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Metastatic pancreatic cancer – Therapeutic management in 2008

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PANCREATIC CANCER : A LETHAL DISEASE

- 227,000 deaths worldwide (50,000 in Europe)
IARC 2002
- USA, 2006: 33,730 estimated new cancer cases and 32,300 expected deaths : **incidence ≈ mortality**
 Fourth leading cause of cancer death in men and women
Jemal A et al. 2006
- Eurocare-3 : 4.6 % five-year survival
Coleman MP et al. 2003
- Only one patient still alive and disease free at 5 years among 4,922 patients treated in Finland (1990-1996)
Carpelan-Holstrom M et al. 2005
- Fulminant clinical course: median survival < 6 months

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HISTORICAL CONTEXT

- 1995: Gemcitabine versus bolus 5-FU
 - 123 LA or M1 patients
 - Small but significant improvement in survival
 - Low objective response rate (5.4 %)
 - Higher rates of grade 3-4 myelosuppression, ↑ LFTs, nausea and vomiting
- 1996: Gemcitabine approved by FDA for advanced pancreatic cancer (APA)

	GEM	5-FU
n	63	63
12.7% censored		4.8% censored
Median survival (months)	5.65	4.41
Survival duration		
6 months	48%	31%
9 months	24%	6%
12 months	18%	2%

Burris HA et al. J Clin Oncol 1997;15:2403-13

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THERAPEUTIC ADVANCES IN APA

- 1996 – 2006
 - one phase III trial of gem-based combination therapy (PEFG) vs gemcitabine (Reni M et al. 2005) : no improvement in survival
 - three phase III trials of new drug vs gemcitabine
 - fourteen phase III trials of new drug + gemcitabine vs gemcitabine alone or with placebo

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GEMCITABINE versus OTHER AGENT

	n	source
• Gem vs marimastat	415	BRAMHALL 2001
• Gem vs BAY 12-9566	277	MOORE 2003
• Gem vs exatecan	339	CHEVERTON 2004

→ no improvement in survival

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HIGH DOSE versus FIXED DOSE-RATE GEMCITABINE

a randomized phase II trial

gemcitabine dose	N	RR	TTF	med S	1-year S
2,200 mg/m ² over 30 min	49	9.1%*	1.8 mo	5 mo	9%
1,500 mg/m ² at 10 mg/m ² /min (150 min)	43	5.9%*	2.1 mo	8 mo	28.8%

* Only 39 patients had measurable disease

Tempero M et al, J Clin Oncol 2003 ;21:3402-8.

GEM ± FLUOROPYRIMIDINE TRIALS

Source	n	drugs	ORR	Survival
BERLIN JCO 2002	322	G G+FU	5.6 % 6.9 %	5.4 mo 6.7 mo
RIESS ASCO 2005	466	G G+FU/LV	7.2 % 4.8%	6.2 mo 5.85 mo
HERRMANN ASCO 2005	319	G G+Cap	7.9 % 10.1 %	7.3 mo 8.4 mo
CUNNINGHAM ECCO 2005	533	G G+Cap	7.1 % 14.2 %*	6 mo 7.4 mo*

