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Preliminary tolerance analysis of adjuvant chemotherapy in older patients after resection of stage III colon cancer from the PRODIGE 34-FFCD randomized trial ☆

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ABSTRACT

Background: Colon adenocarcinoma mainly occurs in older patients. Oxaliplatin-based adjuvant chemotherapy improved disease-free survival after stage III colon cancer resection, but this improvement was not demonstrated in older patients.
Methods: The purpose of ADAGE-PRODIGE 34, randomized open phase III trial is to compare in patients over 70 years oxaliplatin plus fluoropyrimidine with fluoropyrimidine alone in fit patients (Group 1) and fluoropyrimidine with observation in frail patients (Group 2) after resection of stage III colon adenocarcinoma. We report a preliminary tolerance analysis on 50% of the first patients enrolled.
Results: The analysis was conducted on 491 patients (378 in Group 1 and 113 in Group 2). Patients in Group 2 were older and showed more frailty criteria than those in Group 1. Cumulative grade 3–5 toxicities were more frequent in patients treated with oxaliplatin in Group 1 or with fluoropyrimidine in Group 2 than in patients treated with fluoropyrimidine in Group 1. At least one course was deferred in more than half of the patients in all groups. Early treatment cessation was more frequent in Group 2.
Conclusion: No safety concerns were raised for the continuation of accrual. The frailty criteria distribution suggests that the investigator's evaluation for group allocation was accurate.

1. Introduction

Colorectal cancer mainly occurs in older patients. More than 50% of patients diagnosed with colorectal cancer in France are 70 years or older [1]. When diagnosed at a localized stage the older patients had an R0 surgical resection in more than 80% for colorectal cancer cases; a rate similar to what it is reported in younger patients in France [1]. Recent data from the Burgundy registry, reports a 97% resection rate for colon cancer, in patients 70–80 years old, 92% in patients 80–85 years old and 79% in patient over 85 years of age [2]. Adjuvant chemotherapy is recommended after resection of stage III colon cancer, based on trial conclusions comparing fluoropyrimidine with observation [3,4].

Nevertheless, adjuvant chemotherapy is rarely considered for older patients [1,5–7]. A post-hoc analysis of several prospective randomized trials suggested that 5-fluorouracil (5FU)-based chemotherapy improved the prognosis, even in older patients [8]. However, in these trials, older patients were highly selected and the sub-group of patients older than 80 years was very small. Thus, the benefit of 5FU-based adjuvant chemotherapy in very old, frail, unselected patients remains debated.

Currently, the recommended adjuvant treatment for stage III colon cancer is a combination of fluoropyrimidine and oxaliplatin [9]. However, the efficacy of oxaliplatin therapy in older patients is still a matter of debate. A pooled analysis of the sub-group of patients over 70 enrolled in previous randomized trials that compared fluoropyrimidine alone with fluoropyrimidine plus oxaliplatin, showed no advantage in terms of disease-free survival (DFS) [10]. However, another study that retrospectively assessed four other trials, showed better DFS and overall survival (OS) in patients over 70 receiving oxaliplatin than in those treated with fluoropyrimidine alone after resection of stage III colon cancer [11]. Moreover, a large database analysis concluded that doublet chemotherapy was not superior to fluoropyrimidine monotherapy in patients over 72 years old with low-risk stage III colon cancer [12]. The tolerance of adjuvant oxaliplatin-based chemotherapy in older patients was not increased in selected patients 70 years and older, compared to younger patients in the pooled analysis of Haller et al. [11]. Nevertheless, another pooled analysis from a trial evaluating oxaliplatin treatment for both metastatic or adjuvant colorectal cancer settings, observed more hematological toxicity in older patients compared to younger ones [13]. Moreover, in specific trials dedicated to older patients in a metastatic setting, it is reported that when oxaliplatin-based chemotherapy is initiated at reduced doses, it is rarely increased back to full dose [14], and when started at full dose, the treatment is frequently reduced even in fit older patients [15]. Thus, tolerance of oxaliplatin remains a concern in older patients.

The optimal treatment of older patients after colon cancer resection remains a matter of great interest [7]. Moreover, as older patients treated for colorectal cancer are less frequently enrolled in clinical trials [16], it is necessary to assess geriatric parameters that could help determine the best treatment for these older patients through a dedicated study.

Thus, the aim of the PRODIGE 34 - ADAGE phase III trial is to evaluate the impact of adjuvant chemotherapy in older patients for the different chemotherapy regimens. A preliminary tolerance analysis was conducted. Though this analysis was initially unplanned in the study protocol, it was requested and evaluated by the independent study committee, when reaching 50% of the total planned patients to be enrolled. There were no specified criteria for premature termination of the study. We report here the result of this preliminary tolerance analysis. Moreover, we have assessed the accuracy of patients' group allocation according to the investigator's evaluation.

