



# Impact of the IDEA Collaboration Study Results on Clinical Practice in France for Patients With Stage III Colon Cancer: A National GERCOR - PRODIGE Survey

Kaïssa Ouali, Anthony Turpin, Cindy Neuzillet, Benoît Rousseau, Marie Line Garcia-Larnicol, Christophe Tournigand, Emmanuelle Samalin, Julien Taieb, Thierry André, Romain Cohen

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1 **Original research**

2 **Title:**

3 Impact of the IDEA collaboration study results on clinical practice in France for stage III colon  
4 cancer patients: a national GERCOR - PRODIGE survey

5 **Short title:**

6 IDEA collaboration results in real-life practice

7 **Authors:**

8 Kaïssa Ouali<sup>1</sup>, Anthony Turpin<sup>2</sup>, Cindy Neuzillet<sup>3</sup>, Benoît Rousseau<sup>4</sup>, Marie-Line Garcia-  
9 Larnicol<sup>5</sup>, Christophe Tournigand<sup>6</sup>, Emmanuelle Samalin<sup>7</sup>, Julien Taieb<sup>8</sup>, Thierry André<sup>9</sup>,  
10 Romain Cohen<sup>9</sup>

11 **Affiliations:**

12 <sup>1</sup> Medical oncology department, Saint-Antoine hospital, AP-HP, Paris, France,

13 <sup>2</sup> Medical oncology department, CHRU Lille, Lille, France

14 <sup>3</sup> Medical oncology department, Curie Institute, Versailles Saint-Quentin University, Saint  
15 Cloud, France,

16 <sup>4</sup> Department of Medicine - Solid Tumor Division, Memorial Sloan Kettering Cancer Center,  
17 New York, USA,

18 <sup>5</sup> GERCOR,

19 <sup>6</sup> Medical oncology department, Henri Mondor hospital, Créteil, France,

20 <sup>7</sup>Medical oncology Departement, Institut du Cancer de Montpellier (ICM)/ Institut de  
21 Génomique Fonctionnelle, CNRS, INSERM, Univ. Montpellier, Montpellier, France,

22 <sup>8</sup> Gastroenterology and GI oncology, Georges Pompidou European Hospital, APHP, Sorbonne  
23 Paris Cité, Paris Descartes University, Paris, France

24 <sup>9</sup> Sorbonne University and medical oncology department, Saint-Antoine hospital, AP-HP, Paris,  
25 France,

26 **Corresponding Author:** Dr Romain Cohen; ORCID 0000-0001-9602-5162

27 Hôpital Saint-Antoine, 184 rue du faubourg Saint-Antoine, 75012 Paris, France

28 Tel: +33 1 49 28 23 36; Fax: +33 1 49 28 34 98; email address: [romain.cohen@aphp.fr](mailto:romain.cohen@aphp.fr)

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48 **Keywords:** adjuvant chemotherapy; colorectal neoplasms; FOLFOX; CAPOX; guidelines;

#### 49 **MICRO-ABSTRACT**

50 The IDEA study showed that the type and duration of adjuvant chemotherapy might be adjusted  
51 according to level of risk in stage III colon cancer. Hereby, we show that it has been mainly  
52 integrated in routine practice in France with a switch from six to three months and from  
53 FOLFOX to CAPOX regimen in low-risk stage III colon cancer patients.

## 54 CLINICAL PRACTICE POINTS

55 The prospective, pre-planned pooled analysis of six concurrently conducted randomized phase  
56 III trials (IDEA collaboration) was built to evaluate the non-inferiority of three months of  
57 adjuvant treatment with oxaliplatin plus fluoropyrimidine to the six-month standard duration of  
58 therapy for stage III colon cancer patients. Although the non-inferiority was not confirmed in  
59 the overall population, the IDEA study showed that the type (and duration of treatment may be  
60 adjusted according to the level of risk (low risk pT1-3/N1 *versus* high risk pT4 and/or N2).

61 We realized a nationwide survey in France, one year after the publication of the IDEA  
62 collaboration results. We show that a shortened duration of adjuvant treatment using CAPOX  
63 for three months has been integrated in France as standard of care for low risk stage III colon  
64 cancer patients by most physicians. Six months of FOLFOX remains the standard treatment for  
65 the high-risk population.

## 66 ABSTRACT

67 **Background:** The IDEA collaboration showed that the type and duration of adjuvant  
68 chemotherapy in stage III colon cancer (CC) could be adjusted according to level of risk. We  
69 aimed at evaluating the implementation of IDEA's results in real-life practice for stage III CC.

