Final Results of

The intergroup FFCD-GERCOR-FNCLCC 03-07 phase III study

Comparing two sequences of Chemotherapy in Advanced Gastric Cancer

R Guimbaud [1], C Louvet [2], F Bonnetain [3], F Viret [4], E Samalin [5], JM Gornet [2], T André [2], C Rebischung [6], O Bouché [7], JL Jouve [3]

(1) Toulouse; (2) Paris; (3) Dijon; (4) Marseille; (5) Montpellier; (6) Grenoble; (7) Reims.

France

Metastatic and Locally advanced GASTRIC CANCER

- Median survival : < 6 months
- Palliative Chemotherapy > BSC
  - Survival
  - Quality of live
  - In selected patients

  ➔ Several standard schedules of chemotherapy

  ➔ … 9 to 13 months of median survival
- No standard of 2^{d} line

Palliative Chemotherapy

Polychemo.

« Old » cytotoxics

- **5FU /** antimetabolite
- **Anthracyclins**
- **CisPlatinum**

DCF
mDCF

FUP

ECF
(ECX)

FLO
FOLFOX
EOX

IF
FOLFIRI

« Newer » cytotoxics

- **Taxane**
- **Oxaliplatine**
- **Oral 5FU**
- **Irinotecan**

+ Targeted therapies…
(HER2)

Irinotecan and Gastric cancer

Usually done in CRC (FOLFIRI):
Well known and managed by digestive oncologists

In occidental experience:

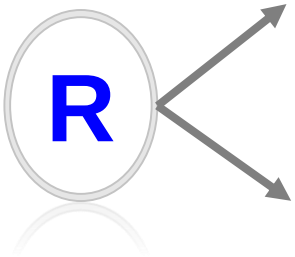
- Many phases II studies:
  - Anti-tumoral activity in gastric cancer
  - In association with 5FU essentially
  - Acceptable
- One large phase III study (IF vs Platine-5FU):
  - Non inferiority of IF vs PF

Dank M et al. Ann Oncol. 2008;19(8):1450-7.
Curran D et al. Qual. Life Res. 2009;18:853-61.

Study design & Objectives:

Stratification :

- Mesurable or not
- PS $_{WHO}$ 0-1 or 2
- Adj (R)CT or not
- Linitis or not
- Cardial or gastric
- Center



A: ECX until progression ; 2d line : **FOLFIRI**

B: FOLFIRI until progression, 2d line : **ECX**

ECX : D1 = Epirubicine 50 mg/m² (15 min.), Cisplatin 60 mg/m² (1 h) ; D2 to 15 : Capecitabine 1 g/m² x 2/d. D1 = D21
Cumulated dose of Epirubicine < 900 mg/m² (about 18 cures)

FOLFIRI : D1 = Irinotecan 180 mg/m² (90 min) + AF 400 mg/m² (2h), 5FU c 2400 mg/m², 5FU c 2400 mg/m² (46h). D1 = D14

- **Objective I :** Time to Treatment Failure **TTF** at 1st line

- **Objective II :** - (TTF 2d line), PFS, OS
  - Toxicity,
  - Response rate, QoL*

  • *By QLQC30 et STO-22*
  • *Results not available*

Time between Randomisation and:
1/ Progression
Or 2/ tt discontinuation
Or 3/ Death

≠ PFS: Time between Randomisation and Progression or Death

Inclusion/exclusion criteriae

Inclusion

- **Gastric or cardia adenocarcinoma histologically proven**
- **Non surgical locally advanced or metastatic tumor**
- Measurable (RECIST) or evaluable lesions
- **PS WHO ≤ 2**
- **No dysphagia**
- …

Exclusion

- **Previous chemotherapy** except adjuvant chemo > 6 months
- **Previous radiotherapy** < 3 weeks
- History of cardiac 5FU or anthracyclin toxicity
- Cardiac or coronary deficiency
- Known cerebral or meningitis metastasis
- ...