2. Patients and methods

2.1. Study design

ADAGE is an academic, French and Belgium study, multi-center, open-label randomized phase III study comparing 3-year DFS following two therapeutic strategies in two groups of older patients with completely resected colon cancer [17]. The hypothesis for Group 1 is to improve 3-year DFS from 65% (arm A) to 72% (arm B) and in Group 2 to extend 3-year DFS from 40% (arm C) to 55% (arm D). An amendment to the protocol was made in December 2016 to modify the one-sided α risk of 5% to a two-sided α risk of 5% with a power of 80%. That increase the total number of patients to enroll from 776 to 982. Eligible patients are over 70 years of age, with stage III colon adenocarcinoma and R0 resection of the primary tumor. All the patients had to have a normal dihydropyrimidine dehydrogenase status to be enrolled. The indication of adjuvant chemotherapy is based on a multidisciplinary team's advice. The team included at least a digestive oncologist, a surgeon and a radiologist. A geriatrician may participate, as per the policy applied by each study site, but their involvement was not mandatory by the study protocol. Adjuvant chemotherapy has to start within 12 weeks after surgery. Written informed consent has to be obtained before randomization and geriatric questionnaires have to

be completed. Patients are selected for one of the two groups by the physician according to its own evaluation or after geriatrician advice depending of the site organization.

- Group 1 (arms A and B): defined as eligible for treatment with doublet chemotherapy
- Group 2 (arms C and D): defined as unsuitable for treatment with doublet chemotherapy

In each group, patients are randomized in a 1:1 ratio using minimization technique by the "Fédération Francophone de Cancérologie Digestive" - FFCD data center and the randomization is stratified according to center, sex, stage (IIIA *vs.* IIIB *vs.* IIIC), presence of occlusion and/or perforation (yes *vs.* no) and instrumental activity of daily living (IADL) (normal *vs.* abnormal). Arm A and D patients receive bimonthly 5FU combine with leucovorin (LV5FU2) or capecitabine (based on the physician's choice), arm B patients receive LV5FU2 combine with oxaliplatin (FOLFOX4) or capecitabine combine with oxaliplatin (XELOX) (based on the physician's choice) and arm C is an observation arm. Patients receive 12 cycles (1 cycle every 2 weeks) if treated with LV5FU2 or FOLFOX4, or 8 cycles (1 cycle every 3 weeks) if treated with capecitabine or XELOX. The total planned number of patients to be enrolled is 982: 378 in each arm A and B and 113 in each arm C and D.

The main objective of the present analysis requested by the independent study committee is to report on the tolerance to the allocated treatment in each arm, at 50% of the planned patients to be enrolled in the study with a minimum of 6 months of follow-up after randomization. Thus, the preliminary analysis was performed on the first consecutive patients enrolled in the trial reaching 189 patients in arm A and B, 57 in arm C and 56 in arm D.

The secondary objectives were defined by the study coordination team to have an overview of the proper application of the main study procedures; though no specific rules were set to stop the study otherwise: 1) to verify that the investigators' choice to allocate a patient to Group 1 or Group 2 is supported by geriatric parameters, and 2) to assessed treatment administration in each arm. The present analysis was submitted to the independent study committee for advice and ruling on safety.

The safety evaluation is based on laboratory test performed before each cycle and clinical evaluation in arms A, B and D, and all observed toxicities are graded according to National Cancer Institute - Common Toxicity Criteria version 4 (NCI-CTCv4).

Baseline geriatric evaluations assessed co-morbidities (actualized Charlson score) [18], quality of life (Spitzer) [19], physical activity assess by a Risk Factor Questionnaire (RFQ) [20], cognitive functions assess by the short cognition questionnaire (mini-COG) [21], nutrition assess by Mini-Nutritional Assessment Short-Form (MNA-SF) [22], Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) [23], depression assessed by the brief version of the Geriatric Depression Scale (mini-GDS) [24], audition, vision, mobility (one-leg balance $<$ 5 s or falls within 6 months) [25] and G8 score [17]. All the geriatric scores were performed by the investigator's team at inclusion and during the follow-up. The scoring takes no more than 10 min.