70 **Material and methods:** All clinicians registered in the French oncology cooperative groups  
71 GERCOR, FFCD and UNICANCER GI mailing lists were invited to participate to an online  
72 anonymized nationwide survey from January 30, 2019 to March 31, 2019. Proportions were  
73 compared using chi-squared test.

74 **Results:** A total of 213 physicians answered the survey. 173 (81%) considered that three  
75 months of adjuvant chemotherapy was the new standard of care for low risk (pT1-3/N1) stage  
76 III CC and 99% that six months remained the standard of care for high risk (pT4 and/or pN2)  
77 stage III CC. In patients under 70 years, CAPOX for three months was prescribed by 74% of  
78 the participants in low risk CC while six months of FOLFOX was preferred for high risk CC in  
79 94% cases. For patients over 70 years with good performance status and no comorbidities, 172  
80 physicians (81%) prescribed oxaliplatin-based chemotherapy for low risk CC (3 months: 144  
81 out of 172, 88%), and 200 physicians (94%) prescribed oxaliplatin-based adjuvant  
82 chemotherapy for high risk CC (6 months: 199 out of 200, 99%).

83 **Conclusion:** IDEA results have been practice changing as French physicians have implemented  
84 three months CAPOX for low risk stage III CC patients, substituting six months FOLFOX  
85 which remains the preferred regimen for high risk patients.

## 86 INTRODUCTION

87 Six months of adjuvant chemotherapy with oxaliplatin plus a fluoropyrimidine has been the  
88 standard of care for stage III colon cancer (CC) patients since 2004 (1–4). However, the  
89 cumulative neurotoxicity related to the use of oxaliplatin led to the evaluation of a shortened  
90 duration of adjuvant chemotherapy in this setting.

91 The IDEA (International Duration Evaluation of Adjuvant Therapy) collaboration study  
92 showed that the type and duration of adjuvant chemotherapy in stage III CC might be adjusted  
93 according to the level of risk (low risk: pT1-3 and pN1; high risk: pT4 and/or pN2) (5).  
94 Although the study did not demonstrate the non-inferiority of three months *versus* six months  
95 of adjuvant chemotherapy in the overall population for Disease Free Survival (DFS) (HR 1.07,  
96 95% confidence interval (95%CI) 1.00-1.15), the non-inferiority of CAPOX (capecitabine plus  
97 oxaliplatin) for three months was demonstrated for low risk stage III CC patients, which  
98 represent 59% of the entire stage III population.

99 International guidelines (6)(7)(8) have been updated accordingly but data concerning the  
100 implementation of IDEA conclusions in real-life adjuvant chemotherapy prescriptions are  
101 lacking. We aimed at assessing the impact of IDEA study on daily practice for stage III CC in  
102 France.

## 103 MATERIAL AND METHODS

104 Physicians registered in three French cooperative groups (FFCD, Fédération Francophone de  
105 Cancérologie Digestive; GERCOR, French Multidisciplinary Group in Oncology; UCGI,  
106 Unicancer Gastrointestinal Group) were invited to fill in an online questionnaire  
107 (supplementary material). Reminder emails were sent every 2 weeks. The survey was composed  
108 of 24 questions, related to daily practices. Clinicians were asked which modality of adjuvant

Commenté [RC1]: Réf à fusionner



109 chemotherapy (FOLFOX or CAPOX, three months or six months) they would choose in  
110 different clinical settings. A 5-point Likert scale was also used (from 1, strongly disagree, to 5,  
111 strongly agree) to evaluate IDEA's impact on their daily clinical practice. Participants were also  
112 asked to indicate the preferred venous access (peripheral or central access) and device (PICC-  
113 line or implanted port). Answers were declarative, individual, and anonymized. Proportions  
114 were compared using chi-squared tests. The level of significance was  $p < 0.05$ .

115

## 116 RESULTS

117 213 physicians participated to the survey from January 30, 2019 to March 31, 2019.  
118 Demographic characteristics are displayed in Table 1. 198 of them completed the survey in its  
119 entirety. 63% of the participants agreed or strongly agreed that IDEA study had an impact on  
120 their clinical practice, whereas 17% disagreed or strongly disagreed. 75% declared that three  
121 months of CAPOX was the new standard of care for low risk stage III CC and 99% that six  
122 months of adjuvant chemotherapy remained the standard of care for the high risk population.

### 123 Patients under 70 years

124 For low-risk stage III CC patients adjuvant chemotherapy was prescribed for 3 months by 84%  
125 of the responders, with a majority of CAPOX regimen (75% vs. 8% with FOLFOX); a six-  
126 month duration of adjuvant chemotherapy was chosen by 16% of physicians (with FOLFOX  
127 only) (figure 1).

