

Strategies to improve the outcome of locally advanced pancreatic cancer patients

Christophe Louvet

Institut Mutualiste Montsouris, Paris

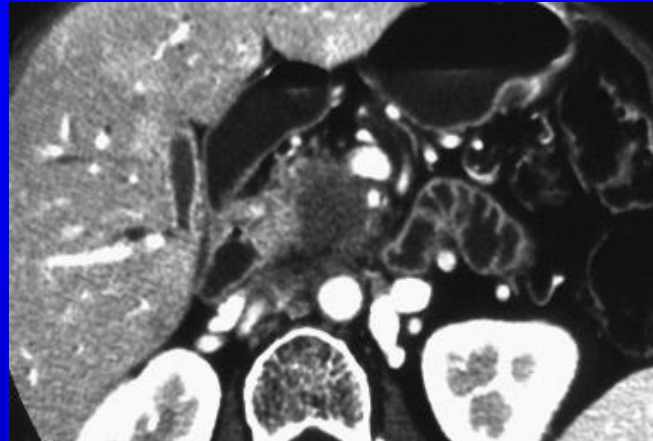
Disclosures C. Louvet

Celgene

Roche

Nucana

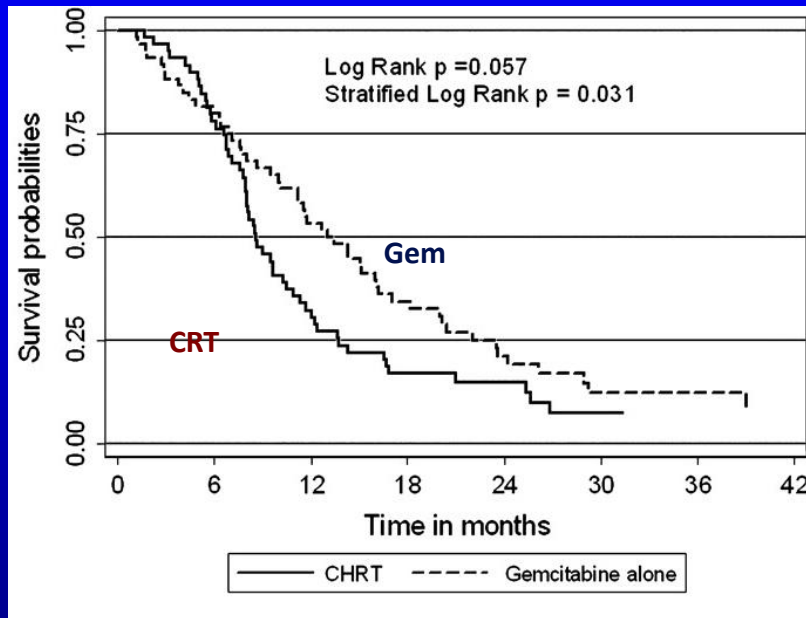
Background



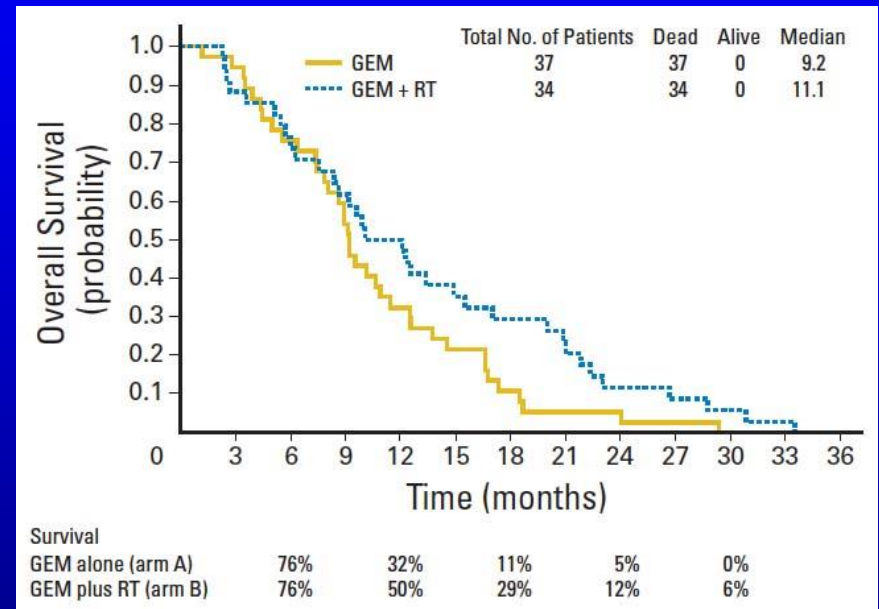
Role of radiation therapy in locally advanced pancreatic cancer highly debated

- **Local control** remains an important issue
 - chemoradiation (CRT)
- High rate of **distant metastasis**
 - chemotherapy

Frontline CRT versus chemotherapy in LAPC



Chauffert B et al. Ann Oncol 2008

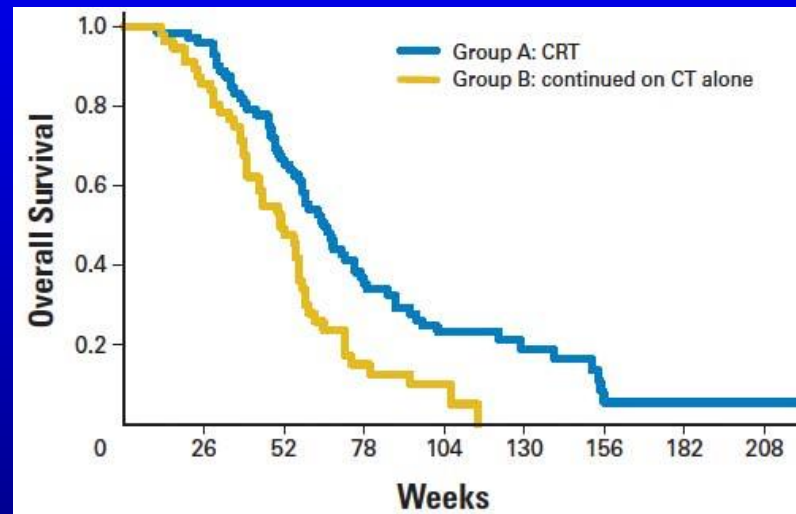


Loehrer P et al. J Clin Oncol 2011

→ **Contradictory** results

Induction CT followed by CRT in LAPC

CRT after 3 months of induction chemotherapy



Huguet F et al, J Clin Oncol 2007

→ **Promising** strategy

Authors	Treatment	N pts	PFS (months)	OS (months)	1-year survival (%)
Huguet (retrosp)	CT CT then CRT	181	7.4 10.8	11.7 15	47.5 65.3
Krishnan (retrosp)	CRT CT then CRT	323	4.2 6.4	8.5 11.9	-
Brunner (retrosp)	CRT CRT then CT	172	-	7.6 13.5	21 65
Ko (phase 2)	CT then CRT (32% PD after CT)	25	10.5 (12.7)	13.5 (17)	62
Schneider (phase 2)	CT - CRT - CT	18	-	12.8	-

Concurrent chemotherapy?