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Statistical methods

- N = **416 patients** (4 years)
  - Median TTF from 3.45 months (15 weeks) ECX to 4.60 months (20 weeks) FOLFIRI (HR=0.75)
  - α bilateral : 0.05 et β : 0.2

- Planned Interim analysis:
  - After 190 failures
  - Results (n = 349)* : following of the study until n = 416.

- ITT analyses
- Chi2 / Wilcoxon tests
- Kaplan Meier estimation / Log-rank tests / Cox univariate hazard ratio (HR with 95% CI)
- Follow-up: Reverse Kaplan Meier

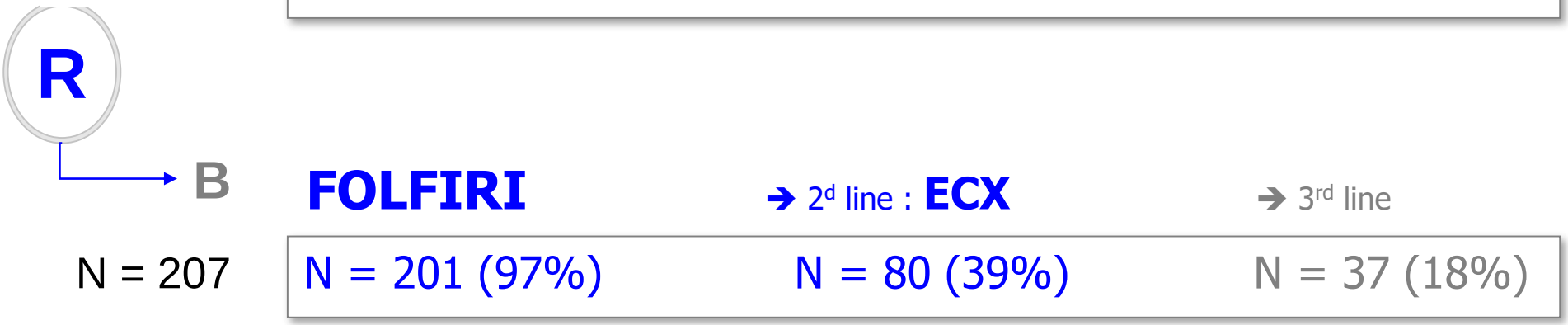
* Planned interim analysis : ASCO 2009

Patients characteristics

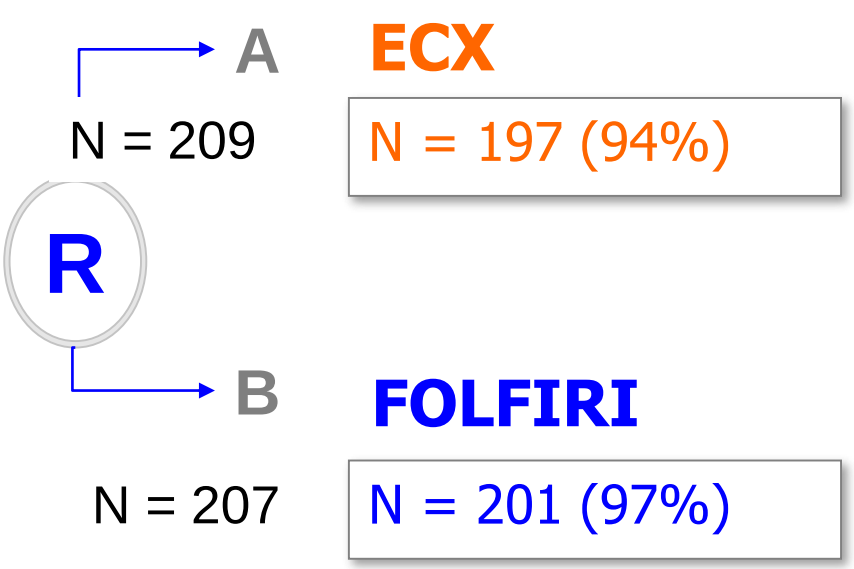
- 416 patients in 71 centres included from June 2005 to May 2008.
- Median Follow-up: ECX / FOLFIRI: 30.65 months [25.95; 39.33]
  FOLFIRI / ECX: 29.31 months [21.59; 33.61]

