FOLFOX6 regimen in high-risk stage III (T4 and/or N2) colon cancer. The rationale for this study is based on the potential synergistic effect of 5-FU plus oxaliplatin and irinotecan combination, which was observed in stage IV colon and pancreatic cancers. The relative poor survival of this subcategory of patients could justify the use of this triplet.

Patients and Methods

Patients and Study Design

The IROCAS study is an open-label randomized (1:1) phase 3 trial conducted in France and Canada comparing the triplet mFOLFIRINOX (experimental arm) with the standard regimen, mFOLFOX6, in patients with high-risk stage III T4 and/or N2 resectable colon cancer. Eligible patients, aged $\geq$ 18 years and $<$ 71 years and with Eastern Cooperative Oncology Group performance status $\leq$ 1, undergo R0 surgical resection within 42 days before randomization. Eligibility criteria are listed in Table 1. The randomization is adjusted for the following stratification factors: perforation or urgent surgery versus no perforation and no urgent surgery; T1-T3N2 versus T4aN1 versus T4bN1 versus T4N2 disease; right colon (right of splenic flexure) versus left colon; and country (France vs. Canada). Patients are enrolled onto one of the two arms and receive treatment every 14 days for 12 cycles (Figure 1): mFOLFIRINOX with oxaliplatin 85 mg/m^2, L-leucovorin 200 mg/m^2, irinotecan 180 mg/m^2 on day 1 and continuous intravenous 5-FU 2400 mg/m^2 for 46 hours; or mFOLFOX6 with oxaliplatin 85 mg/m^2, L-leucovorin 200 mg/m^2, bolus 5-FU 400 mg/m^2 on day 1, and continuous intravenous 5-FU 2400 mg/m^2 for 46 hours.

This study (ClinicalTrials.gov NCT02967289) is performed in accordance with the Declaration of Helsinki and good clinical practice guidelines. The study was approved by a French ethics committee. All patients provided written informed consent before starting the study.

Results

The primary objective of this study is 3-year DFS, defined as the time from date of randomization to date of first local, regional, or distant relapse, second colorectal cancer, or death from any cause, including treatment-related death. Secondary objectives include DFS at 2 years, overall survival, and toxicities according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Tumor assessment is recommended to be performed at baseline and every 3 months, with alternating abdominal echography and thoracoabdominal and pelvic computed tomographic scan after surgery for the first 2 years, then every 6 months for the next 3 years. The carcinoembryonic antigen tumor markers will be assessed according to the same schedule. Five years after surgery, a thoracoabdominal and pelvic computed tomographic scan is recommended once a year.

Table 1 Inclusion and Exclusion Criteria

Inclusion Criteria
• Age $\geq$ 18 years and $<$ 71 years.
• ECOG PS $\leq$ 1.
• Pathologically confirmed high-risk stage III colon adenocarcinoma, restricted to pT4N1 or pT1-4N2 tumor.
• Curative R0 surgical resection within 42 days before randomization.
• Undergone surgery for colon cancer, defined as tumor location $>$ 12 cm from anal verge by endoscopy and/or above peritoneal reflection at surgery (high rectum), without gross or microscopic evidence of residual disease after surgery with curative intent.
• Study drug treatment initiated $<$ 56 days after surgery.
• No prior chemotherapy.
• No prior abdominal or pelvic irradiation.
• Adequate organ function:
○ ANC $\geq 2 \times 10^9$/L.
○ Hemoglobin $\geq$ 9 g/dL.
○ Platelets $\geq 100 \times 10^9$/L.
○ AST/ALT $\leq 2.5 \times$ ULN.
○ Alkaline phosphatase $\leq 2.5 \times$ ULN.
○ Total bilirubin $\leq 1.5 \times$ ULN.
○ Creatinine clearance $\geq$ 50 mL/min (Cockcroft-Gault formula).
○ Kalemia, magnesemia, calcemia $\geq$ 1 LLN.
○ CEA $\leq$ 10 ng/mL after surgery (during screening period).
• Adequate contraception if applicable.
• Able and willing to comply with study procedures as per protocol.
• Able to understand and willing to sign and date written voluntary informed consent form at screening visit before any protocol-specific procedures.
• Affiliated with social security regimen.
• Life expectancy $\geq$ 5 years.
Exclusion Criteria
• Major surgical procedure, open biopsy or significant traumatic injury within 28 days before study treatment start.
• Incompletely healed wounds or anticipation of need for major surgical procedure during course of study.
• Metastatic disease.
• Presence of inflammatory bowel disease and/or ileus.
• Known hypersensitivity reaction to any study treatment component.
• Pregnancy (absence confirmed by β-hCG test) or breast-feeding.
• Clinically relevant coronary artery disease or history of myocardial infarction in last 12 months, or high risk of uncontrolled arrhythmia (men, QT/QTc $\geq$ 450 ms; women, QT/QTc $\geq$ 470 ms).
• Previous malignancy in last 5 years, except curative treated basal-cell skin carcinoma and/or in-situ cervix carcinoma.
• Medical, geographic, sociologic, psychological, or legal conditions that would not permit patient to complete study or sign informed consent.
• History or current evidence at physical examination of central nervous system disease or peripheral neuropathy grade 1 or higher according to CTCAE 4.03.
• Any significant disease which, in investigator's opinion, would exclude patient from study.
• Known dihydropyrimidine dehydrogenase deficiency or UGT1A1 homozygous 7/7.
• Already included in another therapeutic trial involving the experimental drug.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; β-hCG = β-human chorionic gonadotropin; CEA = carcinoembryonic antigen; CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; LLN = lower limit of normal; ULN = upper limit of normal.