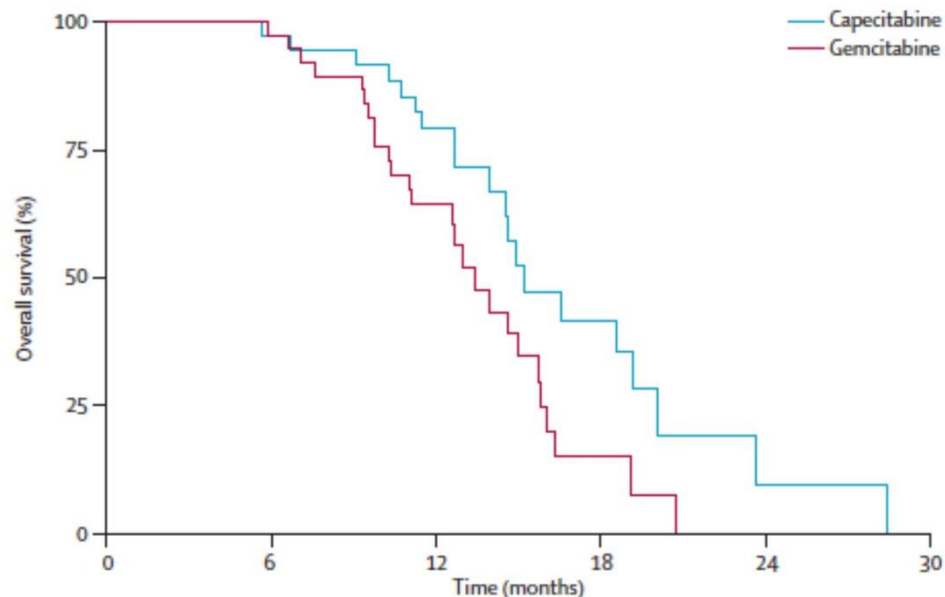
SCALOP (phase 2)

74 pts Gem-Cap x 3 R

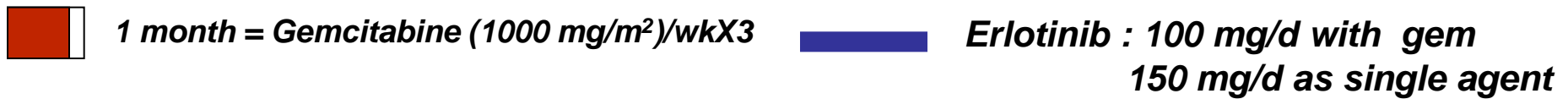
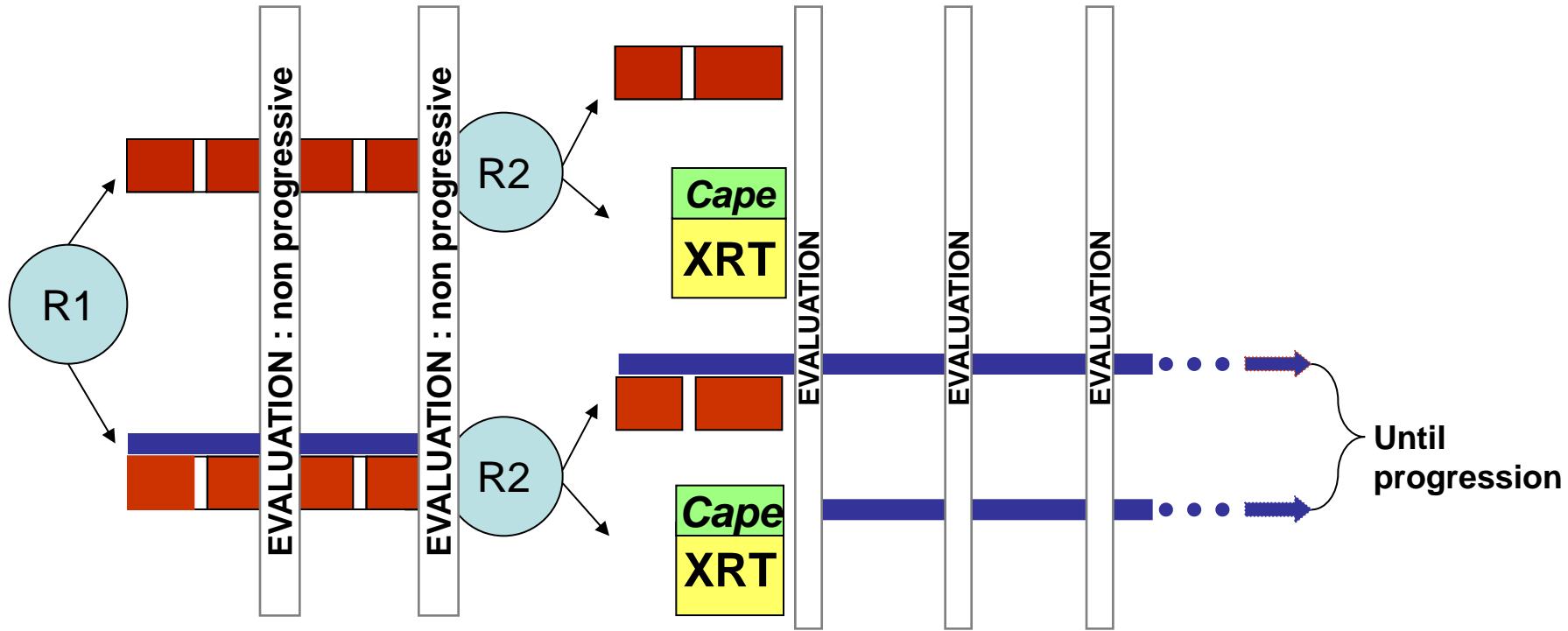
CRT 50.4 Gy with capecitabine 15.2 months