	All patients **N = 416**	ECX / FOLFIRI N = 209	FOLFIRI / ECX N = 207
Male (vs Female)	➔ 74%	74%	74%
Age (medium +/- SD)	➔ 60.7 +/- 11 y	60.7 +/- 11 y	60.6 +/- 11 y
PS WHO 0-1 (vs 2)	➔ 85%	84%	86%
Gastric (vs cardia)	➔ 68%	65%	70%
Linitis	➔ 23%	22%	25%
M+ (vs LA) If M+ : synchro vs metachro.	➔ 83%	82%	85%
Primary Tumor Resected	➔ 25%	26%	23%
Previous Treatment If yes : RCT / CT / other	➔ 10% 58% / 21% / 21%	11% 52%/17%/31%	10% 65%/25%/10%

Administred treatments



Administred treatments: 1st line



Duration of treatment :

3.0 months (arm A: ECX 1st line)

vs

4.8 months (arm B: FOLFIRI 1st line)

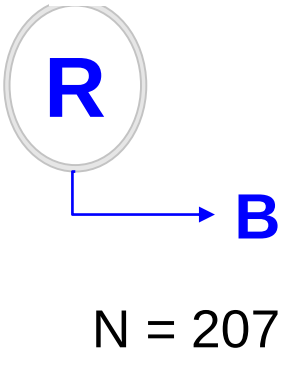
p = 0.002 (Wilcoxon)

% of cycles received in 1st line*

	A: ECX 1st line (n= 197)	B: FOLFIRI 1st line (n= 201)
C1	100%	100%
C2	63%	75%
C3	35%	56%
C4	14%	33%

** At least one dose administred*

Administred treatments: 2d line



ECX ➔ 2d line : **FOLFIRI**

N = 101 (48%)

FOLFIRI ➔ 2d line : **ECX**

N = 80 (39%)

Duration of treatment :

2.3 months (A: FOLFIRI 2d line)

vs

1.2 months (B: ECX 2d line)

p = 0.03 (Wilcoxon)

1st line Toxicities*

(NCI-CTC version 2)

* For patients receiving at least one dose

	ECX 1st line (n = 197)	FOLFIRI 1st line (n = 201)	
Non haematologic toxicities			
Grade 0/1/2	40%	44%	***p = 0.45***
Grade 3/4	58%	55%	
NA	2%	1%	
Haematologic toxicities			
Grade 0/1/2	30.5%	61%	***p < 0.0001***
Grade 3/4	**65.5%**	37%	
NA	3%	2%	
All toxicities			
Grade 0/1/2	13%	29%	***p < 0.0001***
Grade 3/4	**85%**	70%	
NA	2%	1%	
Toxic deaths	3.5%	2.5%	