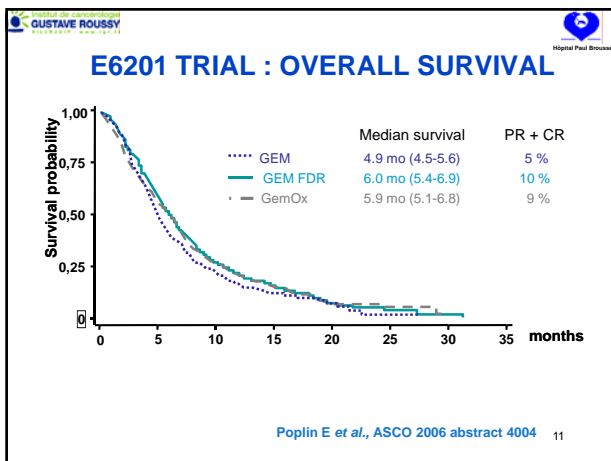
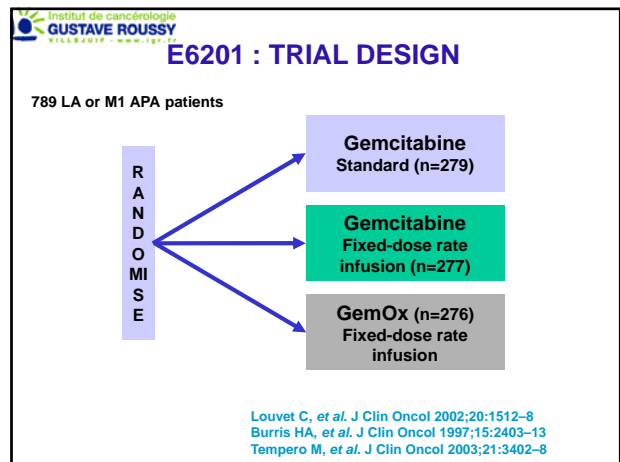
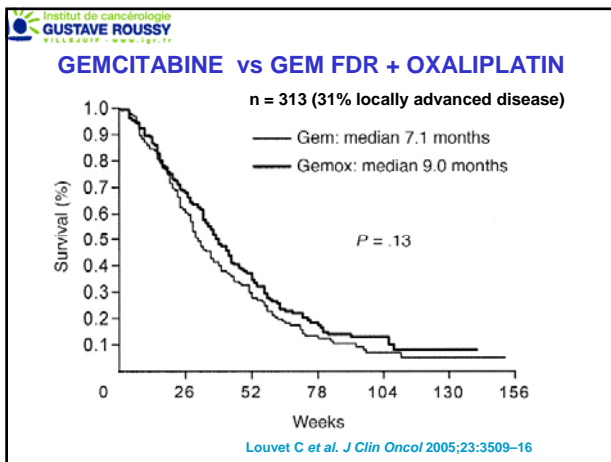
* significant difference with gemcitabine only

GEMCITABINE DOUBLETS TRIALS

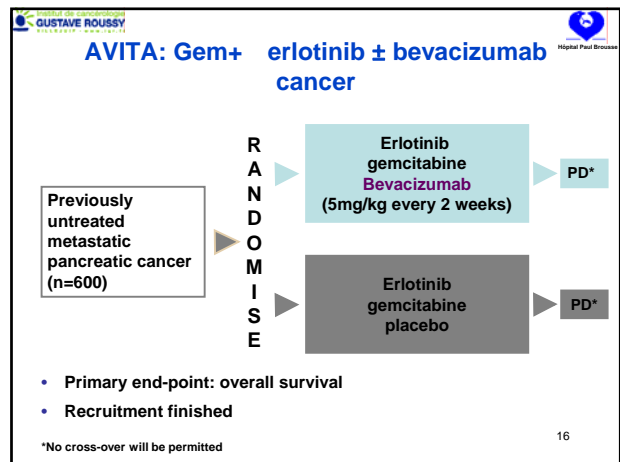
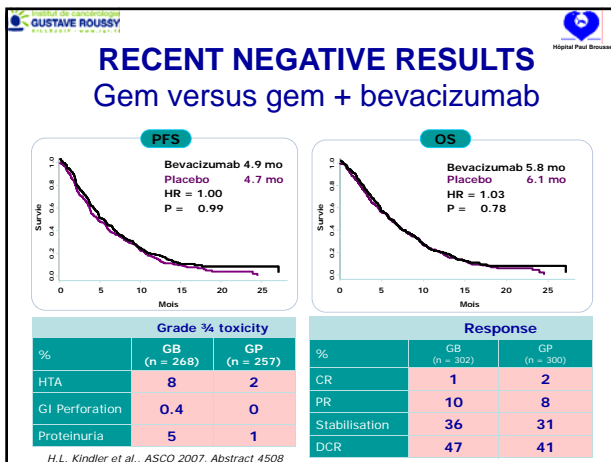
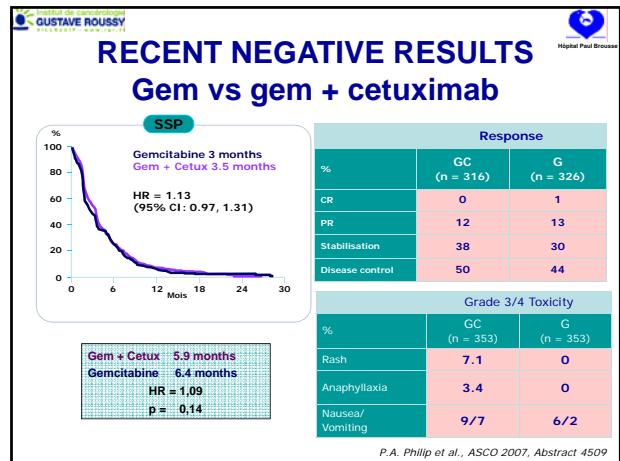
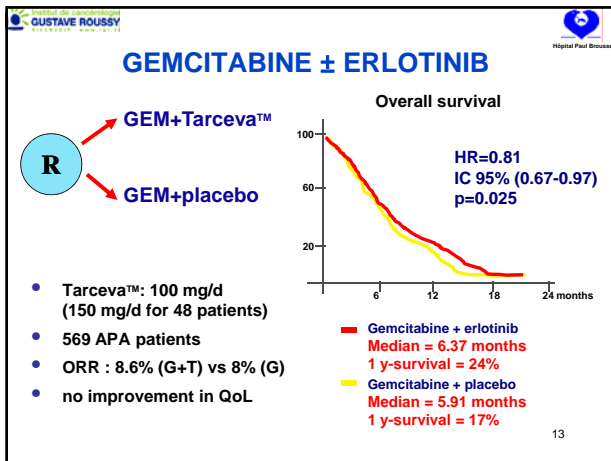
Results in the doublet arm