128 For high-risk stage III CC patients, 94%, 6% and 0.5% of physicians prescribed FOLFOX for  
129 six months, CAPOX for six months or FOLFOX for three months, respectively.

### 130 Patients over 70 years (figure 2)

131 ECOG PS 0-1 and no comorbidity

Commenté [RC2]: Si tu le mets là, on peut le retirer des méthodes

132 For patients > 70 with good PS and low risk stage III CC, oxaliplatin-based chemotherapy was  
133 prescribed by 81% of physicians, for three (68%) or six months (13%). 18% of responders  
134 chose fluoropyrimidine monotherapy for three (3%) or six months (15%).

135 In case of high-risk stage III CC, adjuvant chemotherapy was prescribed for six months by 99%  
136 of responders, mainly with doublets (94% while 6% chose fluoropyrimidine monotherapy).

137 ECOG PS > 1 and/or with comorbidities

138 In older patients with altered PS or comorbidities, in case of low-risk stage III CC, 13%, 61%,  
139 and 25% of the participants declared to prescribe no adjuvant chemotherapy, fluoropyrimidine  
140 monotherapy, or oxaliplatin-based chemotherapy, respectively. Oxaliplatin-based adjuvant  
141 chemotherapy was proposed for three months by most clinicians (65%).

142 In the high-risk population with ECOG PS > 1 or comorbidities, 3%, 44% and 51% declare to  
143 prescribe no adjuvant chemotherapy, a fluoropyrimidine alone, or oxaliplatin-based  
144 chemotherapy (94% for 6 months), respectively.

145 **Venous access**

146 In patients with appropriate venous capital, CAPOX for three months was administered without  
147 central venous access device (CVAD) for two third (66%) of the participants, using an  
148 implantable port (21%) or a PICC-line (12%).

## 149 **DISCUSSION**

150 Our study is the first to report real life practices for stage III CC patients after the publication  
151 of the IDEA study. We show that the modulation of adjuvant chemotherapy duration and type  
152 according to the level of risk has been adopted as standard of care in France for stage III CC.

153 Our results are in line with a survey realized among the Australia and New Zealand SCOT's  
154 participants. It reported that the expected minimum survival benefit warranted to choose a six-  
155 month ACT rather than three-month duration was much larger than the estimates of the IDEA  
156 trial (9). One might have hypothesized that the CAPOX might not be easily integrated into daily  
157 practice in France since FOLFOX was prescribed by a vast majority of French physicians before  
158 (90% in the IDEA France trial (10)). Although the FOLFOX regimen remained largely  
159 prescribed for high-risk stage III CC patients, the combination of capecitabine and oxaliplatin  
160 was the main choice for low risk stage III CC patients in this survey, showing how much impact  
161 IDEA had on real-life patients' care.

162 Oxaliplatin-based adjuvant chemotherapy was mostly prescribed for older patients with good  
163 PS (80%-90%) and, to a lesser extent, for patients with comorbidities and high-risk CC (50%).  
164 However, there is no clear evidence that the addition of oxaliplatin to fluoropyrimidine is  
165 associated with an improvement of DFS or overall survival, as it has been shown in a pooled  
166 analysis of MOSAIC, NSABP C-07 and XELOXA trials (N = 1119; DFS hazard ratio (HR) =  
167 0.94, 95% confidence interval (95%CI) 0.78-1.13 and OS HR = 1.04, 95%CI 0.85-1.27)  
168 (12,13). Though, another analysis from NSABP C-08, XELOXA, X-ACT and AVANT trials  
169 did detect a significant improvement of DFS and OS in patients > 70 treated with XELOX or  
170 FOLFOX (14). The prescription of doublet adjuvant chemotherapy in fit elderly patients  
171 observed in our survey remains to be properly evaluated in dedicated clinical trials, such as the  
172 PRODIGE 34 phase III study (NCT023553790).

173 One third of the physicians used CVAD for patients treated with CAPOX for three months,  
174 despite good venous capital. The feasibility of treating patients with CAPOX on a peripheral  
175 venous access for three or six months has been demonstrated in an analysis of 203 patients  
176 included in the IDEA France study: CAPOX adjuvant chemotherapy without a CVAD was  
177 successful in 88.4% of patients for whom chemotherapy had been planned without the use of  
178 CVAD (15). The reasons for such a high use of central venous devices need to be explored.