This protocol, sponsored by the FFCD, is registered on clinicaltrials.gov with the number NCT02355379. PRODIGE 34 - ADAGE is an intergroup study with a partnership with GERCOR, UNICANCER-GI and the Belgian Group of Digestive Oncology (BGDO). The trial was approved by a national ethics committee (Comité de Protection des Personnes Ile-de-France VIII on the 08th of July 2014). An independent study committee was set up with a statistician, an oncologist, a gastroenterologist and a pharmacovigilant; none of whom were involved in the trial. The data are collected by the FFCD team from the patient's records, after they have provided their written informed consent. Data are stored and analyzed at the FFCD data center in Dijon (France).

2.2. Statistical analysis

In this report, baseline characteristics were described on the intent to treat (ITT) population. The safety analysis (treatment, toxicities) was carried out in the modified ITT (mITT) population, defined as all patients having received at least one dose of chemotherapy. Patients were analyzed according to the treatment received. Toxicities were described by treatment group based on NCI-CTC v4.0 grade. Dose intensity was calculated and reported for each treatment and by treatment group. Qualitative and continuous variables were described using usual descriptive statistics, respectively: numbers and percentages and medians with Q1-Q3. The number of patients with available data is indicated for every variable and the percentages are calculated for each variable accordingly. The cause of death was prospectively reported by the investigator in the case report form. This preliminary tolerance analysis was performed on 50% of the first patients enrolled in the study. The inclusions started on January 2015, and are still ongoing. The database was frozen for this analysis on September 9th, 2020.

3. Results

3.1. Patients' characteristics

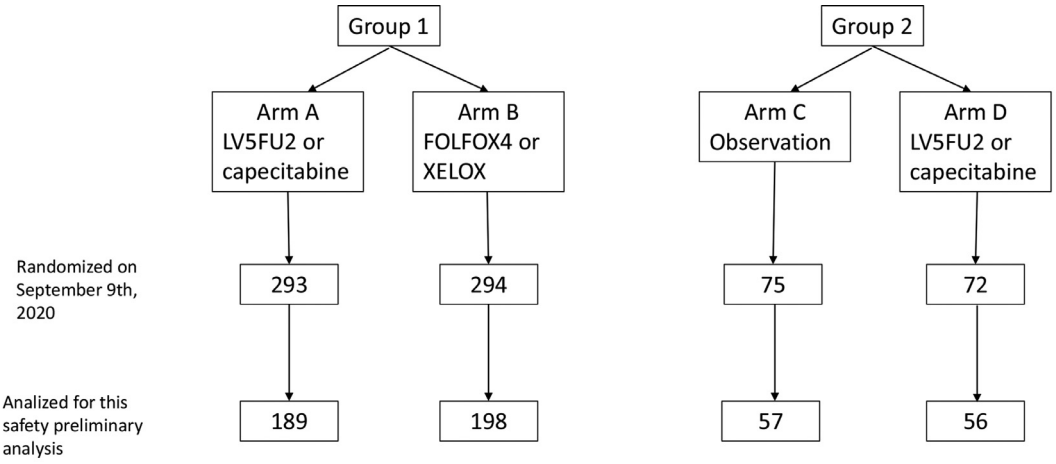
At the time the database was frozen, 734 of the planned 982 patients were enrolled in 108 participating centers. The analysis was conducted on 491 patients, 378 in Group 1 and 113 in Group 2 (Fig. 1). The median follow-up for these 491 patients at the time of analysis was 28 months. Baseline patients' characteristics are reported in Table 1, and the baseline geriatric parameters are reported in Table 2. Patients enrolled in Group 2 were older (83.1 vs 76.4 years), had a worse ECOG and more frequently presented a deficient mismatch repair/high-microsatellite instability (dMMR/MSI-H) tumor (25% *vs* 16.8%) than did patients enrolled in Group 1. Moreover, patients in Group 2 were more likely to have occlusions or perforations at diagnosis (21.4% *vs* 16.8%), as well as anemia (18.7% *vs* 6.4%) and hypoalbuminemia (25% *vs* 15.3%) at baseline. Breakdown of stage at diagnosis and location of the primary tumor were similar in both groups. Geriatric parameters among patients in Group 2 were worse than those in Group 1 except for the presence of a caregiver, that was similar in both groups.

3.2. Treatment administration

The treatment was started in almost all patients of Group 1 but in only 83.9% of Group 2 patients (Table 3). Infusion of 5-fluorouracil was used in more than 80% of the patients in Group 1 but only in 36.2% in Group 2. The median duration of treatment was similar in both groups. A delay in at least one course was more frequently observed in patients treated with oxaliplatin (66.8%) compared to what is observed in arm A and arm D patients (56.2% and 59.6% respectively). Dose reduction was more frequent in Group 1 patients receiving capecitabine and/or oxaliplatin. The early termination of treatment was more frequent in arm D (38.3%) and in arm B (21%) compare to arm A (16.9%).

