

Final Results of

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

Comparing two sequences of Chemotherapy  
in Advanced Gastric Cancer



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France

# Metastatic and Locally advanced GASTRIC CANCER

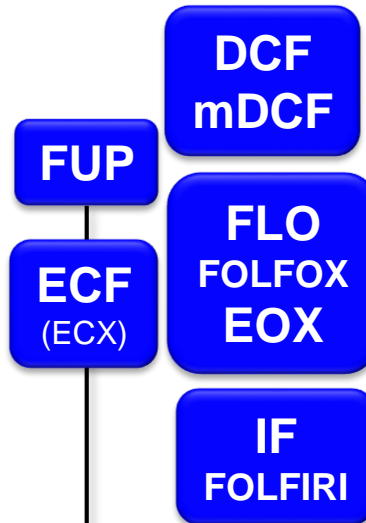
- Median survival : < 6 months
- Palliative Chemotherapy > BSC
  - Survival
  - Quality of live
  - In selected patients
  - Several standard schedules of chemotherapy
  - ... 9 to 13 months of median survival
- No standard of 2<sup>d</sup> line

# Palliative Chemotherapy

## Polychemo.

« Old »  
cytotoxics

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



« 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

# Study design & Objectives:

## Stratification :

- Mesurable or not
- PS<sub>WHO</sub> 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/m<sup>2</sup> (15 min.), Cisplatin 60 mg/m<sup>2</sup> (1 h) ; D2 to 15 : Capecitabine 1 g/m<sup>2</sup> x 2/d. D1 = D21  
*Cumulated dose of Epirubicine < 900 mg/m<sup>2</sup> (about 18 cures)*

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

• **Objective I** : Time to Treatment Failure **TTF** at 1<sup>st</sup> line

• **Objective II** : - (TTF 2<sup>d</sup> 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  $\leq 2$**
- **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)
  - $\alpha$  bilateral : 0.05 et  $\beta$  : 0.2
- Planned Interim analysis:
  - After 190 failures
  - Results (n = 349)\* : following of the study until n = 416.
- ⑨ ITT analyses
- ⑨ Chi2 / Wilcoxon tests
- ⑨ Kaplan Meier estimation / Log-rank tests / Cox univariate hazard ratio (HR with 95% CI)
- ⑨ 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]

	<b>All patients</b> 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)	→ 83%	82%	85%
If M+ : synchro vs metachro.			
Primary Tumor Resected	→ 25%	26%	23%
Previous Treatment	→ 10%	11%	10%
If yes : RCT / CT / other	58% / 21% / 21%	52%/17%/31%	65%/25%/10%

# Administred treatments

→ **A**  
N = 209

**ECX**

N = 197 (94%)

→ 2<sup>d</sup> line : **FOLFIRI**

N = 101 (48%)

→ 3<sup>rd</sup> line

N = 42 (20%)

**R**

→ **B**  
N = 207

**FOLFIRI**

N = 201 (97%)

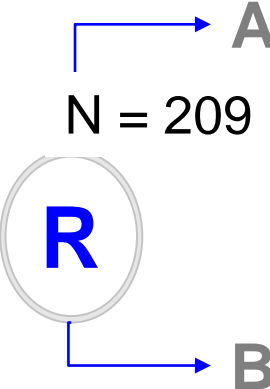
→ 2<sup>d</sup> line : **ECX**

N = 80 (39%)

→ 3<sup>rd</sup> line

N = 37 (18%)

# Administred treatments: 1<sup>st</sup> line


  
 A
   
 N = 209

**ECX**

N = 197 (94%)

B
   
 N = 207

**FOLFIRI**

N = 201 (97%)

Duration of treatment :

**3.0 months** (arm A: ECX 1<sup>st</sup> line)

vs

**4.8 months** (arm B: FOLFIRI 1<sup>st</sup> line)

$p = 0.002$  (Wilcoxon)

% of cycles received in 1<sup>st</sup> line\*

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

\* At least one dose administred

# Administred treatments: 2<sup>d</sup> line

→ **A**  
N = 209

ECX → 2<sup>d</sup> line : **FOLFIRI**

N = 101 (48%)

**R**

→ **B**  
N = 207

FOLFIRI → 2<sup>d</sup> line : **ECX**

N = 80 (39%)

Duration of treatment :

**2.3 months** (A: FOLFIRI 2<sup>d</sup> line)

VS

**1.2 months** (B: ECX 2<sup>d</sup> line)

$p = 0.03$  (Wilcoxon)

# 1<sup>st</sup> line Toxicities\*

(NCI-CTC version 2)