CRT 50.4 Gy with gemcitabine 13.4 months

p= 0.01



LAP07 study



Cape	<i>Capecitabine plus radiation</i>
XRT	<i>Quality assurance</i>

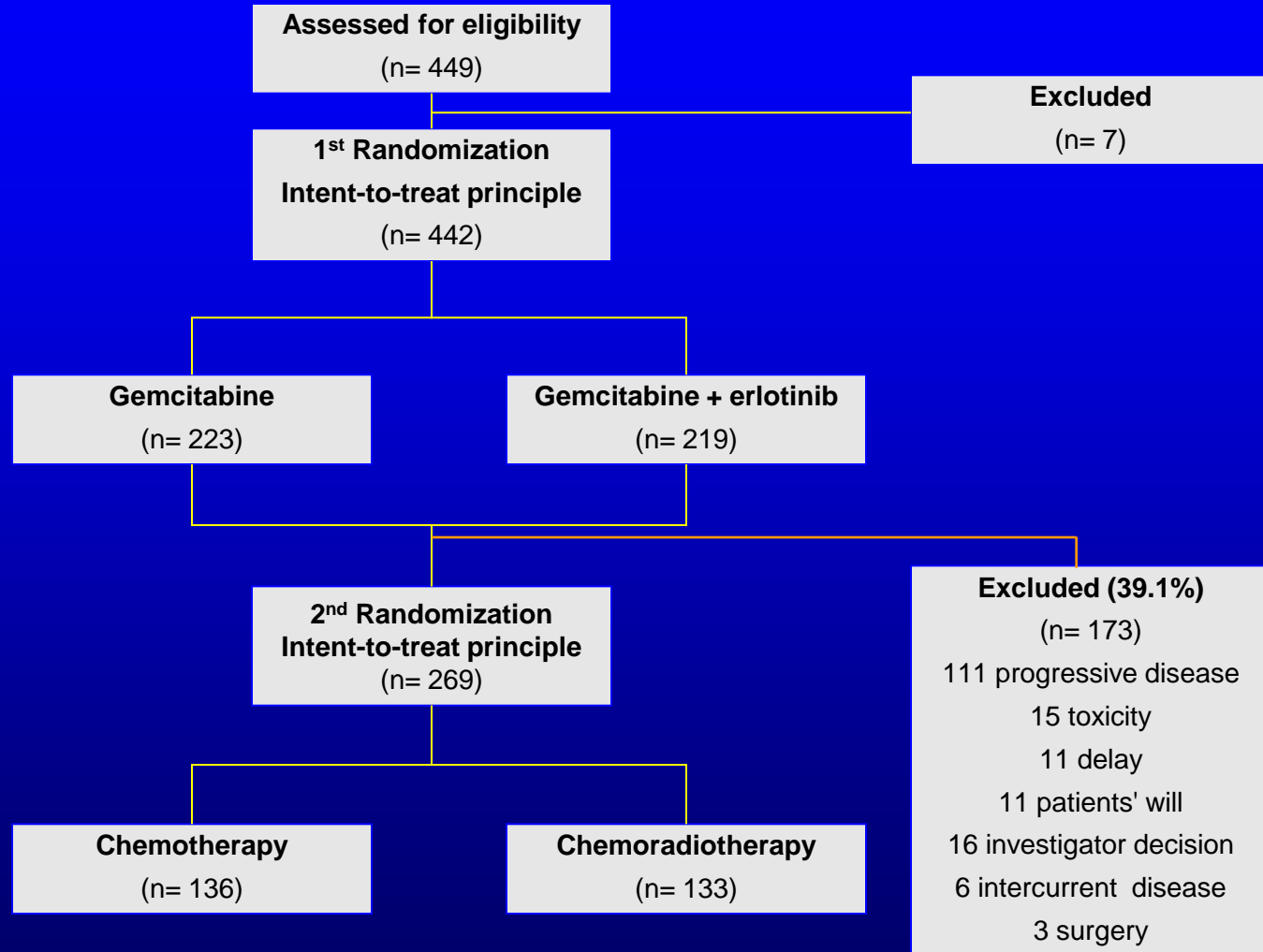
Secondary surgery allowed at any time

Objectives of LAP07 study

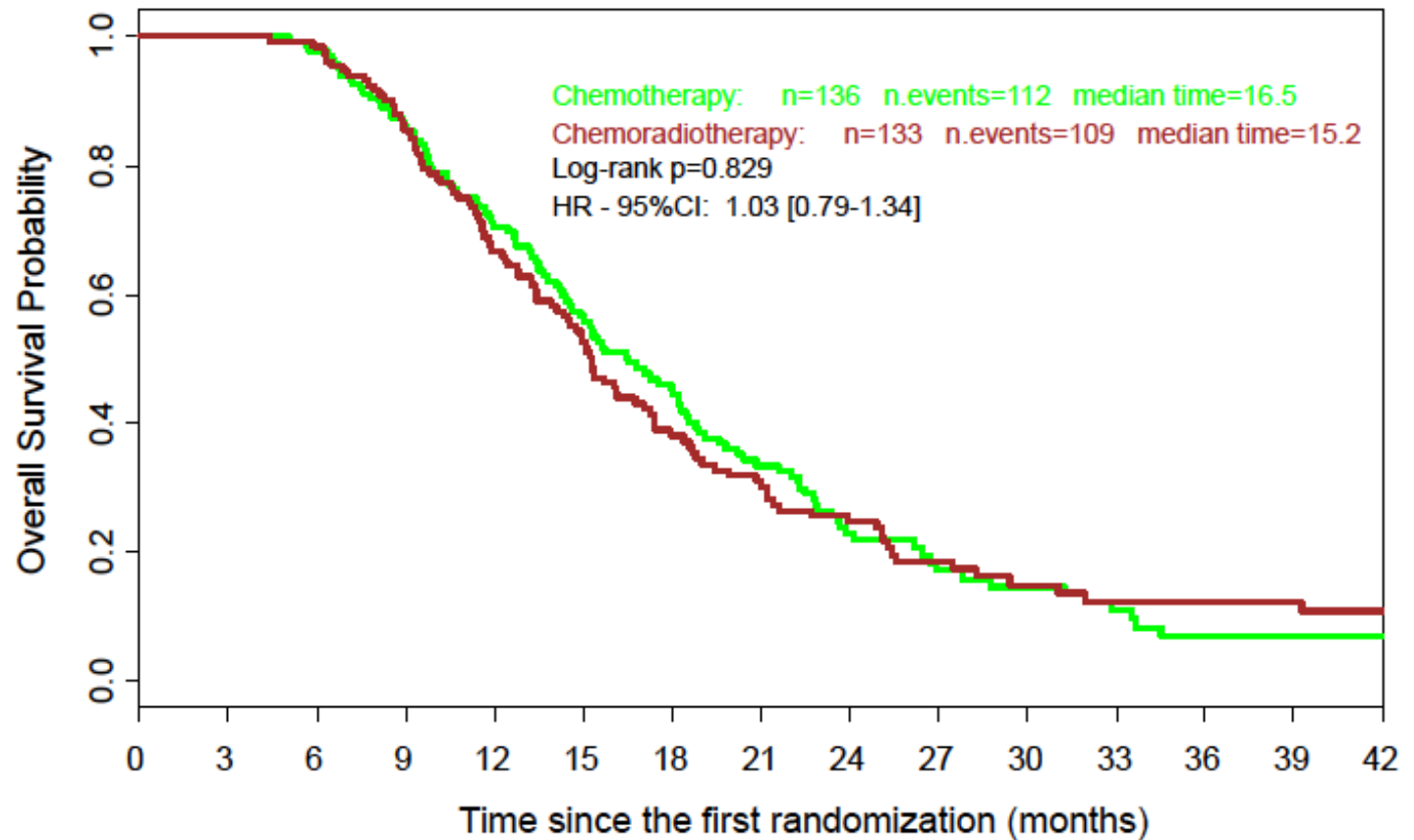
- **Primary objective:** to assess whether administering CRT increases overall survival in patients whose tumor is controlled after 4 months of induction chemotherapy
- **Secondary objectives:**
 - Role of erlotinib
 - Progression free survival (PFS)
 - Tolerance