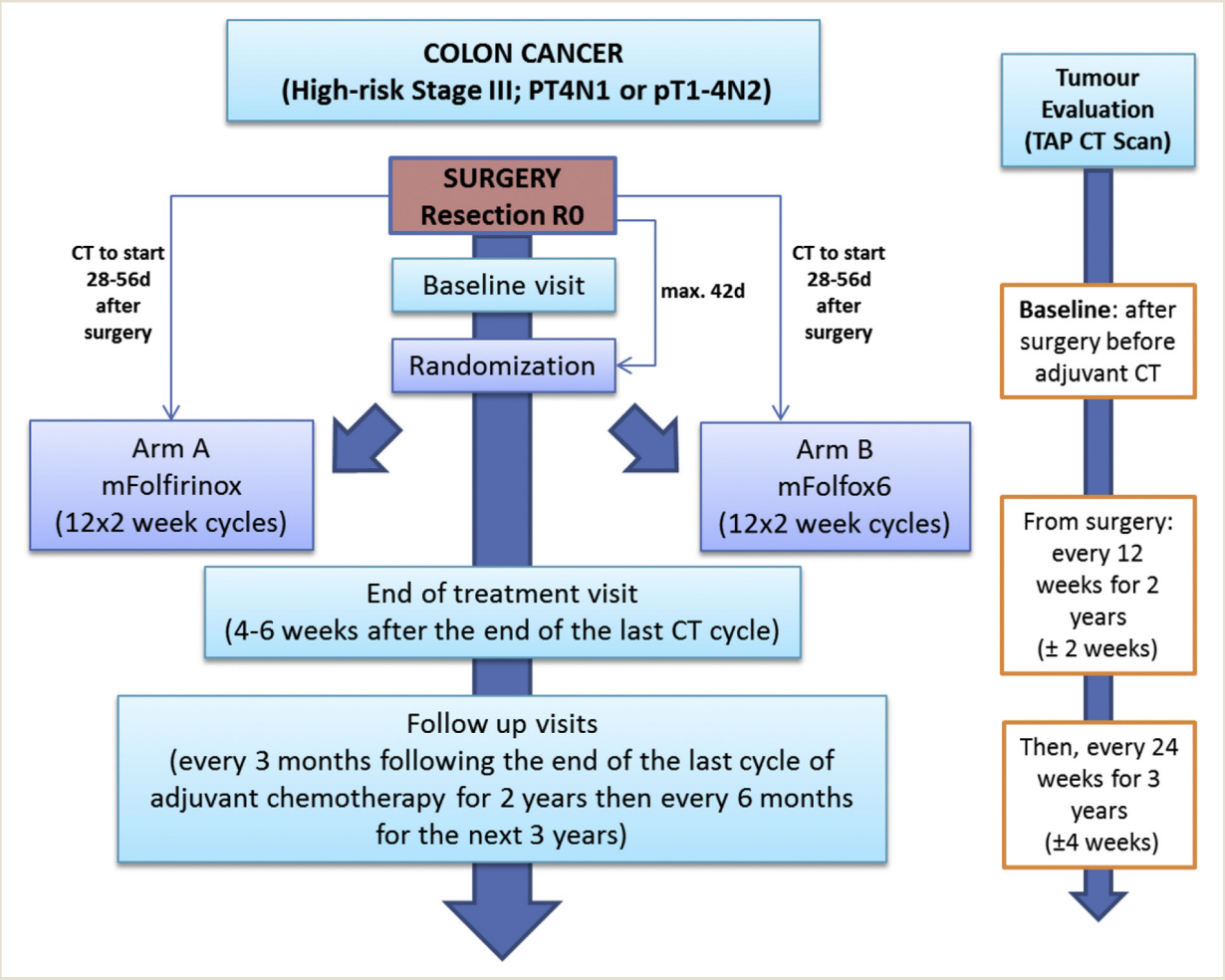
Statistical Analysis

The study will include patients during 48 months of treatment, and follow-up will continue until 36 months after the last patient was randomly assigned (for evaluation of DFS at 3 years). No interim efficacy analysis is planned. We expect a 9% gain for DFS at 3 years in the experimental arm (FOLFIRINOX) compared to the reference arm (mFOLFOX6), with 74% versus 65%, respectively ($\Delta = 6.8\%$ at 2 years). In order to significantly conclude with 80% power and an alpha level of 5% in a 2-sided log-rank test, we need to obtain during follow-up at least a total of 252 events leading to comparison of 2 arms with at least 278 evaluable patients in each one. Considering that 15% of patients will be lost to follow-up, a total of 320 patients per arm will be included.