\* For patients receiving at least one dose

**ECX**  
**1<sup>st</sup> line**  
(n = 197)

**FOLFIRI**  
**1<sup>st</sup> line**  
(n = 201)

## Non haematologic toxicities

Grade 0/1/2	40%	44%	} <b>p = 0.45</b>
Grade 3/4	58%	55%	
NA	2%	1%	

## Haematologic toxicities

Grade 0/1/2	30.5%	61%	} <b>p &lt; 0.0001</b>
Grade 3/4	<b>65.5%</b>	<b>37%</b>	
NA	3%	2%	

## All toxicities

Grade 0/1/2	13%	29%	} <b>p &lt; 0.0001</b>
Grade 3/4	<b>85%</b>	<b>70%</b>	
NA	2%	1%	

## Toxic deaths

3.5%	2.5%
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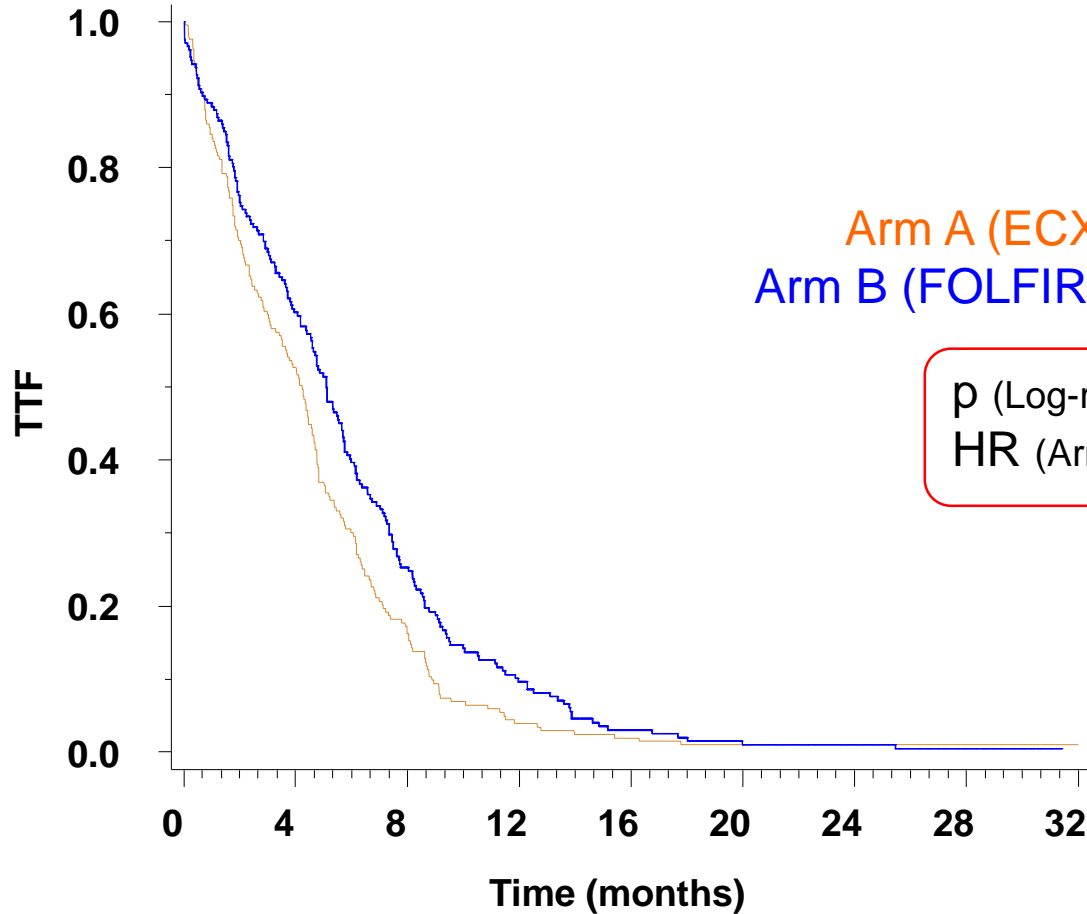
# 2<sup>d</sup> line Toxicities

(NCI-CTC)