 - Impact of Radiation Therapy Quality Assessment (RTQA)¹
 - Predictive molecular markers, circulating tumor cells²

¹ Huguet F et al. ASTRO 2013; ² Bidard FC et al. Ann Oncol 2013

Flow Chart



Overall Survival



N at risk

Chemotherapy	136	136	133	117	94	70	55	39	24	14	12	8	4	4	4
Chemoradiotherapy	133	133	131	113	87	66	45	34	26	18	12	9	9	8	6

Site of progression

- **R2 patients:**

236/269 patients (88%) with tumor progression

93 with local progression only (39.4%)

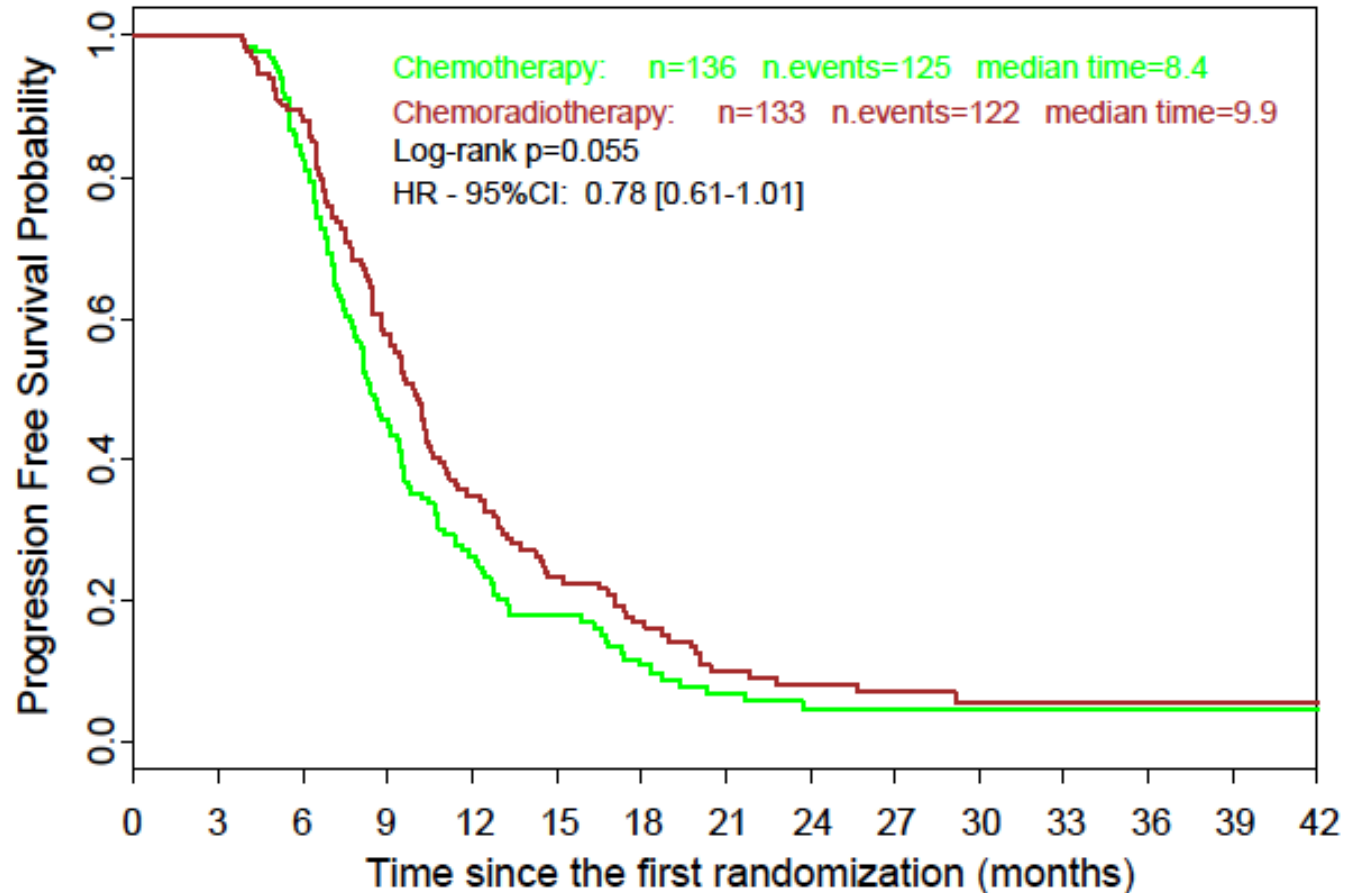
122 with metastatic (\pm local) progression (51.7%)