179 Our study exhibits several weaknesses. First, the study population might have been biased by  
180 its selection through the cooperative groups networks, even if it is representative of the current  
181 French medical demography (16), with physicians working in different types of institution, with  
182 various levels of experience and different medical specialty backgrounds. We acknowledge  
183 that the declarative nature of our study might have biased the results. We observed that the use  
184 of CAPOX for 3 months was lower than the proportion of physicians declaring this treatment  
185 as the new standard of care: 44% of physicians declared they had prescribed it for their last 5  
186 patients with low risk stage III tumor while 75% of them considered CAPOX 3 months as the  
187 new standard of care for this population. Therefore, analyses of prospective cancer registries  
188 are required to validate our study. Besides, it would be interesting to evaluate if the recent  
189 release of OS data from the IDEA study reinforced the observed changes in routine practice(17).

190 To conclude, adjuvant chemotherapy with CAPOX for three months has been mainly integrated  
191 as a new standard of care for low-risk stage III CC. FOLFOX for six months remains the  
192 preferred choice of prescribers for high-risk patients in France.

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29

## 1 FIGURES AND TABLES CAPTIONS

2 Table 1: Population characteristics

3 Figure 1: Type and duration of adjuvant chemotherapy for patients under 70 with low risk stage

4 III colon cancer

5 Figure 2: Type and duration of chemotherapy for patients  $> 70$  with low risk or high risk stage

6 III colon cancer, depending on performance status and comorbidities

Table 1 : Population characteristics

	N (%)
<b>Participants</b>	213 (100)
<b>Specialty</b>	
Gastroenterologist	109 (51.2)
Medical oncologist	84 (39.4)
Radiation therapist	10 (4.7)
Surgeon	10 (4.7)
<b>Workplace</b>	
Academic hospital	65 (30.5)
General Hospital	57 (26.8)
Comprehensive cancer center	56 (26.3)
Private clinic	35 (16.4)
<b>Experience in gastro-intestinal cancers</b>	
< 5 years	28 (13.1)
5 – 10 years	40 (18.8)
10 – 20 years	75 (35.2)
> 20 years	70 (32.9)
<b>Number of stage III colon cancer patients</b>	
< 4 per year	10 (4.7)
4 - 8 per year	53 (24.9)
8 - 12 per year	51 (23.9)
> 12 per year	99 (46.5)