3.3. Toxicity

Cumulative grade 3–5 toxicities were more frequently observed in patients treated with oxaliplatin in Group 1 (57.8%) or with fluoropyrimidine in Group 2 (40.4%) than was the case in Group 1 patients treated with fluoropyrimidine alone (25.9%) (Table 4). Cumulative grade 3–5 neurologic toxicity (20.9%) and neutropenia (21.9%) were more frequent in Group 1 patients treated with ox-



LV5FU2: leucovorin 400 mg/m² as a 2-hour IV infusion, 5FU 400 mg/m² IV bolus and 5FU 2400 mg/m² as a 46-hour continuous infusion, every 2 weeks.
FOLFOX4: LV5FU2 in combination with oxaliplatin administered at D1 as a 120-min IV perfusion 85 mg/m².
Capecitabine: 1000 mg/m² BID from D1 to D14 for cycle 1 and cycle 2 then if no toxicity of grade >1 increase at 1250 mg/m2 BID from D1 to D14 for the following cycles every 3 weeks.
XELOX: capecitabine 800 mg/m² BID from D1 to D14 for cycle 1 and cycle 2 then if no toxicity of grade >1 increase at 1000 mg/m² BID from D1 to D14 for the following cycles combined with oxaliplatin administered at D1 as a 120-min IV perfusion 130 mg/m².

Fig. 1. Flow Chart.

Table 1
Main characteristics of patients and tumors at baseline.

Characteristics		Treatment allocated by randomization					
		Group 1: LV5FU2 or capecitabine	Group 1: t FOLFOX4 or XELOX	Total Group 1	Group 2: Observation	Group 2: LV5FU2 or capecitabine	Total Group 2
		N = 189	*N* = 189	*N* = 378	*N* = 57	*N* = 56	*N* = 113
Sex (*n* = 491)	Male	111 (58.7%)	106 (56.1%)	**217 (57.4%)**	28 (49.1%)	28 (50.0%)	**56 (49.6%)**
Age (*n* = 491)	Median (extremes)	76.9 (70–90)	75.8 (70–89)	**76.4 (70–90)**	83.4 (71–89)	82.7 (70–91)	**83.1 (70–91)**
ECOG (*n* = 462) :	0	110 (60.8%)	104 (57.8%)	**214 (59.3%)**	12 (23.1%)	17 (34.7%)	**29 (28.7%)**
	1	62 (34.3%)	71 (39.4%)	**133 (36.8%)**	27 (51.9%)	21 (42.9%)	**48 (47.5%)**
	2	8 (4.4%)	5 (2.8%)	**13 (3.6%)**	13 (25.0%)	10 (20.4%)	**23 (22.8%)**
	3	1 (0.6%)	0 (0.0)	**1 (0.3%)**	0 (0.0)	1 (2.0%)	**1 (1.0%)**
Hemoglobin (gr/dl) (*n* = 488)	<10 (Women), <11 (Men)	14 (7.5%)	10 (5.3%)	**24 (6.4%)**	10 (17.5%)	11 (20%)	**21 (18.7%)**
Renal insufficiency (*n* = 488)	Creatinine clearance* ≤45 mL/min	10 (5.3%)	15 (7.9%)	**25 (6.6%)**	11(19.3%)	12 (21.8%)	**23 (20.5%)**
Hypoalbuminemia (*n* = 440)	≤35 g/L	28 (16.7%)	24 (14.0%)	**52 (15.3%)**	14 (29.2%)	11 (21.2%)	**25 (25.0%)**
Stage (*n* = 488)	Stage IIIA	19 (10.2%)	24 (12.7%)	**43 (11.4%)**	4 (7.0%)	4 (7.3%)	**8 (7.1%)**
	Stage IIIB	139 (74.3%)	134 (70.9%)	**273 (72.6%)**	43 (75.4%)	43 (78.2%)	**86 (76.8%)**
	Stage IIIC	29 (15.5%)	31 (16.4%)	**60 (16.0%)**	10 (17.5%)	8 (14.5%)	**18 (16.1%)**
Occlusion or perforation (*n* = 488)	Yes	29 (15.5%)	34 (18.0%)	**63 (16.8%)**	10 (17.5%)	14 (25.5%)	**24 (21.4%)**
Primary location (*n* = 487)	Left colon	82 (43.9%)	87 (46.0%)	**169 (44.9%)**	20 (35.7%)	24 (43.6%)	**44 (39.6%)**
	Right colon	103 (55.1%)	96 (50.8%)	**199 (52.9%)**	34 (60.7%)	29 (52.7%)	**63 (56.8%)**
	Left and right colon	0 (0.0)	1 (0.5%)	**1 (0.3%)**	2 (3.6%)	0 (0.0)	**2 (1.8%)**
	Upper rectum	2 (1.1%)	5 (2.6%)	**7 (1.9%)**	0 (0.0)	2 (3.6%)	**2 (1.8%)**
Emergency surgery (*n* = 487)	Yes	27 (14.4%)	26 (13.8%)	**53 (14.1%)**	5 (8.9%)	11 (20.0%)	**16 (14.4%)**
MMR Status (*n* = 154)	MSI-H	10 (17.5%)	9 (16.1%)	**19 (16.8%)**	3 (15.0%)	7 (35.0%)	**10 (25.0%)**