21 unknown (8.9%)

	Chemotherapy (n= 125)	Chemoradiation (n= 111)
LA	58 (46%)	35 (32%)
M+	55 (44%)	67 (60%)
unknown	12 (10%)	9 (8%)

$p=0.035$

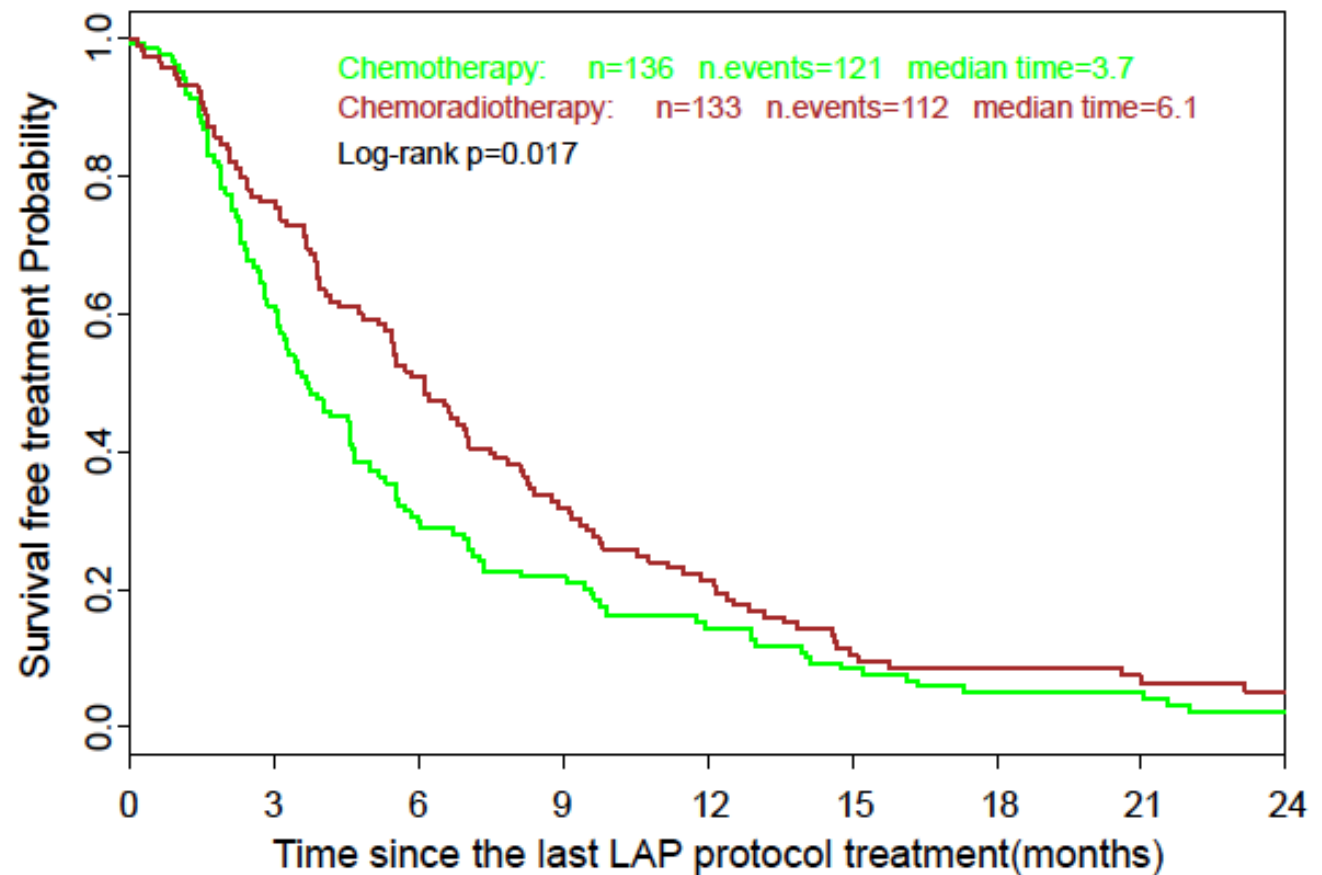
Progression Free Survival



N at risk

Chemotherapy	136	136	113	61	35	21	12	7	3	1	1	1	1	1
Chemoradiotherapy	133	133	117	76	45	30	21	11	8	7	4	4	4	4

