

# # A59 Phase III trial of chemotherapy with or without irinotecan in the front-line treatment of metastatic colorectal cancer in elderly patients. FFCD 2001-02 trial. Results of a planned interim analysis.

E Mitry<sup>1</sup>, JM Phelip<sup>2</sup>, F Bonnetain<sup>3</sup>, S Lavau Denes<sup>4</sup>, X Adhoute<sup>5</sup>, M Gasmi<sup>6</sup>, JL Jouve<sup>7</sup>, F Khemissa<sup>8</sup>, T Lecomte<sup>9</sup>, T Aparicio<sup>10</sup>

<sup>1</sup> CHU A Paré, Boulogne, <sup>2</sup> CHU Grenoble, <sup>3</sup> FFCD, Dijon, <sup>4</sup> CHU Limoges, <sup>5</sup> CHU Bordeaux, <sup>6</sup> Hôpital Nord, Marseille, <sup>7</sup> CHU Dijon, <sup>8</sup> CH Perpignan, <sup>9</sup> CHU Tours, <sup>10</sup> CHU Bichat, Paris, FRANCE

## ABSTRACT

### Background

Metastatic colorectal cancer (mCRC) most frequently occurs in elderly patients (pts), but these are less frequently treated with chemotherapy (CT) than younger ones. Subgroup analyses from previous trials suggested that pts between 70 and 74 years of age, who are well enough to meet eligibility requirements for phase III trials, derive similar benefits as younger pts. We report the results of the planned interim analysis of a phase III trial in elderly pts with mCRC receiving a 5FU-based CT, with or without irinotecan.

### Methods

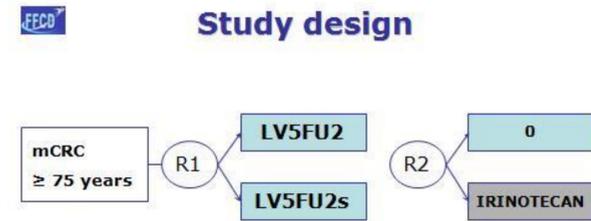
Elderly pts (75+) with previously untreated mCRC were randomly assigned to receive a 5FU-based CT, either alone (FU arms: LV5FU2 or simplified LV5FU2) or in combination with irinotecan (IRI arms: LV5FU2-CPT11 or FOLFIRI). Stratification criteria were: center Charlson index (0 vs 1-2 vs 3+), Karnofsky index (100 vs 90-80 vs 70-60), previous adjuvant CT, sex, age (< 80 vs. ≥ 80 yrs), alkaline phosphatases (≤ 2N vs. > 2N). Primary endpoint was progression free survival (PFS). It was required to observe 240 progressions or deaths and to include 282 pts to demonstrate an improvement of PFS from 9 to 12 months (33% increase) in the IRI arm with bilateral 5% type I error and a power of 80%. Secondary endpoints were overall survival, safety, tumor response, Spitzer QOL index and geriatric evaluation.

### Results

Between 06-2003 and 08-2007, 196 pts were randomized and 142 pts with at least 8 weeks of follow-up were retained for interim analysis (FU: 75, IRI: 67). Median age: 79.5 years [range: 74-91]. Age ≥80: FU 48%, IRI 49%. Karnofsky index 60-70/80-90/100 (%) FU: 29/51/19, IRI: 25/61/10. Charlson index 0/1-2/3+ (%) FU: 48/43/7, IRI: 63/33/3. Metastatic sites FU/IRI (%): liver 77/84, lung 39/46, peritoneum 15/18, lymph nodes 27/24. Tumor response (best response observed after 2 evaluations) OR/SD/PD/NE (%) FU: 18/51/25/5, IRI: 31/57/9/1. Maximal toxicities by patients observed during cycles 1 to 4 are presented in the table. There was no toxic death. All pts received at least one dose of chemotherapy. Pts having received ≥75% of the CT dose during cycles 1 to 4 FU/IRI (%): bolus 5FU 81/67, continuous 5FU 80/87, irinotecan -/87.

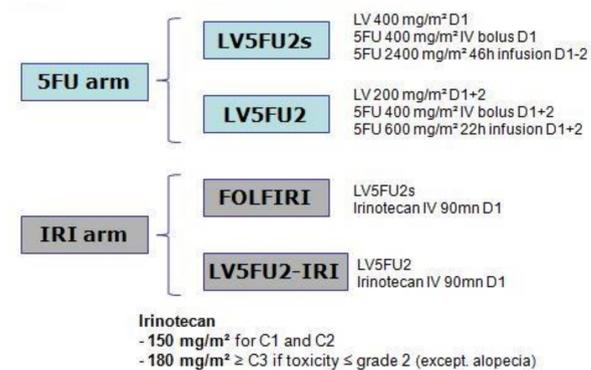
### Conclusions

A phase III trial specific to elderly patients with mCRC is feasible. Preliminary results suggest that patients aged of 75+ years can be treated with standard CT regimens with manageable toxicity.