Drug X	n	LAD (%)	ORR (%)	PFS (mo)	OS (mo)	Source
Irinotecan	360	18	16.1*	3.4	6.3	Rocha-Lima 2004
Irinotecan	145	18	15	2.8	6.4	Stathopoulos 2006
Exatecan	349	21	6.3	3.7	6.7	Abou-Alfa 2006
Pemetrexed	565	9	18.3*	3.3	6.2	Oettle 2005
Cisplatin	195	20	10.2	4.6*	7.5	Heinemann 2006
Oxaliplatin	313	31	26.8*	5.8*	9	Louvet 2005
Oxaliplatin	555	12	9	na	5.9	Poplin 2006

* significant difference with gemcitabine only



- ### GEM-BASED COMBINATION
- Molecular targeted agents
 - Gem vs Gem + marimastat (2002) n = 239
 - Gem vs Gem + tipifarnib (2004) n = 688
 - Gem vs Gem + G17DT (2005) n = 383
- No benefit over gemcitabine only

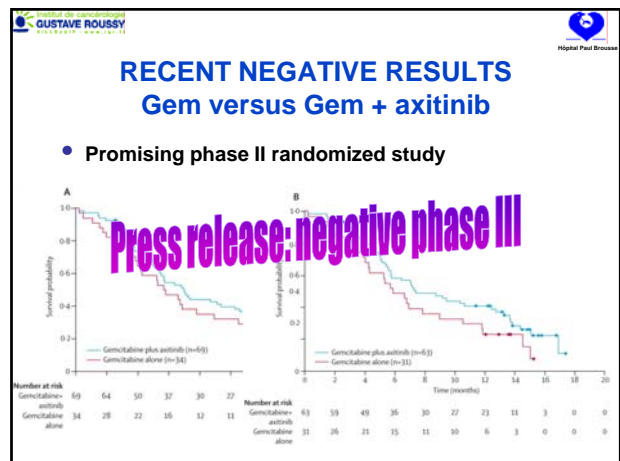


Phase III Gem/Erlotinib +/- Bevacizumab Results

	G+E+B	G+E	p
n	306	301	
Response rate (%)	13.5	8.6	0,057
SSP (months)	4.6	3.6	0.0002
OS (months)	7.1	6	0,21

No difference in terms of grade 3-4 toxicity

17
 W. Vervenne et al., ASCO 2008, A 4507



GEMCITABINE DOUBLET IN APA

- Some improvement in response rate (irinotecan, pemetrexed, oxaliplatin, gemcitabine FDR)
- Modest increase in progression-free survival (cisplatin, gemcitabine FDR)
- Possible longer survival with combination if KPS > 80 (cisplatin, 5-FU, capecitabine)
- Trend for better survival (gemcitabine FDR, capecitabine)
- **Modest increase in survival :**
 erlotinib 2 weeks
 capecitabine 6 weeks

19

THE ON-GOING FRENCH TRIAL

- Phase II study of Folfirinox in advanced pancreatic carcinoma, encouraging results :
 - 47 patients, 76% metastatic disease
 - No toxic death
 - Grade 3-4 neutropenia : 52% (without use of G-CSF)
 - Objective response rate : 26%
 - Median TTP : 8.2 mois, Median OS : 8.2 mois

On going trial

20

THE ON-GOING FRENCH TRIAL

French phase II-III randomized trial (T Conroy)

	Folfirinox	Gemcitabine
Included	44	44
Evaluated	32	34
PR (confirmed)	12 (38.7%)*	4 (11.7%)
NC	12	9
PD	8	21

21

THE ON-GOING FRENCH TRIAL?