Ancillary Study: Biomarker Analysis

All patients enrolled onto this trial will be considered for participation in a biological correlative science study, and informed consent for this translational study will be obtained. Prognostic

Figure 1 Study Design



biomarkers will be studied on blood and on tumor-derived samples. On blood, DNA will be extracted from leucocytes to study polymorphism of genes that could be implicated in metabolism, transport, or target of 5-FU (thymidylate synthase, dihydropyrimidine dehydrogenase), CPT-11 (UDP glucuronosyltransferase), or oxaliplatin (ERCC1, XRCC1, glutathione-S-transferases). Blood samples will be also collected for circulating tumor DNA assessment at day 0, at day 28, and at the end of adjuvant therapy (theoretically, 6 ± 1 months). Molecular and histologic analysis on tumor tissue will be performed by the end of inclusion period. Immunohistochemical analysis will define abnormalities in DNA mismatch repair, P53, SMAD4, PTEN, pERK, pAKT expression, vascular density, and density and nature of intratumoral and peritumoral leukocyte infiltration. Molecular analysis will include microsatellite instability (in case of doubtful immunohistochemistry) and search for mutation in *KRAS, BRAF, PI3KCA,* and *SMAD4*. Allelotype of the tumors will be investigated by single nucleotide polymorphism microarrays; validation of available transcriptomic signatures will be done, as well as assessment for methylation or microRNA signature.

Discussion

IROCAS is the first phase 3 randomized trial evaluating the mFOLFIRINOX regimen in patients with high-risk stage III (pT4 and/or N2) colon cancer. This study plans to include 640 patients; the first patient was treated in May 2017. Overall, 49 centers are open, 36 in France and 13 in Canada. One hundred two patients have been enrolled as of September 2018. The end of patient enrollment is scheduled for the year 2022.

Acknowledgment

Supported in part by Programme Hospitalier de Recherche Clinique (PHRC 2016) from the "Direction Générale de l'Offre de Soins (DGOS)," Ministry of Solidarity and Health, France.

Disclosure

J.B. has received honoraria from Roche, Bristol-Myers Squibb, Astra-Zeneca, Boehringer Ingelheim, MSD, Amgen; has consulting or advisory role at Roche, Bristol-Myers Squibb, Astra-Zeneca, Boehringer Ingelheim, MSD; has received travel,

accommodations, expenses from Roche, Bristol-Myers Squibb. P.A. has received honoraria from Roche, Merck, Amgen, Eli Lilly, Servier, Bayer; and has received travel, accommodations, and expenses: Roche, Merck, Servier, O.B. has played a consulting or advisory role for Roche, Merck, Amgen, Bayer; has been on the speaker's bureau for Eli Lilly, Pierre Fabre, Novartis, Servier; and has received travel, accommodations, and expenses from Eli Lilly, Roche, Merck. J.T. has received honoraria from Merck, Roche, Amgen, Eli Lilly, Sanofi, Sirtex, Servier, Baxalta, Celgene; has played a consulting or advisory role at Roche, Merck KGaA, Amgen, Celgene, Eli Lilly, Shire, Servier, Sirtex; and has served on the speakers' bureau for Servier, Amgen, Shire, Roche, Genentech, Sanofi, Merck, Eli Lilly, Sirtex. The other authors have stated that they have no conflict of interest.

References

1. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; 322:352-8.
2. Wolmark N, Rockette H, Mamounas E, et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. *J Clin Oncol* 1999; 17:3553-9.
3. Haller DG, Catalano PJ, Macdonald JS, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. *J Clin Oncol* 2005; 23:8671-8.
4. Andre T, Colin P, Louvet C, et al. Semimonthly versus monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer: results of a randomized trial. *J Clin Oncol* 2003; 21: 2896-903.
5. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; 350:2343-51.
6. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol* 2007; 25:2198-204.
7. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol* 2011; 29:1465-71.
8. Ychou M, Raoul JL, Douillard JY, et al. A phase III randomised trial of LV5FU2-irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802). *Ann Oncol* 2009; 20:674-80.
9. Van Cutsem E, Labianca R, Bodoky G, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. *J Clin Oncol* 2009; 27:3117-25.
10. de Gramont A, Van Cutsem E, Schmoll HJ, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. *Lancet Oncol* 2012; 13:1225-33.
11. Alberts SR, Sargent DJ, Nair S, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. *JAMA* 2012; 307:1383-93.
12. Allegra CJ, Yothers G, O'Connell MJ, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. *J Clin Oncol* 2011; 29:11-6.
13. Taieb J, Tabernero J, Mini E, et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; 15: 862-73.
14. Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med* 2018; 378:1177-88.
15. André T, Vernerey D, Mineur L, et al. 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy for patients with stage III colon cancer: disease-free survival results from a randomized, open-label, international duration evaluation of adjuvant (IDEA) France, phase III trial. *J Clin Oncol* 2018; 36:1469-77.