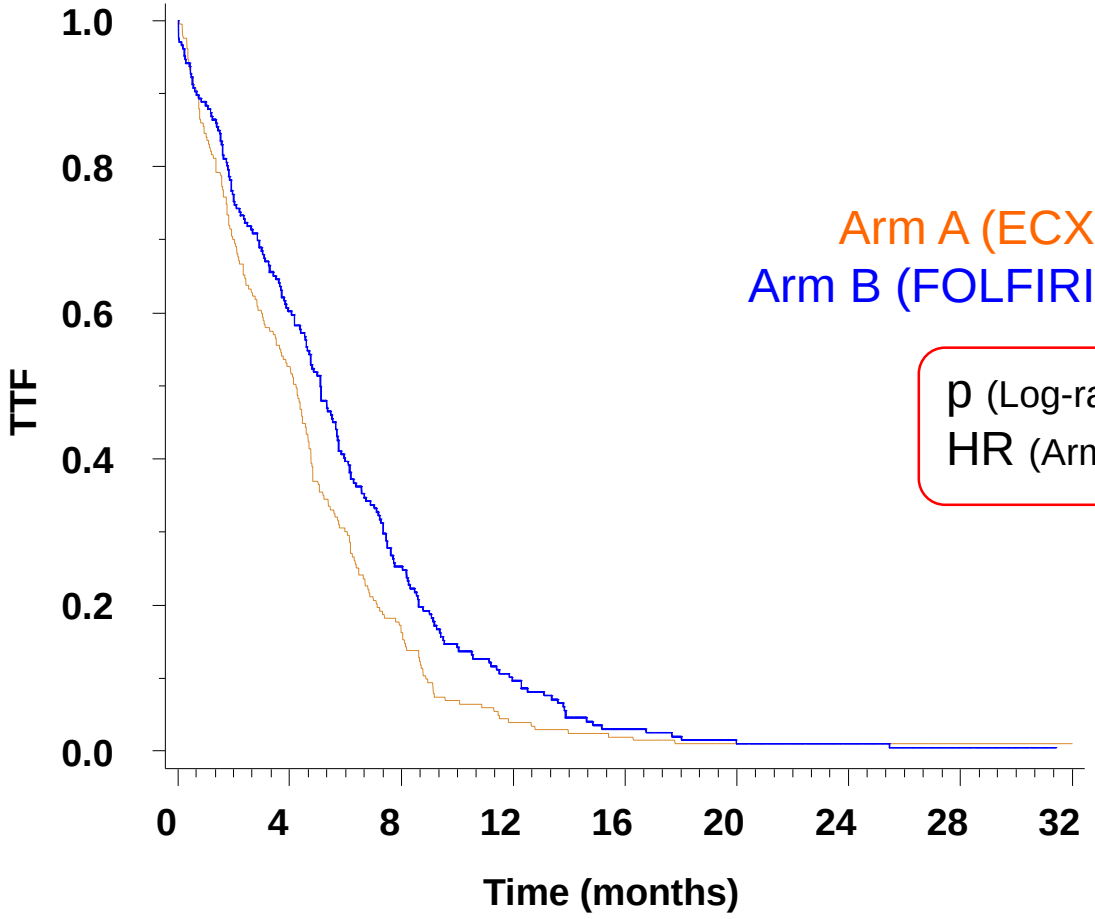
2d line Toxicities

(NCI-CTC)

	ECX 1st line (n = 101) **2d: FOLFIRI**	FOLFIRI 1st line (n = 80) **2d: ECX**	
Non haematologic toxicities			
Grade 0/1/2	48.5%	42.5%	***p = 0.29***
Grade 3/4	47.5%	57.5%	
NA	4%	0	
Haematologic toxicities			
Grade 0/1/2	54.5%	55%	***p = 0.97***
Grade 3/4	41.5%	42.5%	
NA	4%	2.5	
All toxicities			
Grade 0/1/2	29%	26%	***p = 0.59***
Grade 3/4	67%	74%	
NA	4%	0	
Toxic deaths	2%	2.5%	

Primary end point:
Time To Failure treatment at 1st line

Time to Failure Treatment (TTF) :
Time between Randomisation and
1/ Progression before 2d line
Or 2/ tt discontinuation after 1st line
Or 3/ Death during 1st line



Bras A	209	108	33	8	4	2	1	1	1
Bras B	207	123	50	19	6	3	2	1	0

Arm A (ECX 1st line) : 4.24 m [3.48; 4.65]
Arm B (FOLFIRI 1st line) : 5.09 m [4.53; 5.68]

p (Log-rank)= **0.008**
HR (Arm B vs Arm A)= **0.77** [0.63;0.94]