Treatment Free Survival



N at risk

Chemotherapy	136	75	37	27	17	10	6	6	2
Chemoradiotherapy	133	89	60	37	24	11	8	6	5

LAP07 Conclusions

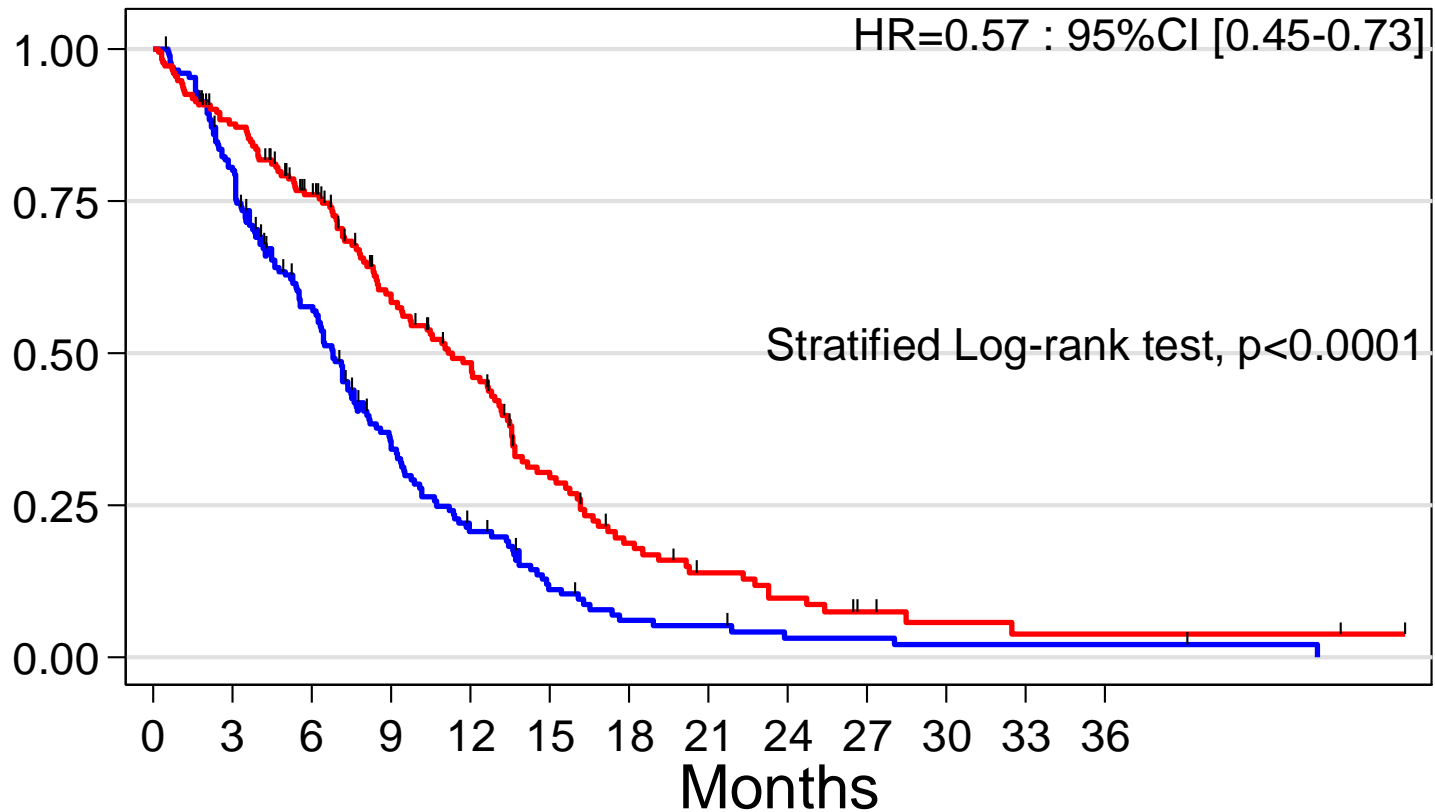
- LAP07 prospectively confirmed the value of frontline chemotherapy in LAPC patients
- Overall survival in CRT arm is not superior to chemotherapy arm in LAPC patients with tumor controlled after 4 months of chemotherapy
- However, trend for PFS in favor of CRT
- In the CRT arm, patients had a significantly less local tumor progression and a longer period without chemotherapy

Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy

FOLFIRINOX

Overall Survival

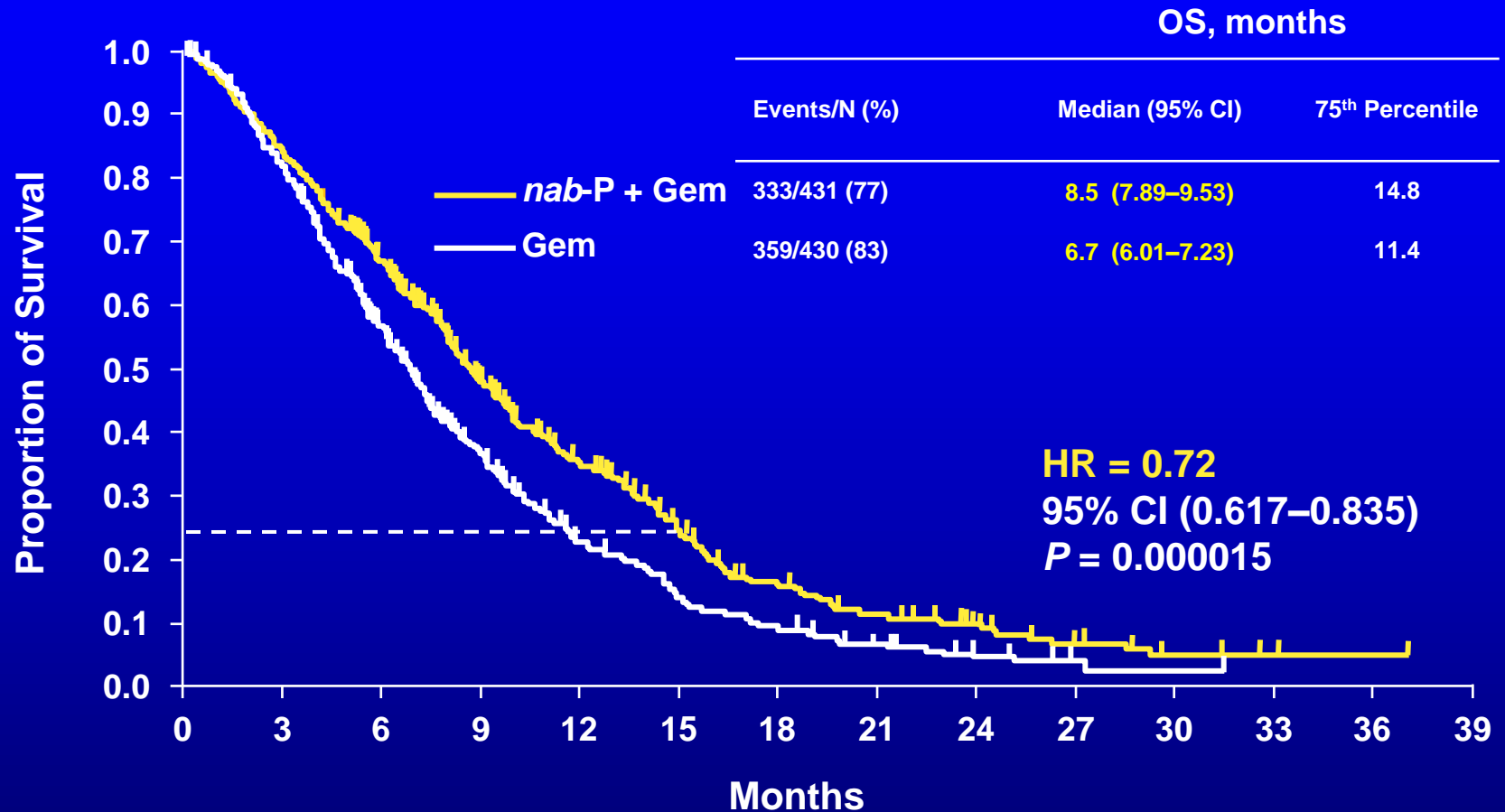


Number at risk

Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2
Folfirinox	171	146	116	81	62	34	20	13	9	5	3	2	2