**Figure 1:** Type and duration of adjuvant chemotherapy for patients under 70 with low risk stage III colon cancer.

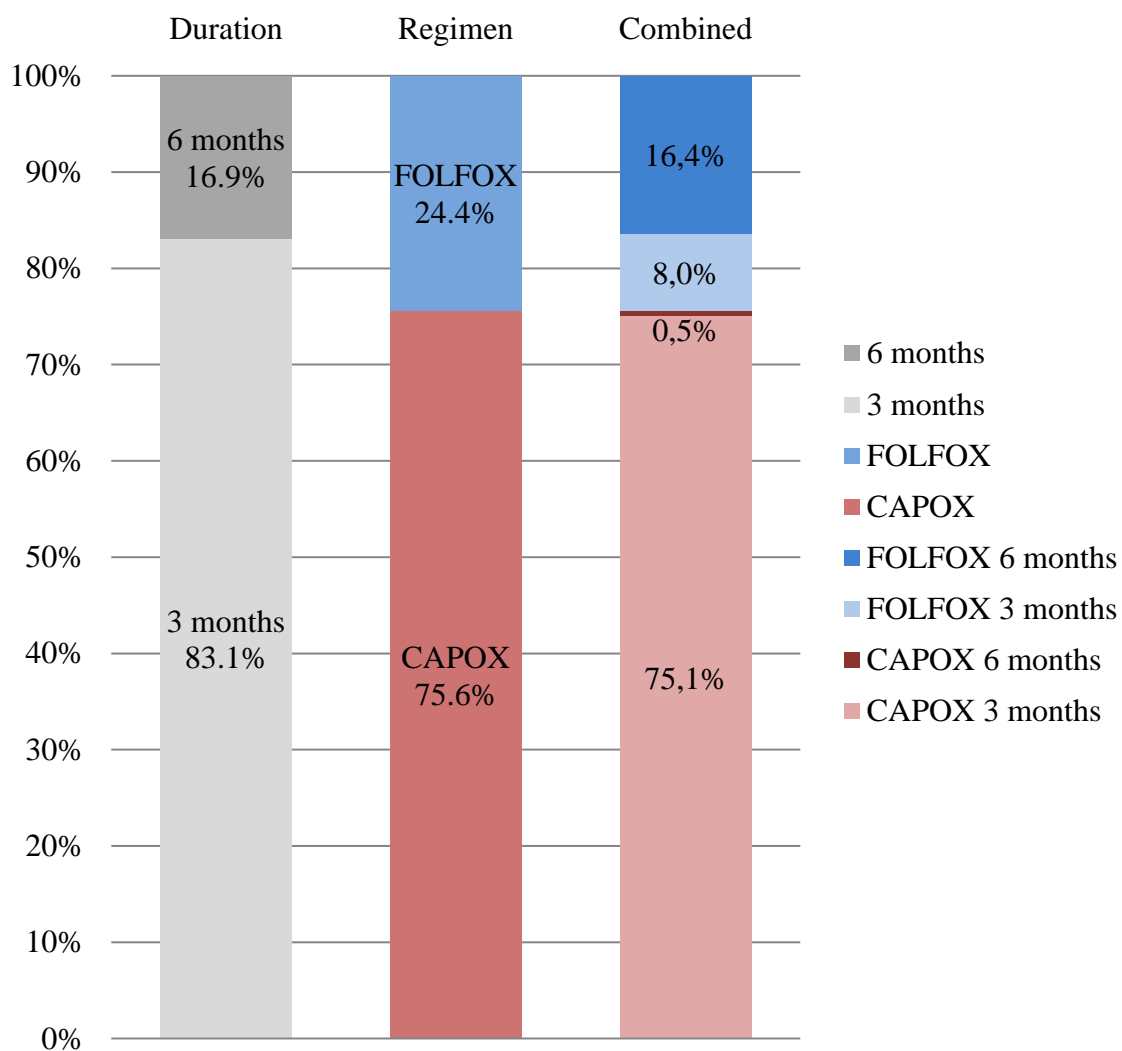
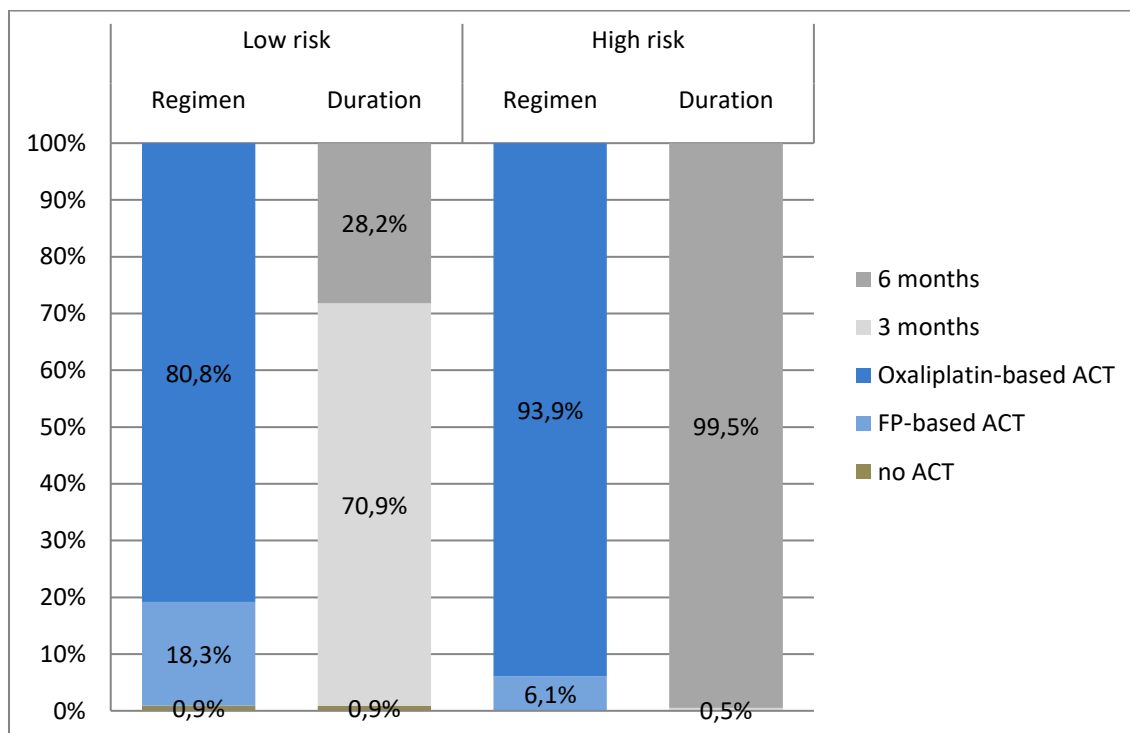
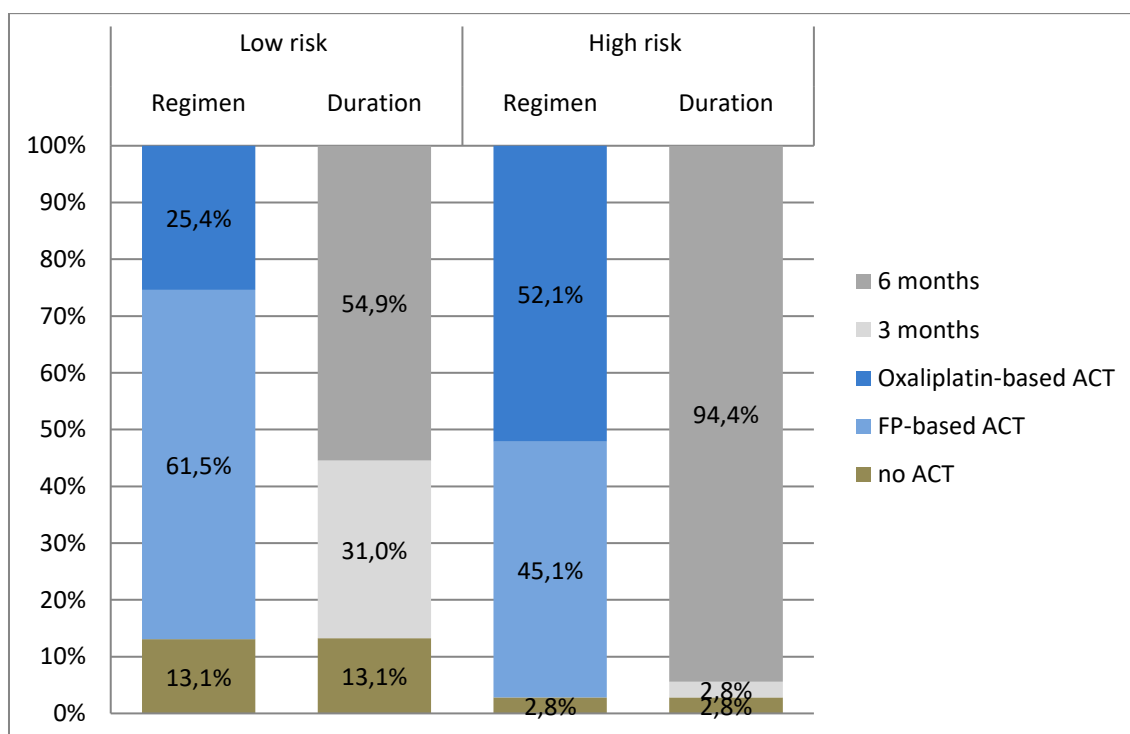


