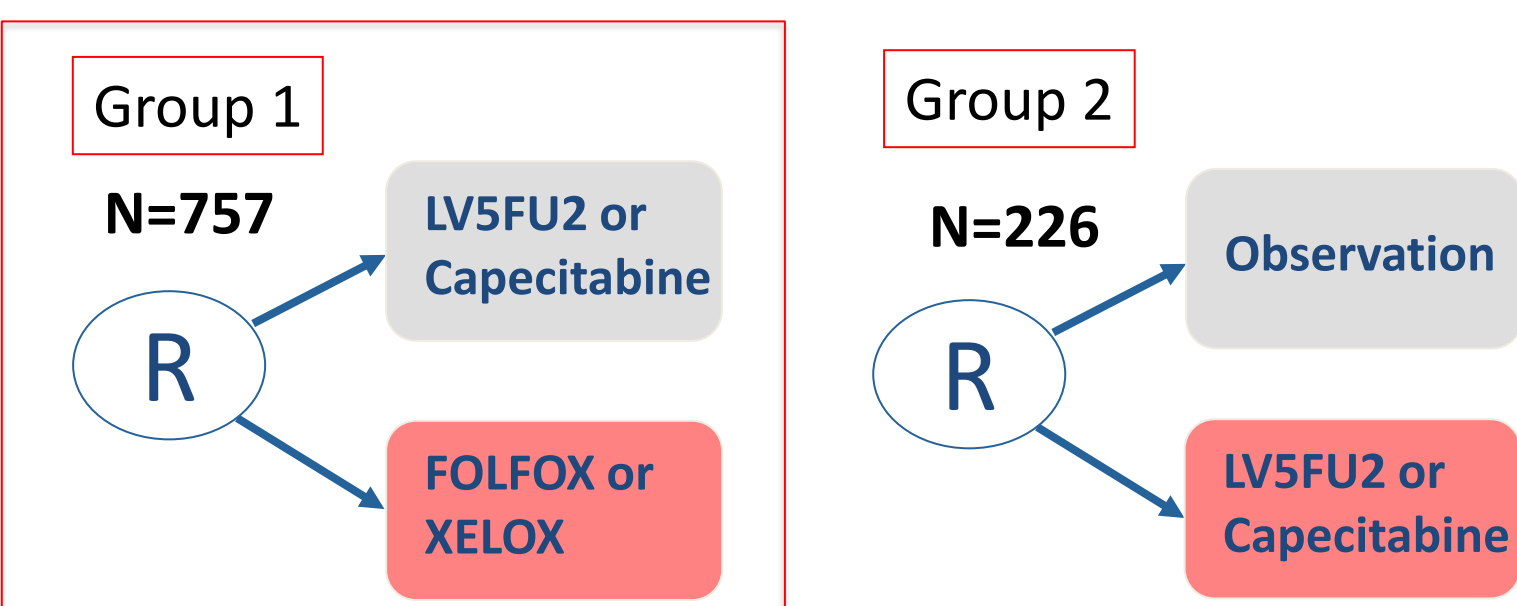


## Background

Colon adenocarcinoma occurs mainly in older patients. Oxaliplatin based adjuvant chemotherapy has demonstrated an improvement on disease-free survival (DFS) after a stage III colon cancer resection in young patients. Nevertheless, the benefit of adjuvant chemotherapy is matter of debate in older patients.

## Patients &amp; Methods

The purpose of ADAGE trial is to compare the DFS obtain with oxaliplatin combined with fluoropyrimidine (**Ox**) to fluoropyrimidine alone (**F**) in fit patients over 70 years (**group 1**) and fluoropyrimidine to observation in frail patients (group 2) after resection of a stage III colon cancer. We report the tolerance at 6 months after the beginning of the treatment, the dose reduction and the early discontinuation of chemotherapy in Group 1



**Treatment:** Planned for 6 months (12 cycles if LV5FU2 or FOLFOX or 8 cycles if capecitabine or XELOX), should start within 12 weeks after surgery

## Main eligibility criteria

- Age over 70 years
- Stage III colon or upper rectal adenocarcinoma
- R0 resection of the primary tumor
- Patient considered able to receive chemotherapy
- No previous chemotherapy for colon cancer
- Written informed consent
- No other cancer uncontrolled for less than 2 years
- Neutrophils >2000/mm<sup>3</sup> for group 1 and neutrophils >1500/mm<sup>3</sup> for group 2, platelets >100,000/mm<sup>3</sup>, haemoglobin >9 g/dL

**Randomization** according to a 1:1 ratio.

**Stratification:** center, gender, stage (IIIA vs IIIB vs IIIC), occlusion and/or perforation (yes vs no) and independent activity of daily living score (IADL: normal vs abnormal).