— Gemcitabine — Folfirinox

Nab-P + Gem Overall Survival



Pts at Risk

<i>nab</i> -P + Gem:	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gem:	430	340	220	124	69	40	26	15	7	3	1	0	0	0

Nab-Paclitacel + FOLFOX

Phase I study (Saffran, ASCO 2014)

Very promising results

Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy

2- Personalized medicine

Strategies to improve the outcome of LAPC patients

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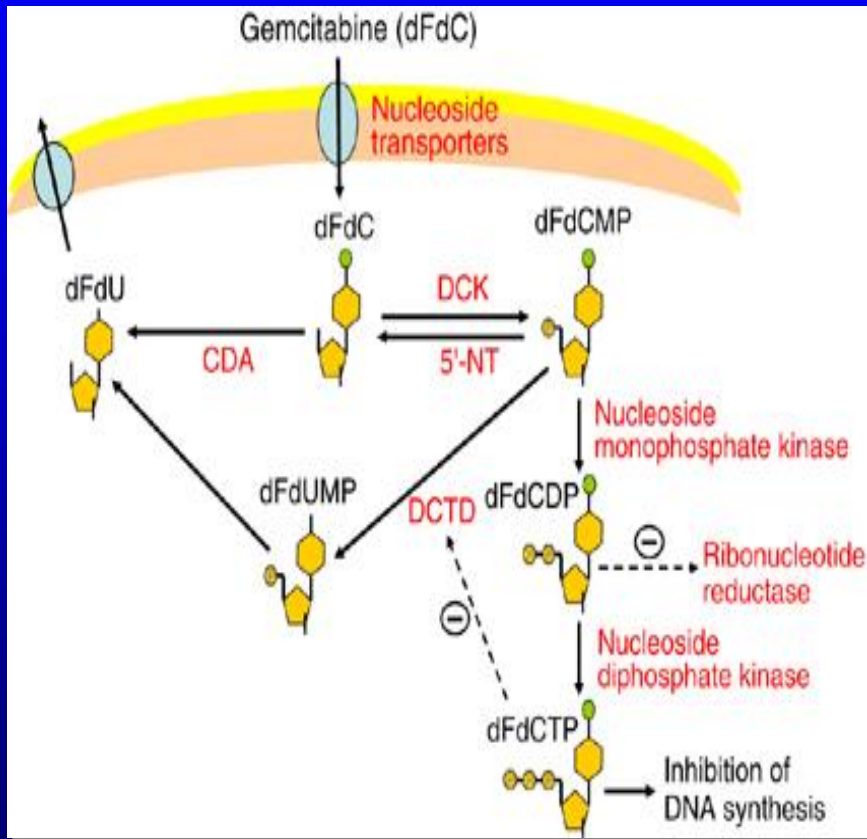
2- Personalized medicine

Prognostic factor analysis from LAP07

Biomarkers and targeted drugs

SPARC

Gemcitabine: mechanisms of action



■ Intracellular uptake

✓ **hENT1**

✓ **hCNT 3**

■ Activation

✓ **dCK**

– Nucleoside Phosphate Kinase

■ Inactivation

– CDA

– DCTD

– 5'-NT

■ Action

– Inhibition DNA synthesis

hENT1

« Positive » trials

RTOG
(adjuvant, retrospective)



French-Belgium series
(adjuvant, retrospective)



ESPAC 1&3
(adjuvant, retrospective)



Negative trials

Clovis C01-101
(metastatic, prospective)

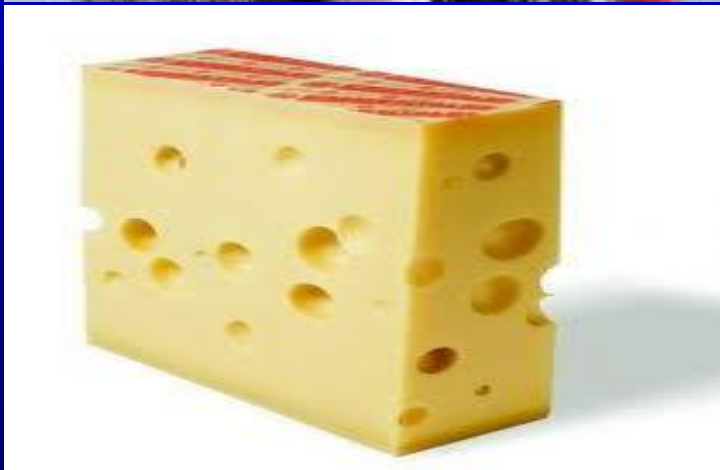


ECOG
(metastatic, retrospective)



CONKO-01
(adjuvant, retrospective)





=



?