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

# Primary end point: Time To Failure treatment at 1<sup>st</sup> 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



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

	Events
<b>Arm A</b>	<b>203</b>
<b>Arm B</b>	<b>203</b>

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

# TTF 1<sup>st</sup> line: Causes of discontinuation.

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

*Several causes possible for each patient*



# Time To Failure treatment at 2<sup>d</sup> line

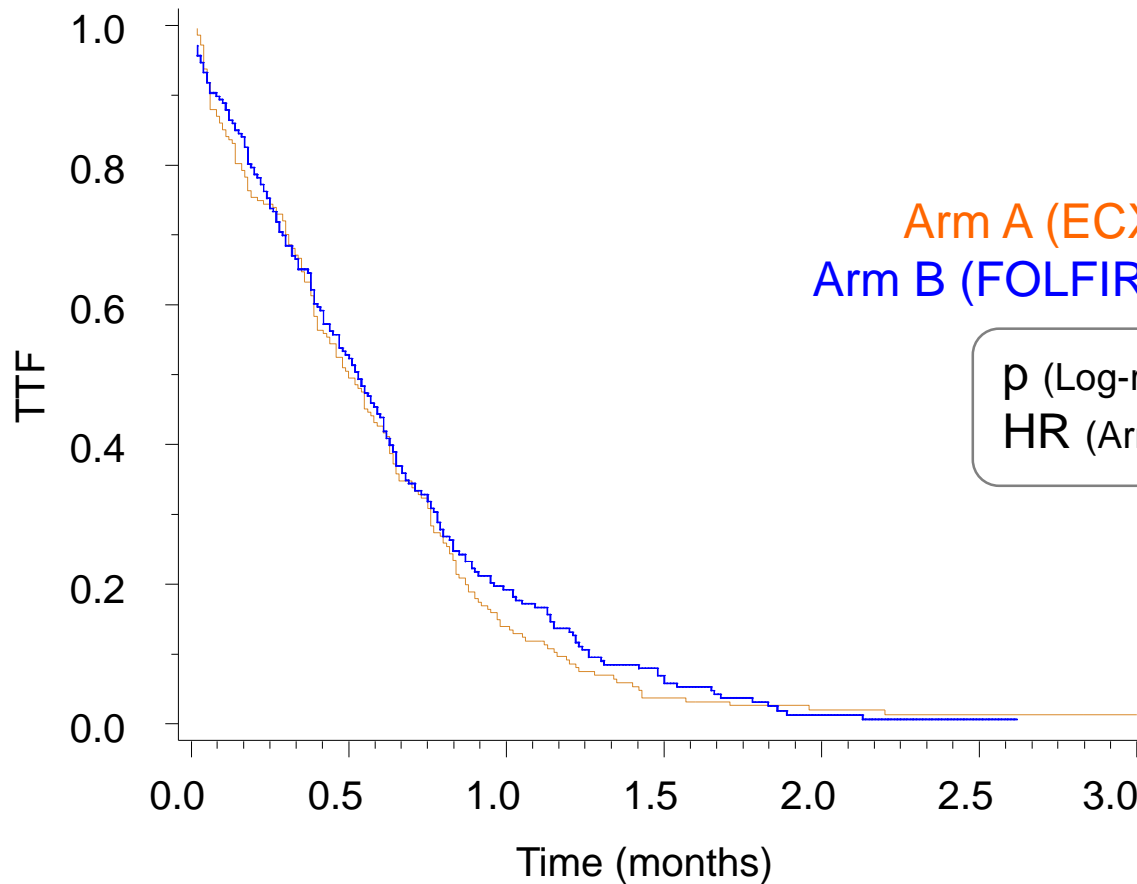
**Time to Failure Treatment (TTF) :**

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



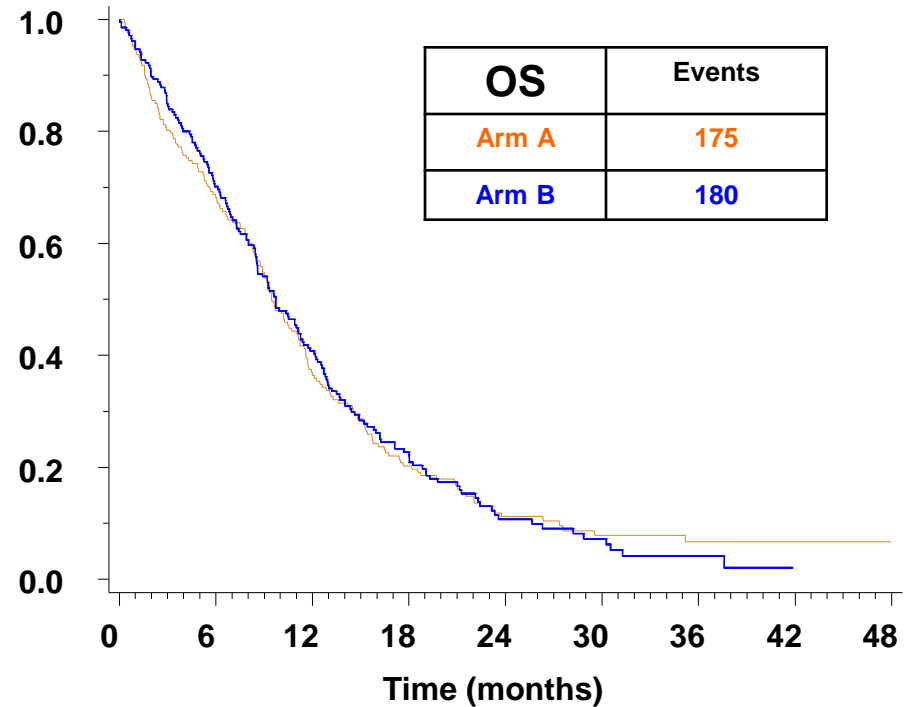
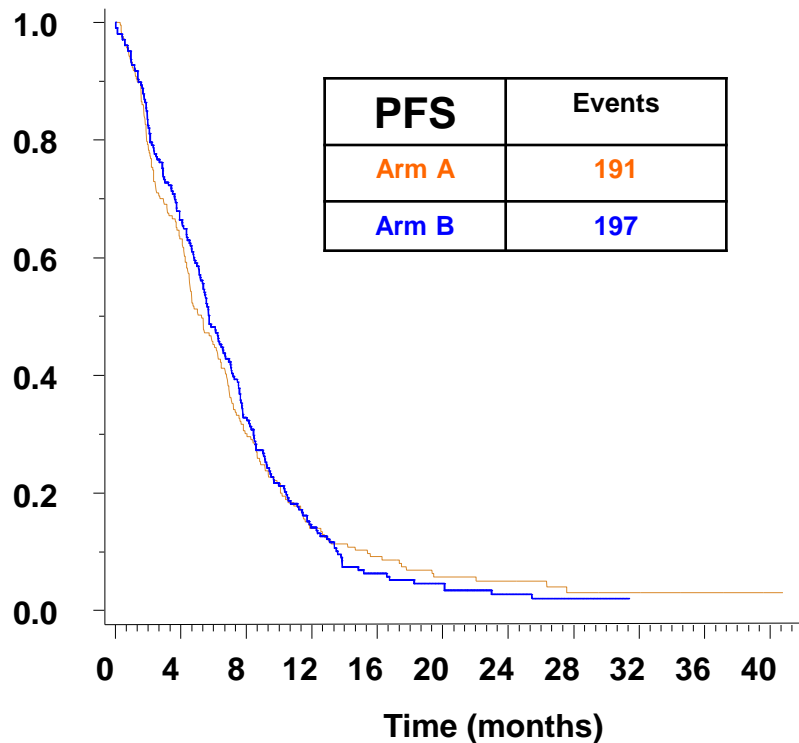
	Events
Arm A	199
Arm B	200

209	103	28	7	3	2	1
207	108	38	13	2	1	0

# Progression Free Survival and Overall Survival

Arm A (ECX 1<sup>st</sup> line) : **5.29 m.** [4.53;6.31]  
 Arm B (FOLFIRI 1<sup>st</sup> 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 1<sup>st</sup> line) : **9.49 m.** [8.77; 11.14]  
 Arm B (FOLFIRI 1<sup>st</sup> line) : **9.72 m.** [8.54; 11.27]  
 p (Log-rank)= 0.95  
 HR (B vs A)= 1.01 [0.82; 1.24]



209 129 57 26 17 9 7 3 3 3 2  
 207 135 65 28 11 8 4 2 0 0 0

209 135 69 35 18 9 5 3 2  
 207 142 79 38 14 7 2 0 0

# CONCLUSION

in metastatic or locally advanced cardiac and gastric cancer:

- FOLFIRI in 1<sup>st</sup> 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 TTF2<sup>d</sup> line, PFS and OS (secondary end point)
- TTF is a composite measure of efficacy and safety useful to assess benefit/risk balance...

# CONCLUSION

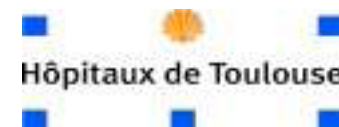
in metastatic or locally advanced cardiac and gastric cancer:

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

The improved safety profile of FOLFIRI 1<sup>st</sup> line could be an advantage to test its association with targeted therapies in gastric cancer.



Sponsor:



# 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. Salpêtrière	St Briec 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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