

OPTIMAL DURATION OF TREATMENT


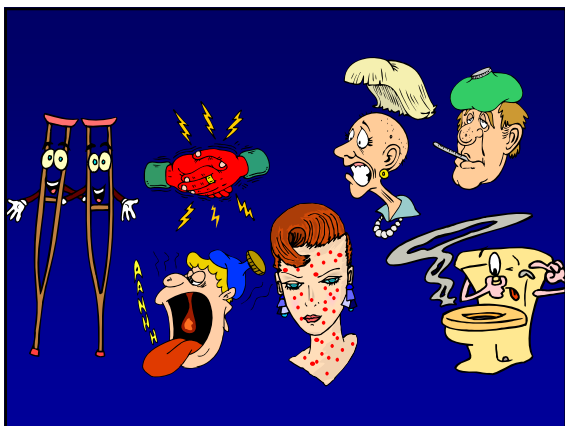
Aimery de GRAMONT
Barcelona 27 June 2009

- ## Answers
- Until the patient is cured
 - Until the disease escapes
 - Until the treatment is tolerated
 - Until the patient wants to stop therapy

Can we stop chemotherapy in patients with advanced colorectal cancer?

Chemotherapy-free interval (CFI):

- at least 3 months,
- without detrimental effect on survival

Rationale

- Chemotherapy-free intervals (CFI) have previously been studied in patients receiving 5FU-based therapy:

Hejna et al (Br J Cancer (1998) have shown that patients can benefit from 5FU reintroduction after a CFI following 6 months of therapy.

Maughan et al (Lancet 2003) have show in a larger phase III that 3 months 5FU-based chemotherapy followed by CFI achieved the same survival than 5FU until progression.

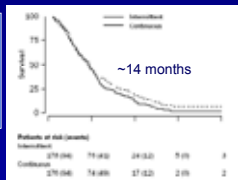
5FU no PD (R)

905 267

continuous

intermittent

37%



~14 months

Median duration of CFI 4.2 months
11% of the total population

Survival	Intermittent	Continuous
270 (30%)	77 (29%)	24 (9%)
270 (30%)	74 (28%)	27 (10%)

Alternating vs continuous LV5FU2-IRI GISCAD trial

2006

N=331

RANDOMIZATION

LV5FU2-IRI 2 months

LV5FU2-IRI 2 months

No Progression


STOP 2 months

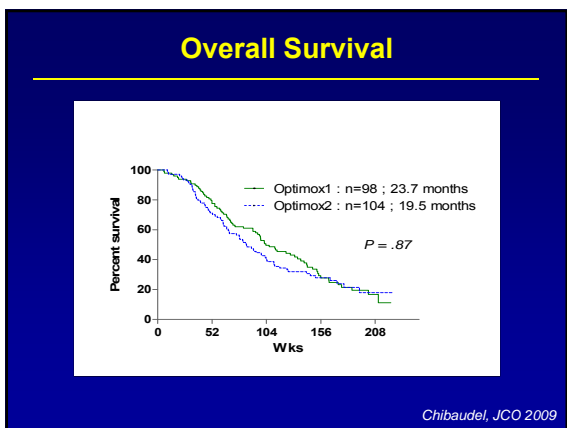
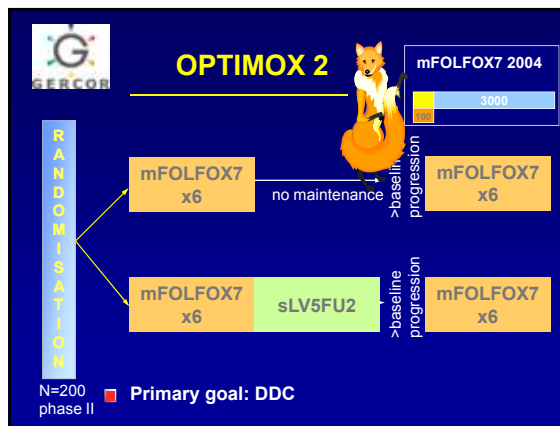
LV5FU2-IRI 2 months