### Stratification criteria

- Center
- Charlson index (0 vs 1-2 vs 3+)
- Karnofsky index (100 vs 90-80 vs 70-60)
- Previous adjuvant CT
- Sex
- Age (< 80 vs. ≥ 80 yrs)
- Alkaline phosphatases (≤ 2N vs. > 2N)



**Irinotecan**  
 - 150 mg/m<sup>2</sup> for C1 and C2  
 - 180 mg/m<sup>2</sup> ≥ C3 if toxicity ≤ grade 2 (except alopecia)

## Main inclusion criteria

- Histologically confirmed unresectable mCRC
- Age ≥75 years
- Karnofsky index ≥60
- Estimated life expectancy > 6 months
- ≥ 1 bi-dimensionally measurable lesion (RECIST)
- No previous CT for metastatic disease
- Adjuvant therapy allowed if stopped at least months before randomization
- Adequate organ and bone marrow function
- Creatinin clearance ≥ 45 ml/mn (Cockcroft)
- Signed informed consent

## Introduction

### CRC is a disease of elderly

- Median age at diagnosis: 73 years (SEER)

### A Public Health problem

- US population ≥65 y. : x2 in 2030
- Suboptimal management
- No improvement in survival

### Palliative CT in elderly

- Standard regimens not prospectively validated
- Subgroup analyses, phase II trials suggest feasibility in fit elderly

### Which optimal regimen in 1<sup>st</sup> line ?

- Tolerance/Efficacy
- Combination with IRI/OXA or 5FU only ?

## Study endpoints

### Primary endpoint

- Progression-free survival**
  - 5FU arm vs IRI arm
  - as assessed by blinded independent review
  - events : progression or death

### Secondary endpoints

- Overall response rate (independently reviewed)
- Overall survival (events: deaths all causes)
- Quality of life (Spitzer scale)
- Geriatric assessment (IADL, Mini Mental State Examination, Geriatric Depression Scale)
- Safety
- Comparison of simplified vs. non simplified regimen

## Statistical considerations

### Assumption for sample size calculation

- 240 progressions or deaths (282 pts)
- increase of median PFS from 5.5 to 8 months in the IRI arm, HR 0.70
- bilateral 5% type I error, 80% power

### Planned interim analysis

- After inclusion of 140 pts with ≥ 8 weeks of follow-up
- Tolerance and response (investigators)
- Only descriptive, no statistical comparisons
- IDMC

## Population

### 06/2003 – 12/2007 :

- 209 pts included

### Interim analysis 08/2007

- 166 pts included
- 142 pts with ≥ 8 weeks of follow-up

## Baseline characteristics

	5FU	IRI
n	75	67
Median age years [range]	79 [74-90]	80 [75-91]
Age group (%)		
<80 yrs	52	51
≥80 yrs	48	49
Gender (%)		
Male/Female	53/47	51/49
Karnofsky index (%)		
100/80-90/60-70/missing	19/51/29/1	10/61/25/3
Charlson index (%)		
0/1-2/3+/missing	48/43/7/3	63/33/3/1
Alkaline Phosphatases (%)		
≤ 2N / > 2N	88/12	85/15
Adjuvant CT (%)	17	6
Metastatic sites (%)		
Liver	77	84
Lung	39	46
Distant lymph nodes	27	24
Peritoneum	15	18

## Administration

- All pts received at least one cycle

Pts with ≥75% of the planned CT dose during cycles 1 to 4

(%)	5FU	IRI
Bolus 5FU	81	67
Continuous 5FU	80	87
Irinotecan	-	87

## Tumoral response

- As estimated by investigators
- RECIST criteria
- Best observed response after 1<sup>st</sup> or 2<sup>nd</sup> evaluation

(%)	5FU	IRI
CR	1	1
PR	17	30
SD	51	57
PD	25	9
NE	5	3

## Toxicity

Maximal toxicities by patient observed during cycles 1 to 4

(%)	All grades		Grade 3-4	
	5FU	IRI	5FU	IRI
Any	93	98	16	48
Anemia	47	60	1	3
Neutropenia	13	66	1	28
Febrile neutropenia	0	9	0	9

(%)	All grades		Grade 3-4	
	5FU	IRI	5FU	IRI
Nausea	37	48	0	6
Vomiting	19	30	0	6
Diarrhea	39	63	0	16
Thromboembolic event	1	3	1	3
Asthenia	32	48	3	6
Mucositis	17	21	0	0
Myocardial infarction	1	0	1	0

## Deaths

- 81 deaths

- 5FU: 43 (57% of pts)
- IRI: 38 (57% of pts)

### Causes of death

- Progression
  - 5FU: 37/43 (86%)
  - IRI: 33/38 (87%)

- 2 toxic deaths

- 60d mortality rate: 12.7%

## Serious adverse events

- 68 SAE among 54 pts (38%)

	All	5FU	IRI
SAE	54	28	25
Death	14	8	6
Not related	7	5	2
Unlikely related	2	0	2
Possibly related	2	2	0
Related	2	1*	1°
ND	1	0	1

\* Febrile neutropenia, ° severe diarrhea

## Conclusion

- Preliminary and descriptive
- A phase III trial specific to elderly patients with mCRC is feasible
- Results suggest that patients aged of 75+ years can be treated with standard CT regimens with manageable toxicity