	Events
Arm A	203
Arm B	203

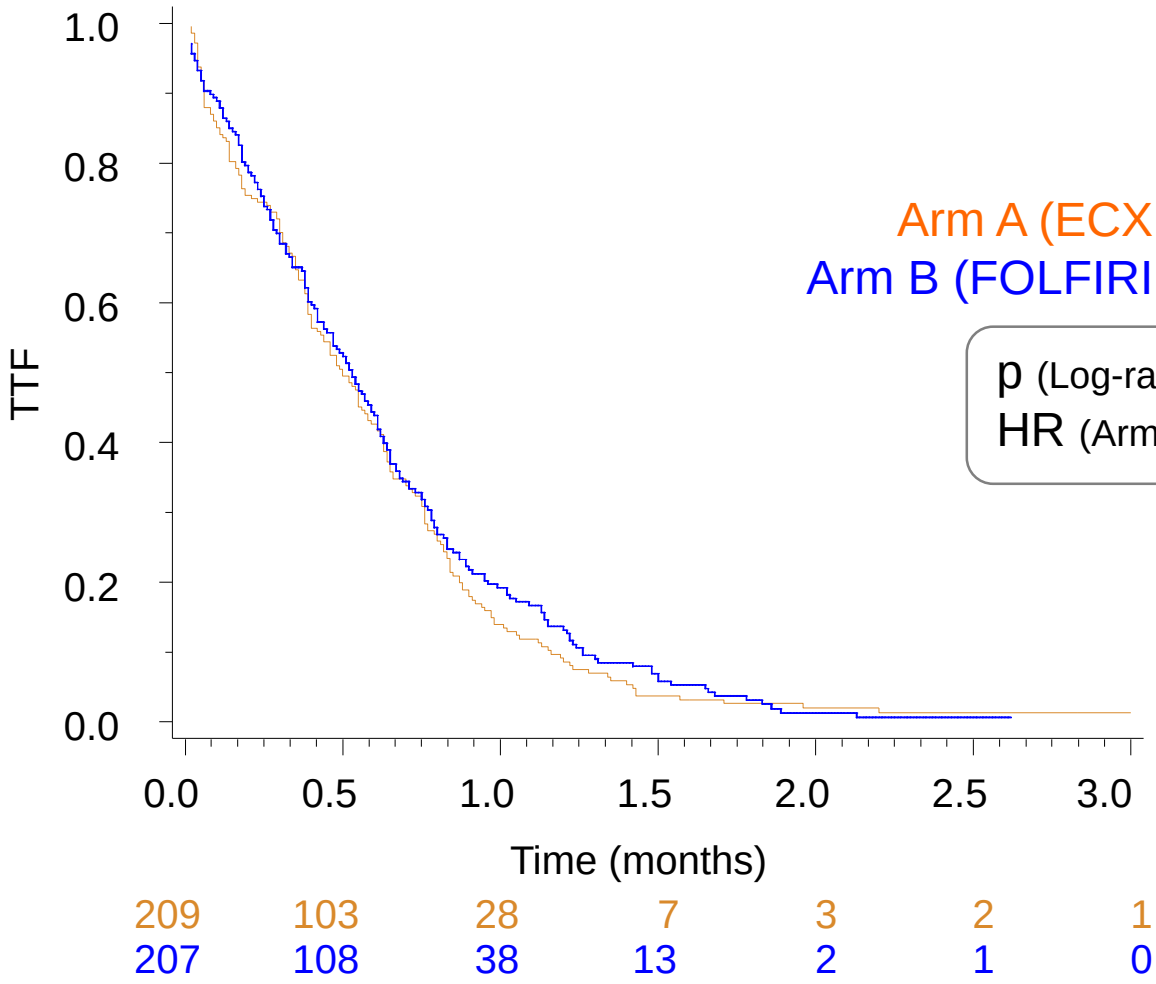
TTF 1st line: Causes of discontinuation.