MMR: Mismatch repair; MSI-H: high microsatellite instability.
* Creatinine clearance was calculated according the Cockroft and Gault formula.

aliplatin, while Group 2 patients more frequently had hand foot syndrome (all grade 40.4%).

A preliminary assessment of deaths is given in Table 5. Only one death was related to treatment toxicity. At the time of analysis, death was more frequently reported in group 2 than in group 1 patients (21% *vs* 11%). Deaths are slightly less related to colon cancer in group 2 than in group 1 (46% *vs* 53%). Moreover, there are more deaths related to other causes in Group 2 than in group 1 (42% *vs* 23%).

4. Discussion

PRODIGE 34 – ADAGE is the first prospective randomized phase III trial to evaluate adjuvant chemotherapy after R0 resection of stage III colon cancer specifically in older patients [17]. In view of the results presented in this preliminary safety analysis, the independent study committee gave it's approval for study continuation.

The characteristics of the two groups were distributed as expected. Group 2 patients were older and had more frailty

Table 2
Baseline geriatric evaluation.

Geriatric characteristics		Treatment allocated by randomization					
		Group 1: LV5FU2 or capecitabine	Group 1: FOLFOX4 or XELOX	Total Group 1	Group 2: Observation	Group 2: LV5FU2 or capecitabine	Total Group 2
		N = 189	*N* = 189	*N* = 378	*N* = 57	*N* = 56	*N* = 113
IADL* (*n* = 472)	Abnormal	41 (23.2%)	43 (23.2%)	**84 (23.2%)**	38 (66.7%)	30 (56.6%)	**68 (61.8%)**
ADL (*n* = 473)	≤5	24 (13.5%)	26 (14.1%)	**50 (13.8%)**	19 (33.3%)	11 (20.8%)	**30 (27.3%)**
Caregiver (*n* = 472)	Yes	144 (80.9%)	161 (87.0%)	**305 (84.0%)**	44 (78.6%)	45 (84.9%)	**89 (81.7%)**
Living at home (*n* = 471)	Yes	171 (96.1%)	167 (91.3%)	**338 (93.6%)**	46 (80.7%)	44 (83.0%)	**90 (81.8%)**
Hospitalization <12 months (*n* = 486)	Yes	137 (77.8%)	149 (81.0%)	**286 (79.4%)**	51 (91.1%)	42 (80.8%)	**93 (86.1%)**
Fall <6 months (*n* = 471)	Yes	14 (7.9%)	17 (9.2%)	**31 (8.6%)**	8 (14.0%)	8 (15.1%)	**16 (14.5%)**
One-leg balance (*n* = 461)	>5 s	139 (79.9%)	142 (79.8%)	**281 (79.8%)**	22 (38.6%)	23 (44.2%)	**45 (41.3%)**
Gait speed (*n* = 286)	>4 s	24 (22.9%)	27 (24.1%)	**51 (23.5%)**	18 (45.7%)	16 (45.7%)	**34 (49.3%)**
Mini GDS (*n* = 467)	≥1	51 (29.0%)	49 (27.1%)	**100 (28.0%)**	25 (43.9%)	19 (35.8%)	**44 (40.0%)**
Mini-COG (*n* = 463)	Abnormal	39 (22.5%)	35 (19.3%)	**74 (20.9%)**	26 (46.4%)	16 (30.2%)	**42 (38.5%)**
Energy score (*n* = 470)	≤5	29 (16.6%)	25 (13.5%)	**54 (15.0%)**	22 (38.6%)	14 (26.4%)	**36 (32.7%)**
RFQ score (*n* = 466)	≤2	76 (43.4%)	70 (38.5%)	**146 (40.9%)**	37 (64.9%)	30 (57.7%)	**67 (61.5%)**
Weight loss >4 kg (*n* = 470)	Yes	103 (58.9%)	107 (57.8%)	**210 (58.3%)**	36 (63.2%)	40 (75.5%)	**76 (69.1%)**
MNA-SF (*n* = 464)	<11	61 (34.9%)	64 (35.6%)	**125 (35.2%)**	29 (50.9%)	23 (44.2%)	**52 (47.7%)**
Hearing impairment (*n* = 469)	Yes	60 (34.3%)	50 (27.0%)	**110 (30.6%)**	26 (46.4%)	18 (34.0%)	**44 (40.4%)**
Lee score (*n* = 469)	Median (Q1; Q3)	8 (7; 10)	8 (7; 9)	**8 (7; 9)**	12 (9; 13)	11 (9.5; 12.5)	**11 (9; 13)**
Modified Charlson score (*n* = 468)	>2	30 (17%)	22 (12%)	**52 (14.5%)**	21 (36.8%)	21 (40.4%)	**42 (38.5%)**
Spitzer index (*n* = 469)	<9	40 (22.6%)	52 (28.4%)	**92 (25.6%)**	35 (62.5%)	26 (49.1%)	**61 (56.0%)**
G8 score (*n* = 464)	≤14	130 (74.3%)	138 (76.7%)	**268 (75.5%)**	54 (94.7%)	48 (92.3%)	**102 (93.58%)**

