

# Final Results of a Randomized Phase III Study Evaluating the Addition of Oxaliplatin First Line to 5-FU Followed by Irinotecan at Progression in Advanced Colorectal Cancer (LIFE Study)

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## ABSTRACT

**Background:** The LIFE study was designed to demonstrate a 10% absolute improvement in survival at 2 years (from 20% to 30%), with the addition of oxaliplatin in first line to the 5-FU followed by irinotecan sequence in advanced colorectal cancer (ACRC).

**Method:** A total of 725 ACRC patients from the UK (46%), Poland (39%), and other countries (15%) were randomized from March 2001 to March 2002 to receive 5-FU monotherapy (Lockich or de Gramont regimens) or the same regimen plus oxaliplatin 85 mg/m<sup>2</sup>, repeated every 2 weeks. Second-line therapy was standardized with irinotecan 350 mg/m<sup>2</sup> single agent repeated every 3 weeks, in both arms.

**Results:** Patients' characteristics were well balanced except for metastatic sites (liver + other in 88% versus 76% of patients receiving oxaliplatin/5-FU or 5-FU, respectively). Safety results are in line with the safety profiles of the drugs, without any unexpected toxicities (Cassidy, ASCO 2003). Median number of cycles (10) was the same in both arms, with a higher dose of 5-FU in the control arm. Median cumulative dose of oxaliplatin was 845 mg/m<sup>2</sup>. Relative oxaliplatin dose intensity was 87%. Direct efficacy evaluation of the first-line treatment showed improvement in response rate (RR) (54% versus 30%, p<0.0001) and progression-free survival (PFS) (7.9 versus 5.9 months, p<0.0001) in the oxaliplatin arm in accordance with previously reported trials. This did not translate into overall survival advantage (15.9 versus 15.2 months), with a median in the oxaliplatin arm below the 19–20 months obtained in more recent studies.

**Conclusion:** These results confirm the improvement in RR and PFS observed with combination therapy in first-line ACRC. Overall survival results could be explained by the low number of patients receiving second-line irinotecan therapy in the oxaliplatin arm (41%) and thus being exposed to the three active agents: 5-FU, oxaliplatin, and irinotecan.

## INTRODUCTION

Randomized Phase III trials in advanced colorectal cancer (ACRC) have shown that a combination of oxaliplatin with 5-fluorouracil (5-FU), with or without leucovorin, has a supra-additive effect irrespective of 5-FU regimen or delivery approach used.<sup>1-3</sup> This combination more than doubled the response rate (RR) – with objective RRs reaching 50–60% – and increased progression-free survival (PFS) by 2–3 months. At the time of study initiation, single-agent irinotecan was considered standard second-line therapy for ACRC, after demonstrating beneficial effects on survival in patients pretreated with 5-FU.<sup>4,5</sup>

This randomized Phase III trial evaluated the effects of the whole therapeutic sequence of oxaliplatin added to two different 5-FU regimens as first-line therapy followed by second-line single-agent irinotecan in patients with ACRC.

## OBJECTIVES

### Primary objective

- Overall survival (OS)

### Secondary objectives

- PFS, RR, safety.

## METHODS

### Patients and treatment

- Patients with ACRC were enrolled in this randomized Phase III trial, which was initiated in 2001.
- Exclusion and inclusion criteria are listed in Table 1. The study design is summarized in Figure 1.
- As there was no consensus on the best first-line 5-FU regimen for CRC, physicians had the option to choose between the 5-FU continuous intravenous infusion (CIV) or 5-FU bolus plus leucovorin (LV5FU2) regimens; the same regimen was then given to all patients treated at the institution.

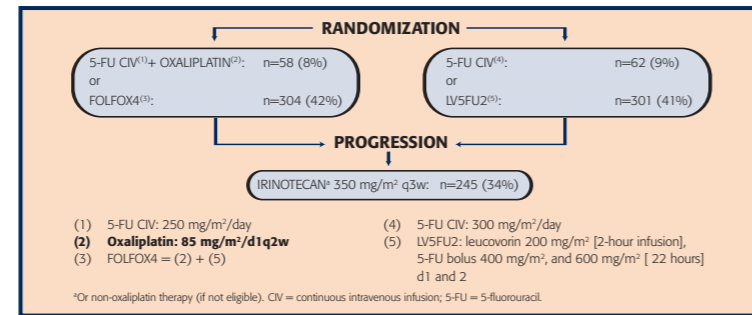


Figure 1. Study design.

### KEY ELIGIBILITY CRITERIA

- Histologically proven CRC with distant metastases
- No previous chemotherapy for metastatic disease
- Age  $\geq 18$  years
- WHO PS  $\leq 2$
- No major biochemical or hematologic abnormalities
- Unidimensionally measurable disease
- Adjuvant chemotherapy  $\geq 6$  months before study entry and not containing oxaliplatin and/or irinotecan
- Written informed consent

### KEY EXCLUSION CRITERIA

- Resectable disease
- CNS metastasis, unresolved bowel obstruction/diarrhea
- Peripheral neuropathy (NCI-CTC grade  $\geq 1$ )
- Pregnant or breast-feeding women
- Previous malignancies
- Investigational drug within 30 days prior to randomization
- History of sensitivity to 5-FU
- Other medical condition making it unlikely the patient will complete the study as planned

CRC = colorectal cancer; CNS = central nervous system; WHO PS = World Health Organization performance status; NCI-CTC = National Cancer Institute Common Toxicity Criteria; 5-FU = 5-fluorouracil.