Figure 2: Type and duration of chemotherapy for patients > 70 with low risk or high risk stage III colon cancer, depending on performans status and comorbidies

Panel A: Performans score 0-1 and no comorbidity



Panel B: Performans score > 1 and/or comorbidity



## **SUPPLEMENTARY MATERIAL : QUESTIONNAIRE**

### **PART I :**

**1 /** In which region are you working :

- A. Auvergne-Rhône-Alpes
- B. Bourgogne-Franche-Comté
- C. Bretagne
- D. Centre-Val de Loire
- E. Corse
- F. Grand-Est
- G. Hauts-de-France
- H. Ile-de-France
- I. Normandie
- J. Nouvelle-Aquitaine
- K. Occitanie
- L. Pays de la Loire
- M. Provence-Alpes-Côte d'Azur
- N. DOM-TOM

**2/ :** Do you work :

- A. In a teaching hospital
- B. In a general hospital
- C. In a private health institution of collective interest/Comprehensive cancer center
- D. In a private clinic
- E. Other

**3/** Number of years of practice :

- A. < 5 years
- B. Between 5 and 10 years
- C. Between 10 and 20 years
- D. > 20 years

**4/** What is your speciality :

- A. Medical oncologist
- B. Radiation oncologist

- C. Gastro-enterologist with an expertise in oncology
- D. Surgeon
- E. Other

5/ Number of patients with a stade III colon cancer or high rectal cancer that you newly took care of in the last 12 months :

- A. < 4 patients
- B. Between 4 and 8 patients
- C. Between 8 and 12 patients
- D. > 12 patients

## **PART II:**

1/ Since the publication of the IDEA study (Grothey, A. *et al.* Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. *N. Engl. J. Med.* **378**, 1177–1188 (2018)), did you change your practices ?

Likert scale from 0 (not at all) à 10 (completely).