LV5FU2-IRI 4 months

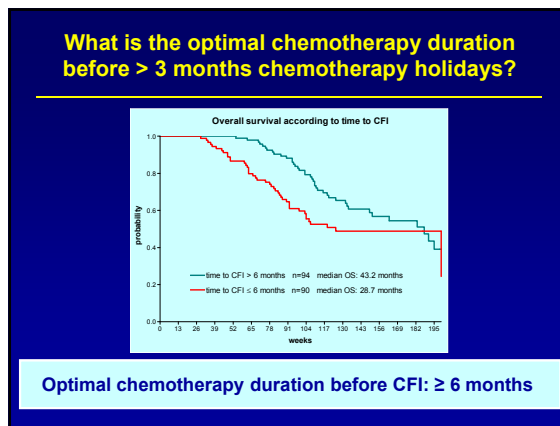
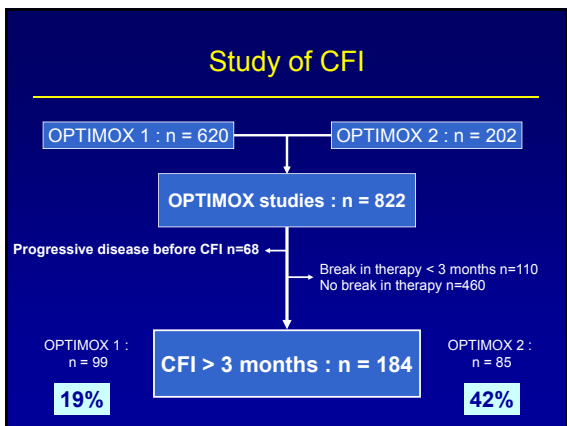
PFS: 6.2 m

PFS: 6.5 m





- ### Pitfalls
- Patients were randomized before therapy
 - Patients with progressive disease on FOLFOX therapy, patients having metastase resection were not eligible for CFI but were analyzed in intent-to-treat



What is the duration of chemotherapy holidays ?

Does the duration of CFI depend on the duration of chemo before?

CFI duration
— median CFI duration 5.9 months
n=184

Probability

Weeks

Median duration of CFI is almost 6 months

NO: prolonged chemotherapy does not improve the duration of CFI

Correlation between chemotherapy and CFI durations

duration of CFI (months)

duration of chemotherapy (weeks)

Can we predict which patients can benefit of prolonged survival after CFI?

- The CFI subpopulation has a good prognostic, median OS>30 months
- We should compare to patients with similar prognostic factors and similar response and PFS to therapy
- A new trial is not easy to perform due to the emergence of targeted therapies and the controls to do before CFI

Case-Control Study

OPTIMOX studies : n = 822

- CFI > 3 months : n = 184
no PD, no R0 or R1 resection before 3 months
- Other : n = 570

non matchables: n=17

CFI **Matched patients n=167** **Matching criteria** **Matched controls n = 167** **No CFI**

13829	CR-PR/3D	13530
99/59/10	PS Q1/2	99/64/8
90/46	LDH N1-N	79/65
108/48/7	ALP N1-10N10-100N100N	91/65/11
44/61/38/16	CEA N1-10N10-100N100N	31/61/51/18
100/67	Synchro/Metachrone	111/58
99/67	Male/Female	103/64
69 yf	Median age	63 yf
74mm	Median size	75mm
92/74	Site 1>1	84/83
88/69	Colon/rectum	107/62
28	Adjuvant chemotherapy	40

PFS 2 time to CFI + 3 months

Survival in matched patients

Overall Survival

— no pause 21.2 months
— pause 42.1 months
n=334

Probability

Weeks

Surgery excluded, no pause vs. pause
Median PFS 9.9 vs 12.2 months
2-Year Survival 40% vs 65%

Overall Survival

— no pause 21.2 months
— pause 35.4 months
n=202
R0/R1 surgery excluded

Probability

Weeks

All patients, no pause vs. pause
Median PFS 9.9 vs 12.9 months
2-Year Survival 40% vs 70%

The two groups of patients have been matched on baseline prognostic factors, response to chemotherapy and PFS ≥ time to CFI+3 months

What are the predictive factors of OS in the matched patients ?

Multivariate analysis: 3 months CEA (p=.002), ALP (p=.023)

— CEA N n=131 median OS 28.7 months
— CEA 1-10N n=135 median OS 24.8 months
— CEA>10N n=37 median OS 18.2 months

probability

weeks

3m Normal CEA
Median OS
CFI 43 months
No 28 months

What are the predictive factors in the CFI patients ?

Normal CEA within 3 months P=0.03

OS according to CEA < 3 months

— CEA N n=79 median OS 43.2 months
— CEA>N n=77 median OS 27.4 months
p=0.03

probability

weeks

Conclusions

- Many patients benefited from chemotherapy holidays. Baseline characteristics do not allow to select these patients
- Median duration of CFI was almost 6 months
- Optimal duration of chemotherapy before CFI was 6 months. There was no correlation between chemotherapy duration and CFI duration
- A normal CEA level during chemotherapy was the single identified predictive factor of prolonged survival with a CFI

Conclusions

- More than 30% of the patients had a normal CEA after >3 months of combination therapy (824 patients OPTIMOX1&2 database) :
- **18%** of the patients had a normal CEA which remained normal
- **16%** of the patients had an anormal CEA which became normal
- **Patients with a normal CEA at 3 months enjoyed a better survival (43 months) when they had a CFI than those who did not stop therapy (28 months)**

2009