Table 1. Exclusion and inclusion criteria.

### Statistical analysis

- The study was designed to accrue approximately 350 patients per treatment arm in order to detect an increase in survival rate at 2 years of 10% (from 20% to 30%; hazard ratio = 0.75).
- Survival was analyzed using a two-sided log-rank test:  $\alpha = 0.05$ ; power = 90%.

## RESULTS

### Patient characteristics and treatment

- In total, 725 patients were enrolled from March 2001 to March 2002 at 67 centers in 6 countries (Table 2). All patients were included in the survival analysis (intent to treat [ITT]) and median follow-up was 28 months.

CHARACTERISTIC	OXALIPLATIN/5-FU ARM (N=362)	5-FU ARM (N=363)
Male/female, %	65/35	61/39
Median (range) age, years	61 (29–81)	62 (29–81)
$\geq 2$ metastatic sites, %	55	56
Prior adjuvant therapy, %	27	26
Performance status (WHO), %		
0	48	50
1	45	44
2	7	6
Median time since initial diagnosis, months	2.6	3.3
Organ involvement: liver $\pm$ other, %	88	76

Table 2. Characteristics of randomized patients.

- The median number of cycles was similar in both treatment arms, with a higher dose of 5-FU in the control arm (Table 3). The median cumulative dose of oxaliplatin was 845 mg/m<sup>2</sup>.

	OXALIPLATIN/5-FU ARM		5-FU ARM	
	5-FU CIV + OXALIPLATIN	FOLFOX4	5-FU CIV	LV5FU2
No. of patients treated	57	301	62	300
Median (range) No. of cycles	11 (1–40)	10 (1–37)	11 (1–32)	10 (1–35)
Relative dose intensity, %				
Oxaliplatin	88	87	NA	NA
5-FU	79	85	78	93
Equivalent 5-FU dose, mg/m <sup>2</sup> /cycle	2770	1710	3286	1861

Table 3. Drug delivery (first line).

- Reasons patients did not receive treatment: 5-FU CIV/oxaliplatin, death (n=1); FOLFOX4, physician decision (n=2) and patient withdrawal (n=1); LV5FU2, intercurrent medical problem (n=1).

### Efficacy

- First-line treatment showed that RR and PFS were significantly higher in the oxaliplatin/5-FU arm compared with the control arm (both p<0.0001; Figures 2 and 3).

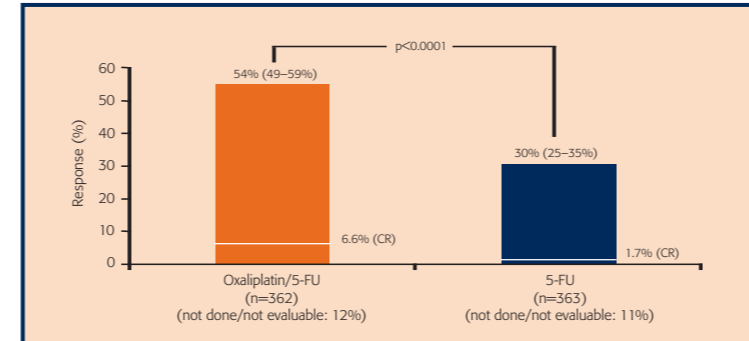


Figure 2. Best overall response rate and complete response (CR) rate by Response Evaluation Criteria In Solid Tumors (RECIST) [intent-to-treat population].

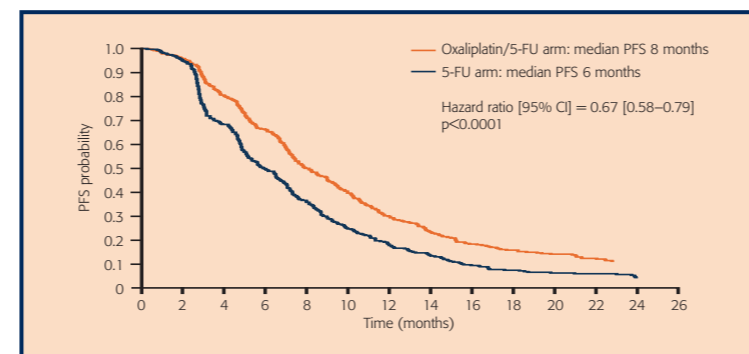


Figure 3. Progression-free survival (PFS) [intent-to-treat population].

- The improvements in RR and PFS seen with the addition of oxaliplatin to 5-FU were not paralleled by advantages in OS (Figure 4).