	Arm A **ECX 1st line** (N = 203)	**Arm B** **FOLFIRI 1st line** (N = 203)
Progression	**48%**	**61%**
Toxicity	**14.5%**	**4%**
Patient requirement	**10%**	**6.5%**
Degradation of PS	15%	15%
Other	12.5%	10.5%
Death	6.5%	10%
Data not available	7%	6%

Several causes possible for each patient

Time To Failure treatment at 2d line

Time to Failure Treatment (TTF) :
Time between Randomisation and
1/ Progression in 2d line
Or 2/ tt discontinuation after 2d line
Or 3/ Death during 2d line
Or 4/ Event at 1st line for patients with only 1 line



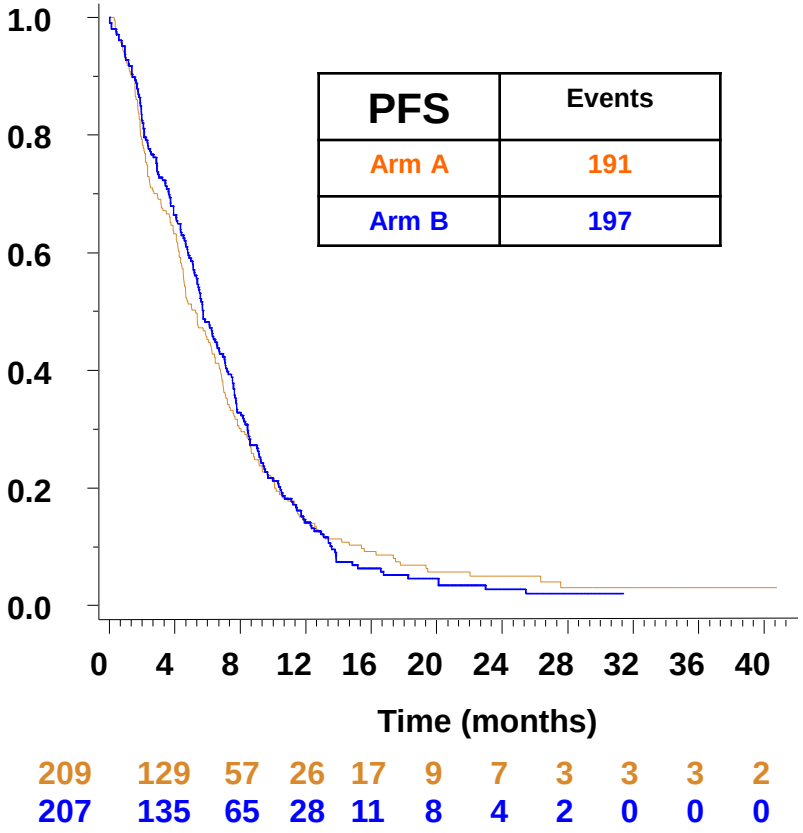
Arm A (ECX 1st line) : 0.50 m [0.41;0.59]
Arm B (FOLFIRI 1st line) : 0.53 m [0.44;0.61]

p (Log-rank)= 0.50
HR (Arm B vs Arm A)= 0.94 [0.77;1.14]