ADL: autonomy daily living, IADL: instrumental activity of daily living, mini-GDS: mini-Geriatric Depression Scale, mini-COG: mini-cognition evaluation, RFQ: Risk Factor Questionnaire, MNA-SF: mini-nutritional assessment short-form.
* IADL adapted for sex-specific questions according to the patient.

Table 3
Treatment delivered.

	Allocation arm		
	Group 1 LV5FU2 or capecitabine *n* = 189	Group 1 FOLFOX4 or XELOX *N* = 189	Group 2 LV5FU2 or capecitabine *N* = 56
	Treatment received		
Treatment started	185 (98.4%)	187 (98.4)%	47 (83.9%)
Type of fluoropyrimidine	LV5FU2: 154 (82.7%)[a] Capecitabine: 31 (16.8%)	FOLFOX: 166 (88.8%) XELOX: 21 (11.2%)	LV5FU2: 17 (36.2%) Capecitabine: 30 (63.8%)
Median duration of treatment	5.1 months	5.3 months	5.0 months
At least one cure delayed	104 (56.2%)	125 (66.8%)	28 (59.6%)
Median ratio of cumulative received dose / theoretical dose (Q1; Q3)			
- Bolus 5FU	99.0% (73.7; 100.0)	62.5% (32.6; 96.2)	85.1% (61.7; 98.7)
- Continuous 5FU	99.4% (87.5; 100.0)	92.0% (77.4; 99.8)	90.9% (73.9; 100.1)
- Capecitabine	79.3% (68.0; 87.2)	80.1% (66.3; 95.4)	75.8% (25.9; 84.2)
- Oxaliplatin	NA	70.2%	NA
Cumulative number of courses with reduce dose / total number of courses			
- Bolus 5FU	149/1570 (9.5%)	325/1304 (24.9%)	42/156 (26.9%)
- Continuous 5FU	192/1698 (11.3%)	518/1265 (29.0%)	48/175 (27.4%)
- Capecitabine	119/234 (50.9%)	55/143 (38.5%)	48/182 (26.4%)
- Oxaliplatin	NA	650/1597 (40.7%)	NA
Early cessation of treatment	31 (16.9%)	39 (21.0%)	18 (38.3%)

[a] One patient received FOLFOX instead of LV5FU2 by mistake during one course.

characteristics than did those in Group 1. This suggest that the evaluation of the patients by the oncologist, eventually completed by a geriatric evaluation, before study enrollment was accurate. This preliminary result is important to verify the feasibility of the study based on investigator evaluation for group allocation. A comparison of accuracy of group allocation by oncologist according to pre-inclusion geriatric evaluation or not is planned for the final analysis. The scoring performed in PRODIGE 34 - ADAGE trial was already used in the PRODIGE 20 study [26]. Although the purpose of this trial was not to evaluate the accuracy of the geriatric scoring, it is noteworthy that since we have designed our trial, and open it for enrollment, another consensual scoring system (G-CODE) for oncogeriatric studies has been published [27]. Thus, we were not able to use it, but the G-CODE is close to our scoring system.