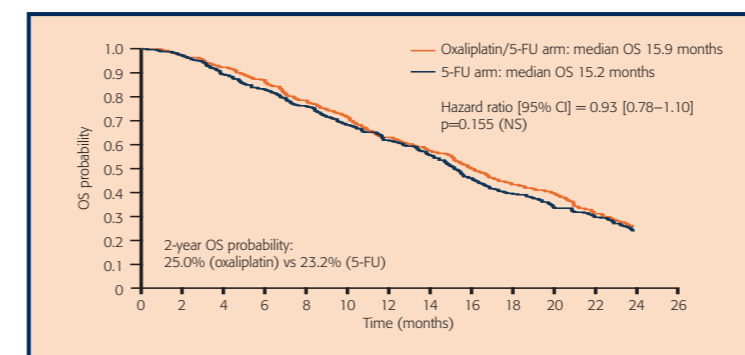


Figure 4. Overall survival (OS) [intent-to-treat population].

- In the oxaliplatin/5-FU arm, fewer patients received second-line irinotecan (41% vs 49%) compared with the 5-FU arm, with a median irinotecan treatment duration of 2.1 months in both arms. In centers where  $>50\%$  of patients received second-line irinotecan therapy, median OS was improved (Figures 5 and 6).

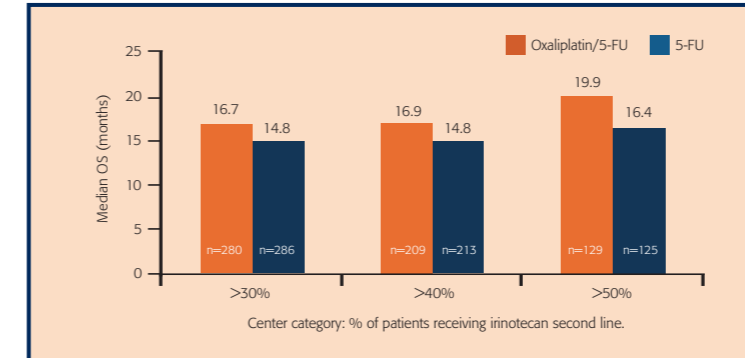


Figure 5. Overall survival (OS) in centers where  $>30\%$ ,  $>40\%$ , or  $>50\%$  of patients received irinotecan second line.

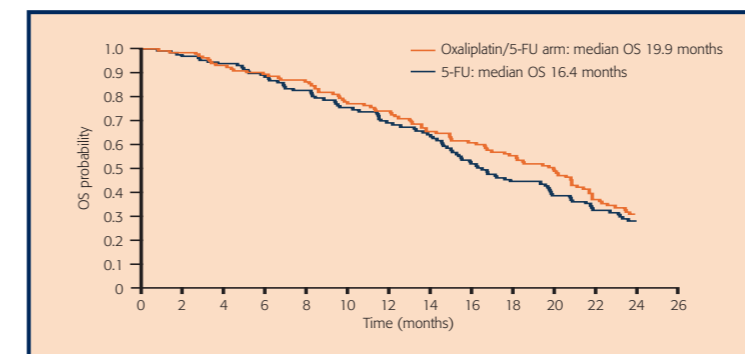


Figure 6. Overall survival (OS) in centers where  $>50\%$  of patients received irinotecan second line.

### Toxicity

- All treated patients were included in the safety analysis (Table 4).

ADVERSE EVENT	OXALIPLATIN/5-FU ARM (N=358)		5-FU ARM (N=362)	
	5-FU CIV + OXALIPLATIN (N=57)	FOLFOX4 (N=301)	5-FU CIV (N=62)	LV5FU2 (N=300)
Fatigue	4	10	10	8
Neutropenia	2	39	0	6
Febrile neutropenia	0	3	0	1
Stomatitis	2	3	5	2
Diarrhea	30	11	13	7
Vomiting	18	5	5	3
Nausea	11	3	2	2
Neuropathy-sensory	12	13	3	1
Skin	11	1	15	4
Toxic deaths	0.8		0.5	

Table 4. Grade 3/4 adverse events (first line) [% of patients].

## SUMMARY OF RESULTS

- Addition of oxaliplatin to 5-FU in the first-line treatment of ACRC significantly improved RR and PFS, which supports findings of previously reported trials.
- No advantage in OS was shown for oxaliplatin/5-FU over 5-FU alone. These findings may be explained by the low number of patients receiving second-line irinotecan (41%) in the oxaliplatin/5-FU arm and therefore being exposed to all three active drugs (5-FU, oxaliplatin, and irinotecan).
- Toxicity results were in line with the safety profiles of the drugs evaluated, with no unexpected adverse events reported.

## CONCLUSIONS

- The improvements in RR and PFS seen with the combination of 5-FU and oxaliplatin in first-line treatment of ACRC confirm observations from earlier studies.<sup>1-3</sup>
- OS was lower than previously seen in studies where all three active drugs were administered to the majority of patients.<sup>4</sup> In the present study, second-line irinotecan use was low, with less than half of each treatment group receiving this agent and for only a short duration (median 2.1 months).
- In centers where  $>50\%$  of patients received second-line therapy with irinotecan, OS was consistent with that reported previously.<sup>4</sup>

### References

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