**Safety** is evaluated based on laboratory and clinical tests before each cycle.

## Patients and tumor characteristics of Group 1

The analysis was performed on 757 patients (378 in **Ox arm** and 379 in **F arm**).

Characteristics	LV5FU2 or capecitabine n=379	FOLFOX4 or XELOX n=378	Total n=757	
<b>Sex</b> (n=757)	Male	215 (56.7%)	216 (57.1%)	431 (56.9%)
<b>Age</b> (n=757)	Median (extremes)	77.5 (70-91)	76.9 (70-88)	77.2 (70-91)
	0	200 (54.9%)	210 (57.2%)	410 (56.1%)
<b>ECOG</b> (n=731)	1	153 (42.0%)	151 (41.1%)	304 (41.6%)
	2-3	11 (3.0%)	6 (1.6%)	17 (2.3%)
<b>BMI</b> (kg/m <sup>2</sup> ) (n=748)	Median (extremes)	25.6 (16.4-43.5)	25.7 (16.6-45.1)	25.4 (16.4-45.1)
<b>Hemoglobin</b> (gr/dl) (n=756)	<10 (Women), <11 (Men)	30 (7.9%)	24 (6.3%)	54 (7.1%)
<b>Creatinine</b>	>N	56 (15%)	55 (14.8%)	111 (14.9%)
<b>Hypoalbuminemia</b> (n=696)	≤35 g/L	47 (13.5%)	48 (13.8%)	95 (13.6%)
	Stage IIIA	35 (9.2%)	41 (10.8%)	76 (10.0%)
<b>Stage</b> (n=757)	Stage IIIB	274 (72.3%)	272 (72.0%)	546 (72.1%)
	Stage IIIC	70 (18.5%)	65 (17.2%)	135 (17.8%)
<b>Occlusion or perforation</b> (n=757)	Yes	58 (15.3%)	75 (19.8%)	133 (17.6%)
	Left colon	144 (38.3%)	167 (44.2%)	311 (41.2%)
<b>Primary localization</b> (n=754)	Right colon	204 (54.3%)	195 (51.6%)	399 (52.9%)
	Left and right colon	1 (0.3%)	1 (0.3%)	2 (0.3%)
	Upper rectum	27 (7.2%)	15 (4.0%)	42 (5.6%)
<b>Emergency surgery</b> (n=754)	Yes	50 (13.3%)	56 (14.8%)	106 (14.1%)
<b>MMR Status</b> (n=366)	MSI	31 (16.3%)	29 (16.5%)	60 (16.4%)
<b>Geriatric scoring</b>				
<b>Updated Charlson score</b> (n=730)	>2	52 (14.3%)	44 (12%)	96 (13.2%)
<b>IADL (4 item)</b> (n=738)	≤3	28 (7.6%)	18 (4.9%)	46 (6.2%)
<b>Caregiver</b> (n=734)	None	75 (20.5%)	61 (16.6%)	136 (18.5%)
<b>Fall ≤6 months</b> (n=737)	Yes	37 (10.1%)	30 (8.1%)	67 (9.1%)
<b>One-leg balance</b> (n=718)	<5 second	83 (23.2%)	69 (19.1%)	152 (21.2%)
<b>Depression</b> (n=730)	MINI-GDS ≥1	102 (27.9%)	97 (26.6%)	199 (27.3%)
<b>Cognition</b> (n=728)	Impaired MINI-COG	77 (21.2%)	71 (19.5%)	148 (20.3%)
<b>Nutrition</b> (n=728)	MNA-SF <11	242 (66.9%)	246 (67.2%)	488 (67%)
<b>G8 score</b> (n=729)	<14	267 (73.6%)	274 (74.9%)	541 (74.2%)
<b>Quality of life</b> (n=736)	Spitzer <9	79 (21.6%)	94 (25.4%)	173 (23.5%)

## Conclusions

- Adjuvant chemotherapy with oxaliplatin is feasible in fit older patients
- Oxaliplatin cause an increase of severe toxicity and a decrease of dose intensity.
- Patients over 75 and women are more at risk for toxicity.