Biomarker	Prognostic	Predictive	Current clinical impact
CA 19.9	Yes	No	No
CTC / cDNA	Yes	No	No
miRNAs	Yes	No	? (Anti-sens)
Proteomic / LAMC	Yes	No	No
Genomic profiles	Yes	No	No
hENT1	No	Yes (Gem)	Likely (Gem)
dCK	No	Yes (Gem)	Likely (Gem)
CDA	No	Yes (Gem toxicity)	Likely (Gem)
SPARC	Yes	?	? (Abraxane)
Histone modifications	Yes	?	? (5FU)
Hedgehog	Yes	?	? (HH inhibitors)
CXCR4	Yes	?	? (CXCR4 inhibitors)
HGF / c-Met	Yes	?	? (c-Met inhibitors)
SMAD4	?	?	?
HER2	?	?	? (HER2 inhibitors)
EGFR	? (No)	No	No
VEGFR	? (No)	No	No
IGFR	? (No)	No	No

Strategies to improve the outcome of LAPC patients

- 1– Improvement of systemic chemotherapy**
- 2- Personalized medicine**
- 3- Improvement of chemoradiation**

Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy

2- Personalized medicine

3- Improvement of chemoradiation

Dose radiation

Target volume

IMRT, gating

concurrent radiosensitizer

Strategies to improve the outcome of LAPC patients

- 1- Improvement of systemic chemotherapy**
- 2- Personalized medicine**
- 3- Improvement of chemoradiation**
- 4- Improvement in strategy and techniques**

Strategies to improve the outcome of LAPC patients

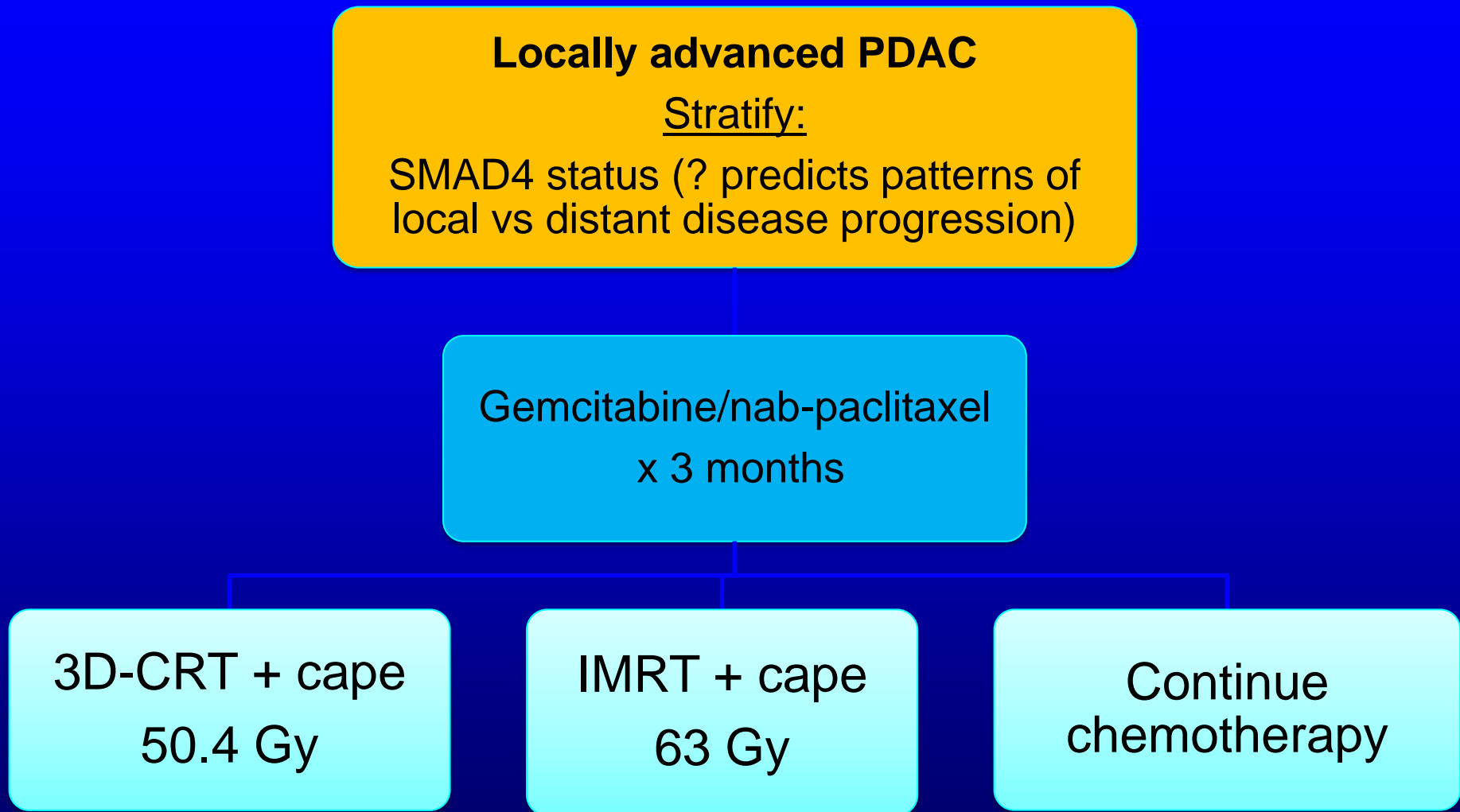
- 1- Improvement of systemic chemotherapy**
- 2- Personalized medicine**
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- 4- Improvement in strategy and techniques**

Increased time of systemic CT before CRT ?

Place of secondary surgery after systemic CT and CRT ?

Place of HIFU ?

RTOG 1201 will help address the question of whether more effective chemotherapy impacts the role of radiation in locally advanced disease



(P.I.: Christopher Crane, MD Anderson)

Phase III SCALOP 2 design

LAPC patients, PS 0-1
255 pts

GEM/Nab-Paclitaxel ou GEMCAP x 3
cycles



Randomise if eligible for CRT (65%) 1:1:1:1:1 between arms A-E
Then GEM/Nab-Paclitaxel x 1 cycle whilst RT is planned



Arm A
n=33
Gemcap



	- Nelfinavir n=66	+ Nelfinavir n=66
50.4 Gy n=66	Arm B n=33 CAPE 50.4Gy/28F	Arm C n=33 CAPE 50.4Gy/28F +Nelfinavir
60 Gy n=66	Arm D n=33 CAPE 60Gy/30F	Arm E n=33 CAPE 60Gy/30F + Nelfinavir

Methodological and medico-economic issues

Systematic QoL studies ?

Composite endpoints ?

Amount of requested material for genomic issues ?

Place of « liquid biopsies » ?

Cost of new drugs and of CTRT ?

Strategies to improve the outcome of LAPC patients

- 1- Improvement of systemic chemotherapy**
- 2- Personalized medicine**
- 3- Improvement of chemoradiation**
- 4- Improvement in strategy and techniques**
- 5- Methodological and medico-economic issues**