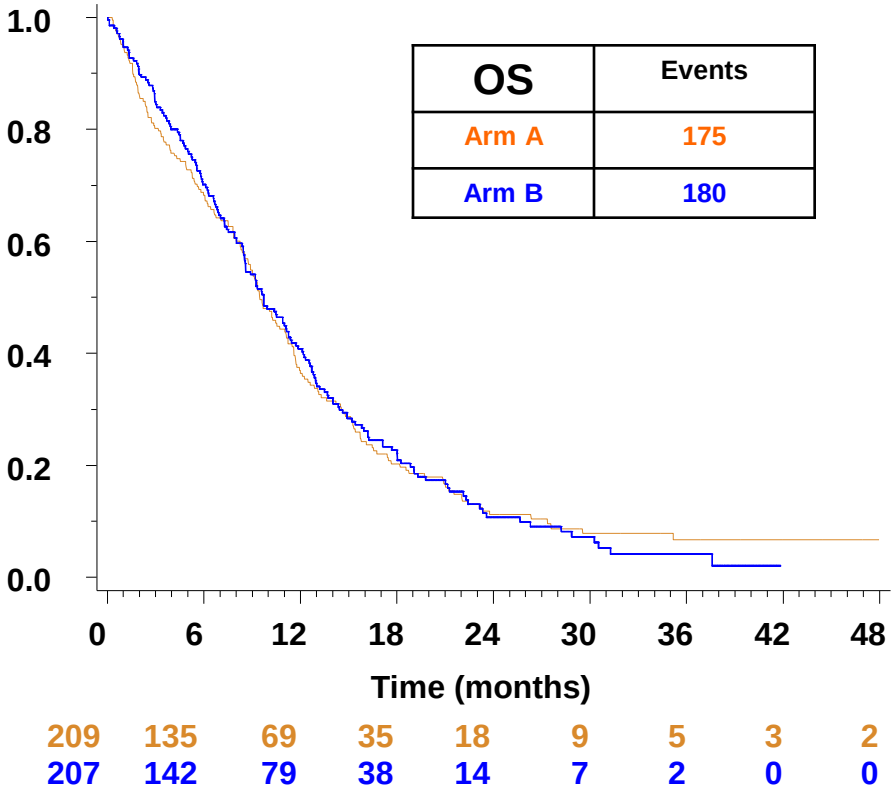
	Events
Arm A	199
Arm B	200

Progression Free Survival and Overall Survival

Arm A (ECX 1st line) **: 5.29 m.** [4.53;6.31]
Arm B (FOLFIRI 1st line) : **5.75 m.** [5.19; 6.74]
p (Log-rank)= 0.96
HR (B vs A)= 0.99 [0.81; 1.21]



Arm A (ECX 1st line) : **9.49 m.** [8.77; 11.14]
Arm B (FOLFIRI 1st line) : **9.72 m.** [8.54; 11.27]
p (Log-rank)= 0.95
HR (B vs A)= 1.01 [0.82; 1.24]



CONCLUSION

in metastatic or locally advanced cardial and gastric cancer:

- FOLFIRI in 1st line provides:
  - a significantly longer TTF than ECX (primary end point)
  - less grade 3-4 toxicities (resulting in less failure related to adverse effects)
- No difference between the two sequences (FOLFIRI then ECX or reverse sequence) in term of TTF2d line, PFS and OS (secondary end point)
- TTF is a composite measure of efficacy and safety useful to assess benefit/risk balance…

CONCLUSION

in metastatic or locally advanced cardial and gastric cancer:

A sequence of chemotherapies with FOLFIRI in 1st line should be preferred to ECX 1st line since its better tolerance provides a longer TTF with an equivalent OS.

The improved safety profil of FOLFIRI 1st line could be an advantage to test its association with targeted therapies in gastric cancer.

Sponsor: Hôpitaux de Toulouse

Thanks to

° ° ° patients ° ° °

Investigator's centers:

Albi Clin	Bourgoin Jallieu	Grenoble CHU	Marseille Timone	Perigueux
Altkirch	Briey CH	La Roche s/ Yon	Meaux CH	Perpignan CH
Angers I. Angevin	Caen CFB	Le Coudray	Metz -Thionville CH	Pierre Bénite
Annecy	Caen CHU	Le Kremlin	Mont de Marsan	Reims CHU
Avignon Clin	Chalons en C. - CH	Le Mans Clin	Montfermeil - le raincy	Rennes CEM
Avignon CH	Clamart	Libourne CH	Montpellier Val	Rouen CHU
Beauvais CH	Clermont Ferrand	Lille CAC	Nancy CAV	Semur en Auxois CH
Belfort CH	Clichy	Lille CHRU	Nîmes	Senlis CH
Besançon	Colombes	Limoges CHU	Paris p. Salpétrière	St Brieuc Clin
Blois CH	Colmar	Lormont clin	Paris St Antoine	Suresne CH
Bobigny	Creteil	Lyon CAC	Paris St Louis	Toulouse Purpan
Bordeaux CAC	Dijon CAC	Lyon Clin St J	Paris Bichat	Toulouse Rangueil
Bordeaux Clin	Dijon CHU	Marseille IPC	Paris HEGP	Toulouse Regaud
Boulogne ambroise Paré	Elbeuf CH	Marseille St Joseph	Paris Tenon	Tours CHU
				Villejuif IGR

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