### **Concerning the duration of treatment :**

2/ For the T1-T3 et N1 tumors, concerning the duration of treatment :

- A – Yes, 3 months is the new duration for the majority of my patients in this case
- B- No

If you answered no, why? (*multiple replies are possible*) :

- a/ the study does not allow to conclude non inferiority on its main judgment criteria
- b/ the analysis of the results by level of risk (stage III of low risk versus high risk) was not planned in the protocol ; so I don't think this subgroup analysis is robust enough
- c/ the analysis of the IDEA France study show that 6 months of FOLFOX6m is better than 3 months of FOLFOX6m, even for the low risk, and I prefer to use FOLFOX
- d/ Other : *Specify [free text]*

3/ For the T4 eand/or N2 tumors, concerning the duration of treatment :

- A – Yes, 3 months is the new duration for the majority of my patients in this case
- B- No

If you answered no, why? (*multiple replies are possible*) :

- a/ the study shows the superiority of 6 month in this subgroup
- b/ the analysis of the results by level of risk (stage III of low risk versus high risk) was not planned in the protocol and does not allow to conclude statistically at the non inferiority of 3 months vs 6 months, so sub-group analyses don't seem valid to me
- c/ the analysis of the IDEA France study showing that 6 months of FOLFOX6m is better than 3 months of FOLFOX6m.
- d/ Other : *Specify [free text]*

**Concerning the treatment regimen :**

**4/ For the T1-T3 et N1 tumors, concerning the treatment regimen :**

- A – Yes, CAPOX is the treatment regimen that I prescribe to the majority of my patients in this case, and I prescribe it for 3 months
- B – Yes, CAPOX is the treatment regimen that I prescribe to the majority of my patients in this case, and I prescribe it for 6 months
- C- No

If you answered no, why? (*multiple replies are possible*) :

- a/ the analysis of the IDEA France study shows that 6 months of FOLFOX6m is better than 3 months of FOLFOX6m.
- b/ I'm rather partial to FOLFOX6m for tolerance reasons.
- c/ I'm rather partial to FOLFOX6m for observance reasons.
- d/ Other : *Specify [free text]*

**5/ For the T4 and/or N2 tumors, concerning the treatment regimen :**

- A – Yes, CAPOX is the treatment regimen that I prescribe to the majority of my patients in this case, and I prescribe it for 3 months
- B – Yes, CAPOX is the treatment regimen that I prescribe to the majority of my patients in this case, and I prescribe it for 6 months
- C- No

If you answered no, why? (*multiple replies are possible*) :

- a/ the analysis of the IDEA France study shows that 6 months of FOLFOX6m is better than 3 months of FOLFOX6m.
- b/ I'm rather partial to FOLFOX6m for tolerance reasons.
- c/ I'm rather partial to FOLFOX6m for observance reasons.
- d/ Other : *Specify [free text]*

**PART IIIA : In the case of a patient under 70 years of age in good shape with a stage III colon cancer or high rectal cancer treated by surgery :**

**1/ If this was a stage pT3N1 :**

a/ What treatment regimen would you propose as first line therapy ?

- A- CAPOX
- B- FOLFOX

b/ For how long ?

- A- 3 months
- B- 6 months

**2/ For the last 5 patients under 70 years of age you took care of for a pT3N1, to how many did you prescribe :**

- A- CAPOX 3 months : (n)
- B- CAPOX 6 months : (n)
- C- FOLFOX 3 months: (n)
- D- FOLFOX 6 months: (n) [A+B+C+D=5]

**3/ If this was a stage pT3N2 :**

a/ What treatment regimen would you propose as first line therapy ?

- A- CAPOX
- B- FOLFOX

b/ For how long ?

- A- 3 months
- B- 6 months

**4/ If this was a stage pT4N1 :**

a/ What treatment regimen would you propose as first line therapy ?

- A- CAPOX
- B- FOLFOX

b/ For how long ?

- A- 3 months
- B- 6 months

**5/ If this was a stage pT4N2 :**

a/ What treatment regimen would you propose as first line therapy ?

- A- CAPOX
- B- FOLFOX

b/ For how long ?

- A- 3 months
- B- 6 months

**6/ For the last 5 patients under 70 years of age you took care of for a pT4 or N2, to how many did you prescribe :**

- A- CAPOX 3 months : (n)
- B- CAPOX 6 months : (n)
- C- FOLFOX 3 months : (n)
- D- FOLFOX 6 months : (n) [A+B+C+D=5]

**PART IIIB : In the case of a patient over 70 years of age in good shape (OMS 0 or 1, without co-morbidities) with a stage III colon cancer or high rectal cancer treated by surgery :**

**1/ If this was a stage pT3N1 :**

a/ What treatment regimen would you propose as first line therapy ?

- A- Simple monitoring
- B- CAPECITABINE
- C- LV5FU2
- D- CAPOX
- E- FOLFOX

b/ For how long ?

- A- 3 months
- B- 6 months
- C- Not applicable (Simple monitoring)

c/ About the last 5 patients you took care of, how many did you treat with :

- A- Simple monitoring: (n)
- B- CAPECITABINE : (n)
- C- LV5FU2 : (n)
- D- CAPOX : (n)

E- FOLFOX : (n) [A+B+C+D+E=5]

d/ Based on your chemotherapy prescription data, for those who had chemotherapy, what was the duration of treatment?