Several prognostic factors differed according to the group. The proportion of patients with dMMR/MSI-H tumors was higher in Group 2 due to older age, in accordance with previously published data [28]. This difference probably affected the disease prognosis in Group 2, as dMMR/MSI-H tumors have a better prognosis [29].

T stage and number of metastatic lymph nodes at diagnosis were similar in both groups. However, patients in Group 2 were more likely to have perforated tumors or occlusions at diagnosis. This is in line with the documented high frequency of emergency surgery in older patients [30], which in turn is associated with a worse prognosis, especially in older patients [31].

Table 4
Main toxicities observed.

Toxicities grade 1–2 / 3–5	Treatment received		
	Group 1: LV5FU2 or capecitabine $n = 189$	Group 1: FOLFOX4 or XELOX$N = 189$	Group 2: LV5FU2 or capecitabine $N = 56$
Neurologic	20.5% / 0.5%	87.2% / 20.9%	19.1% / 4.3%
Asthenia	58.9% / 3.8%	63.6% / 8.0%	48.9% / 10.6%
Anorexia	7.6% / 1.1%	28.3% / 2.1%	12.8% / 0%
Diarrhea	42.2% / 4.3%	48.7% / 8.6%	40.4% 6.4%
Mucositis	23.8% / 0.5%	24.6% / 1.6%	19.1% / 0%
Hand foot syndrome	26.5% / 2.2%	11.2% / 0.5%	38.3% / 2.1%
Vomiting	7.0% / 1.1%	13.4% / 2.1%	4.3% / 0%
Nausea	30.8% / 0.5%	44.4% / 2.7%	21.3% / 0%
Cardiac disorder	2.2% / 0.5%	1.6% / 1.1%	6.4% / 4.3%
Neutropenia grade	18.4% / 2.7%	35.8% / 21.9%	17.0% / 6.4%
Anemia	55.1% / 0%	69.5% / 0%	70.2% / 2.1%
Elevated ALAT	10.3% / 0.5%	18.7% / 1.1%	2.1% / 0%
Elevated ASAT	9.2% / 0.5%	34.2% / 0.5%	4.3% / 0%
Elevated bilirubin	9.7% / 0%	2.7% / 0%	17.0% / 0%
Cumulated grade 3–5	25.9%	57.8%	40.4%
≥ 1 serious adverse event related to treatment	7.5%	10.2%	9.7%

Table 5
Main causes of death.

			Treatment received			
	Group 1: LV5FU2 or capecitabine $n = 189$	Group 1: FOLFOX4 or XELOX$N = 189$	Total Group 1 $N = 378$	Group 2: LV5FU2 or capecitabine$N = 56$	Group 2: Observa-tion$N = 57$	Total Group 2 $N = 113$
Total of all deaths	27 (14%)	16 (8%)	43 (11%)	10 (18%)	14 (25%)	24 (21%)
Death related to colon cancer	15 (56%)	8 (50%)	23 (53%)	4 (44%)	7 (50%)	11 (46%)
Death related to toxicity	0 (0%)	1 (6%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Death related to another cancer	1 (4%)	2 (12%)	3 (7%)	0 (0%)	0 (0%)	0 (0%)
Death related to other disease	7 (26%)	3 (19%)	10 (23%)	4 (44%)	6 (43%)	10 (42%)
Death with unspecified cause	4 (15%)	2 (12%)	6 (14%)	1 (11%)	1 (7%)	2 (8%)

Capecitabine was more frequently used in Group 2 than in Group 1. The investigator had the choice to treat with capecitabine or 5FU before randomization. Capecitabine monotherapy is an attractive oral treatment that needs no central venous access port. This preliminary analysis shows more toxicity and more early treatment discontinuation in arm D than in arm A. It could be speculated that it could be partially due to a worst tolerance of capecitabine compare to 5FU in older patients. However, this preliminary analysis in 50% of the first enrolled patients was not designed to assess the toxicity profile of capecitabine compared to 5FU. The final analysis will have an exploratory comparison of 5FU *vs* capecitabine.