Grade 3-4	FOLFIRINOX n = 41	Gemcitabine n = 40
G 3 Neutropenia	32%	1,5%
G 4 Neutropenia	19.5%*	0%
G 3 Thrombopenia	12%	0%
G 3 Fatigue	25%	15%
G 3 Vomiting	17%	2,5%
G 3 Transaminases	0%	15%

* No febrile neutropeniae

22

PROPORTION OF PATIENTS RECEIVING A SECOND LINE CHEMOTHERAPY IN GEMCITABINE ALONE ARM OF RECENT PHASE III TRIALS

source	n	LAD	% second line	Survival
BRAMHALL 2002	119	29%	19%	5.4 mo
STATHOPOULOS 2006	70	18%	31%	6.5 mo
ROCHA-LIMA 2004	180	14%	46%	6.6 mo
OETTLE 2005	283	9.5%	43%	6.3 mo
LOUVET 2005	326	31%	55%	7.1 mo

23

EFFICACY OF SECOND LINE MONOTHERAPIES

Drug	n	RR	TTP (mo)	OS (mo)	Source
Paclitaxel	18	5%	na	4	OETTLE 2000
Rubitecan	58	7%	2	3	BURRIS 2005
Oxaliplatin	18	0%	na	3.5	ANDROULAKIS 2005
Raltitrexed	19	0%	2.5	4.3	ULRICH-PUR 2003
Irofulven	53	4%	na	3	VON HOFF 2000
S-1	33	12%	2.1	ns	MORIZANE 2006
Pemetrexed	54	4%	1.6	4.6	BOECK 2006

24

SECOND LINE COMBINATION THERAPIES

Chemotherapy	n	RR	TTP (mo)	OS (mo)	Source
G-FLIP	34	24%	3.9	10.3	KOZUCH 2001
5-FU + Celecoxib	17	12%	2	3.4	MILELLA 2004
Gemox	33	25%	4.2	6	DEMOLS 2006
Tomiri	19	16%	4	6.5	ULRICH-PUR 2003
Folfox	30	23%	5	6	TSAVARIS 2005
OXFU	32	0%	0.9	4.9	MITRY 2006
Xelox	39	2%	ns	5.8	XIONG 2006

25

FUFOX versus best supportive care (CONKO 003)

Phase III trial planned with 165 planned patients but prematurely closed after 46 pts because of recruitment problems (BSC arm no more accepted)

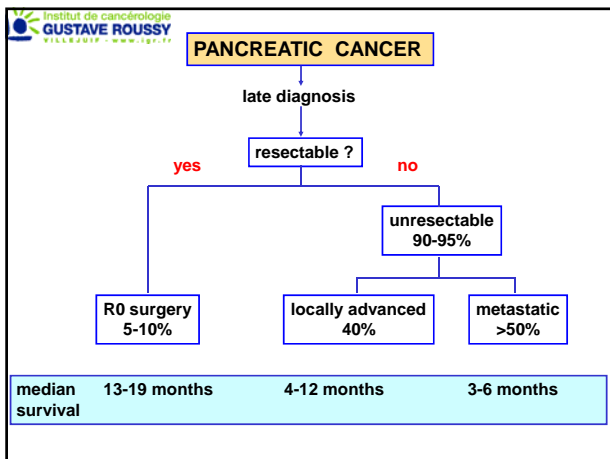
FUFOX : 5FU 2 g/m² / FA 200 mg/m²
 d1, d8, d15 and d22

Oxaliplatin 85 mg/m² d8 and d22
 new cycle at d43

Survival	first line	second line	overall
FUFOX	19.8 wks	21 wks	40 wks
BSC	20.7 wks	10 wks	34.4 wks
p		0.008	0.032

Oettle H et al. ASCO 2005, abstract 4031

26



PROGNOSTIC FACTORS ASSOCIATED WITH SURVIVAL

Adverse prognostic factors in multivariate analysis

LOUVET 2005 N = 349	OETTLE 2005 N = 565	VAN CUTSEM 2004 N = 688
T4 STAGE Ca 19.9 > 350 u/ml PS 2	PS 2 liver metastases	weight loss > 10% pain albumin < 35 g/l multiple M1 sites body or tail

- ### CONCLUSIONS
- Worst survival statistics of any cancer
 - Improving outcomes in APA has been more difficult than anticipated and gemcitabine is still (one of) the standard of care for APA
 - Modest increase in survival with first line gemcitabine doublet with erlotinib and capecitabine
 - 20-50% of APA patients may receive a second line therapy
 - Combination of 5FU and oxaliplatin is an interesting proposal for second line therapy
- 29