## Treatment delivered

	Arm F N=366 Fluoropyrimidine	Arm Ox N=373 FOLFOX or XELOX
<b>Type of fluoropyrimidine</b>	5FU: 304 (83.1%) Cape: 62 (16.9%)	FOLFOX: 332 (89%) XELOX: 41 (11%)
<b>Median treatment duration</b>	5.1 months	5.3 months
<b>Early stop of treatment</b>	13.9%	18.5%
<b>Mean dose intensity</b>		
- 5FU bolus	81.2%	59.9%
- 5FU continuous	89.8%	84.3%
- Capecitabine	72.2%	72.7%
- Oxaliplatin	NA	63%

## Univariate analysis to predict grade 3-5 toxicity

Characteristics		Odd ratio [95% CI]	p value
<b>Treatment</b>	Ox vs F	<b>3.64 [2.68-4.95]</b>	<b>&lt;0.0001</b>
<b>Sex</b>	Male vs Women	<b>0.73 [0.54-0.98]</b>	<b>0.035</b>
<b>Age</b>	>80 vs ≤80	1.09 [0.79-1.51]	0.591
<b>ECOG</b>	≥1 vs 0	1.11 [0.82-1.48]	0.502
	<22	0.99 [6.64-1.55]	
	22-25	Ref	0.438
	25-30	1.16 [0.81-1.65]	
	≥30	0.80 [0.50-1.28]	
<b>BMI</b> (kg/m <sup>2</sup> )			
<b>Updated Charlson score</b>	>2 vs ≤2	1.09 [0.70-1.68]	0.708
<b>IADL (4 items)</b>	≤3 vs 4	0.99 [0.54-1.82]	0.989
<b>Fall ≤ 6 months</b>	Yes vs no	0.83 [0.49-1.39]	0.467
<b>One-leg balance</b>	≤5 sec vs >5 sec	1.05 [0.73-1.51]	0.794
<b>Nutrition (MNA-SF)</b>	<11 vs ≥11	1.19 [0.87-1.63]	0.279
<b>Cognition (MINI-COG)</b>	Impaired vs normal	1.23 [0.86-1.78]	0.260
<b>Depression (MINI-GDS)</b>	≥1 vs 0	1.00 [0.72-1.39]	0.997
<b>Hemoglobin</b>	<normal vs normal	1.33 [0.75-2.25]	0.336
<b>Clearance creatinine</b>	>60 vs ≤60 ml/min	0.76 [0.54-1.07]	0.111
<b>Albuminemia</b>	≤35 vs >35 g/L	1.05 [0.67-1.63]	0.843
<b>G8 score</b> (n=729)	≤14 vs >14	1.21 [0.86-1.69]	0.277
<b>Quality of life</b>	Spitzer <9 vs ≥9	0.97 [0.69-1.37]	0.873

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## Observed toxicities

Main toxicities grade 1-2 / 3-5	Arm F: N=366 Fluoropyrimidine	Arm Ox: N=373 FOLFOX or XELOX
Anaemia	56.6% / 0%	64.1% / 0.5%
Neutropenia	19.4% / 3%	31.4% / 22.5%
Thrombopenia	18% / 0%	69.7% / 2.1%
Diarrhoea	42.1% / 4.9%	46.6% / 8.6%
Mucositis	25.7% / 0.3%	27.6% / 0.8%
Vomiting	8.2% / 0.5%	10.7% / 1.3%
Anorexia	11.7% / 0.5%	25.2% / 1.6%
Hepatic disorder	32.2% / 1.1%	52% / 7.2%
Hand foot syndrome	27.6% / 2.5%	11% / 0.8%
Asthenia	59.8% / 3.3%	70% / 5.9%
Neurotoxicity	<b>10.9% / 0.3%</b>	<b>82% / 19.8%</b>
<b>Cumulated grade 3-5</b>	<b>97.5% / 27.9%</b>	<b>99.7% / 58.4%</b>

## Multivariate analysis for grade 3-5 toxicity in all patients

	OR [95% CI]	p
<b>Treatment Ox vs F</b>	3.86 [2.80-5.32]	<0.0001
<b>Age: &lt;75 [75-80] &gt;80</b>	Ref 1.64 [1.13-2.39] 1.43 [0.94-2.17]	0.031
<b>Male vs women</b>	0.72 [0.52-0.99]	0.042

## Multivariate analysis for grade 3-5 toxicity in Arm F

	OR [95% CI]	p
<b>5FU vs capecitabine</b>	0.67 [0.37-1.22]	0.187
<b>Male vs women</b>	<b>0.60 [0.38-0.96]</b>	<b>0.034</b>
<b>Creatinin clearance &gt;45 vs ≤45 ml/min</b>	0.39 [0.14-1.06]	0.064

## Multivariate analysis for grade 3-5 toxicity in Arm Ox

	OR [95% CI]	p
<b>FOLFOX vs XELOX</b>	1.66 [0.83-3.31]	0.151
<b>Age: &lt;75 [75-80] &gt;80</b>	Ref 2.05 [1.21-3.47] 1.29 [0.70-2.35]	0.025
<b>Cognition Impaired vs normal</b>	1.52 [0.86-2.68]	0.151