In this preliminary analysis, we found a trend towards a lower proportion of patients starting adjuvant treatment in Group 2 than in Group 1. Frail patients enrolled in Group 2 may not have been able to start the planned chemotherapy. Both intent-to-treat and per-protocol analyses will be carried out in Group 2. Moreover, an early cessation of treatment was more frequent in Group 2 than in Group 1. It has already been reported that increasing age is associated with early discontinuation of adjuvant chemotherapy [32]. Interestingly, the rate of early discontinuation was twice higher in arm D than in arm B, but the severe toxicity rate is higher in arm B than in arm D. This observation suggests that early discontinuation of treatment is not only a matter of toxicity grade but also a matter of patients' ability to handle toxicity, and their willingness to continue a treatment despite its toxicity and/or the willingness of the physician to continue the treatment in a frail patient. This result advocate for a tailored treatment according to patients' global health state. The duration of adjuvant chemotherapy is still a matter of debate. The IDEA study showed that 3 months of XELOX was equivalent to 6 months of XELOX in terms of disease-free survival for patients who had an R0 resection of a T1–3N1 colon cancer [33]. It must be pointed out that XELOX was chosen by the investigator, only for a minority of the patients of arm B. Nevertheless, an evaluation of the efficacy of adjuvant treatment according to treatment duration will be performed in the final analysis. It is noteworthy that the purpose of the PRODIGE 34 – ADAGE trial is not to compare different durations of chemotherapy. No study has explored the effect of shortening adjuvant chemotherapy with fluoropyrimidine alone to 3 months. Thus, it will be very interesting to compare DFS in patients treated with 6 months *vs.* 3 months of monotherapy.

As expected, cumulative grade 3–5 toxicities were more frequently observed in patients treated with oxaliplatin + fluoropyrimidine than in those treated with fluoropyrimidine alone. Nevertheless, the toxicity observed in the arm with oxaliplatin in our study was similar to that observed in the pivotal study of oxaliplatin, except for neutropenia [9]. Neutropenia was also less frequent in our study than was the case in a pooled *post-hoc* analysis of prospective trials assessing the toxicity of oxaliplatin according to age [13]. It must be pointed out that in the PRODIGE 34 - ADAGE trial, hematological toxicity is assessed before each cycle and not at the nadir of hematological toxicity.

Cumulative grade 3–5 toxicity in the monotherapy arm was higher in Group 2 than in Group 1. This may be due to the greater vulnerability of older patients, but poorer tolerance to capecitabine cannot be ruled out in older patients, especially for hand foot syndrome [34]. Few patients were treated with capecitabine in Group 1, probably because investigators were reluctant to use capecitabine + oxaliplatin, as this combination has been reported to be poorly tolerated in older patients [35,36]. Moreover, we observed a high rate of early discontinuation of treatment especially in Group 2. This suggests that a severe toxicity rate is not accurate to assess the global tolerability of a treatment in older and frail patients.

The number of deaths related to the cancer was higher in Group 1 than in Group 2; in Group 1 around half of the deaths were related to the cancer compared with only 40% in Group 2. Death unrelated to cancer in Group 2 were probably due to frailty. Nevertheless, in both groups, the large number of deaths related to cancer underlines the need to improve adjuvant therapy after resection of a stage III tumor in older patients. Nevertheless, the follow-up is too short and the number of events too low to draw conclusions about death occurrence according to group attribution. These results are preliminary, and should be confirmed by a further analysis with a longer follow-up.

Our study has some limitations. First, it is a preliminary assessment of toxicity in half of the planned number of patients to be enrolled. Thus, conclusions should be taken with caution and sub-group analysis are limited due to the lack of power. Second, successive quality of life assessments were not available for the present analysis and will be reported with the final analysis. Third, chemotherapy regimen did not plan a systematic dose reduction as it is often proposed in trials dedicated to older patients [14,15,37]. This may explain the high rate of treatment discontinuation. Finally, the choice to treat patients with capecitabine or 5-fluorouracil is not controlled in this study, thus comparison between these two drugs may be biased.

In conclusion, the frailty criteria distribution suggests that the investigator's evaluation for group allocation was accurate. The toxicities of adjuvant chemotherapy after resection of stage III colon adenocarcinoma observed in this preliminary toxicity analysis is comparable to the toxicity rate observed in previous studies. The high rate of early treatment cessation in patients deemed by the investigator to be ineligible for doublet chemotherapy is a concern and needs further evaluation in the final analysis of the trial. The PRODIGE 34 – ADAGE trial is continuing its accrual.

Conflict of interest

Thomas Aparicio declared Honoraria from Sanofi, Roche, Amgen, Servier, Pierre Fabre and Astra Zeneca; Consultancy / Advisory role for Bioven, Pierre Fabre, MSD and Sirtec; Travel accommodations from Roche.

Olivier Bouché reports personal fees as a speaker and/or in an advisory role from Merck KGaA, Roche, Bayer, Astra-Zeneca, Grunenthal, MSD, Amgen, Sanofi, Servier, and Pierre Fabre, outside the submitted work.

Pierre-Luc Etienne declared Travels and congress accomodations Roche, BMS, Servier, and research honoraria BMS

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