*Likert scale: Always 3 months / mainly 3 months / as much 3 months as 6 months / mainly 6 months / always 6 months*

**2/ If this was a stage pT4N2 :**

a/ What treatment regimen would you propose as first line therapy ?

A- Simple monitoring

B- CAPECITABINE

C- LV5FU2

D- CAPOX

E- FOLFOX

b/ For how long ?

A- 3 months

B- 6 months

C - Not applicable (Simple monitoring)

c/ About the last 5 patients you took care of, how many did you treat with :

A- Simple monitoring: (n)

B- CAPECITABINE : (n)

C- LV5FU2 : (n)

D- CAPOX : (n)

E- FOLFOX : (n) [A+B+C+D+E=5]

d/ Based on your chemotherapy prescription data, for those who had chemotherapy, what was the duration of treatment?

*Likert scale: Always 3 months / mainly 3 months / as much 3 months as 6 months / mainly 6 months / always 6 months*

**PART IIIC : In the case of a patient over 70 years of age in good shape, but OMS 2 or with co-morbidities, with a stage III colon cancer or high rectal cancer treated by surgery :**

**1/ If this was a stage pT3N1 :**

a/ What treatment regimen would you propose as first line therapy ?



- A- Simple monitoring
- B- CAPECITABINE
- C- LV5FU2
- D- CAPOX
- E- FOLFOX

b/ For how long ?

- A- 3 months
- B- 6 months
- C - Not applicable (Simple monitoring)

c/ About the last 5 patients you took care of, how many did you treat with :

- A- Simple monitoring: (n)
- B- CAPECITABINE : (n)
- C- LV5FU2 : (n)
- D- CAPOX : (n)
- E- FOLFOX : (n) [A+B+C+D+E=5]

d/ Based on your chemotherapy prescription data, for those who had chemotherapy, what was the duration of treatment?

*Likert scale: Always 3 months / mainly 3 months / as much 3 months as 6 months / mainly 6 months / always 6 months*

**2/ If this was a stage pT4N2 :**

a/ What treatment regimen would you propose as first line therapy ?

- A- Simple monitoring
- B- CAPECITABINE
- C- LV5FU2
- D- CAPOX
- E- FOLFOX

b/ For how long ?

- A- 3 months
- B- 6 months
- C - Not applicable (Simple monitoring)

c/ For the last 5 you took care of, how many did you treat with :

- A- Simple monitoring: (n)
- B- CAPECITABINE : (n)
- C- LV5FU2 : (n)
- D- CAPOX : (n)
- E- FOLFOX : (n) [A+B+C+D+E=5]

d/ Based on your chemotherapy prescription data, for those who had chemotherapy, what was the duration of treatment?

*Likert scale: Always 3 months / mainly 3 months / as much 3 months as 6 months / mainly 6 months / always 6 months*

#### **PART IV :**

1/ a/ During the realization of an adjuvant chemotherapy by CAPOX during 3 months, in case of good clinical venous state, do you preferentially do the treatment on :

- A- An importable port
- B- A PICC-line
- C- A peripheral venous line

b/ Of the 5 last patients for whom who prescribe CAPOX for 3 months, to how many did you do the treatment on :

- A. An implantable port : X
- B. A PICC-LINE : Y
- C. Not on a central line : Z [X+Y+Z =5]

2/ a/ During the realization of an adjuvant chemotherapy by CAPOX during 6 months, in case of good clinical venous state, do you preferentially do the treatment on:

- B- An importable port
- D- A PICC-line
- E- A peripheral venous line

b/ Of the 5 last patients for whom who prescribe CAPOX for 3 months, to how many did you do the treatment on :

- A. An implantable port : X
- B. A PICC-LINE : Y
- C. Not on a central line : Z [X+Y+Z =5]

**3/** When you decided to do a chemotherapy by CAPOX on a peripheral venous line,

A- a/ In which proportion of the cases you had to secondarily put a central line (an importable port or a PICC-line) during treatment :

A- Less than 25%

B- Between 25 et 50%

C- Between 50 et 75%

D- More than 75%

b/ Was it :

*Likert scale: Always an importable port / mainly an importable port / as much an importable port as a PICC-line / mainly a PICC-line / always a PICC-line*

c/ What was the reason for secondary use of a peripheral venous line ? *[free text]*

**4/** When you decide to do a chemotherapy by FOLFOX, do you do :

A- FOLFOX6m (1 infuser of 46h)

B- FOLFOX4 (2 infuser of 23h)