PANCREAS CANCER ACADEMY

Pancreatic Cancer Academy

Nov. 30th – Dec. 1st 2019

Vienna

CECOG ACADEMY

Pancreatic cancer treatment
« The L1 dilemna »

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- Pierre Fabre
- Servier
- Sanofi
- Lilly
- SIRTEX

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IMPROVEMENT IN OS SINCE 20 YEARS

However OS remains poor for metastatic pancreatic cancer

OS

Before 1997: 3-4 mo

1997 Gemcitabine : 5-6 mo

2005 Gemcitabine ; option «doublet »

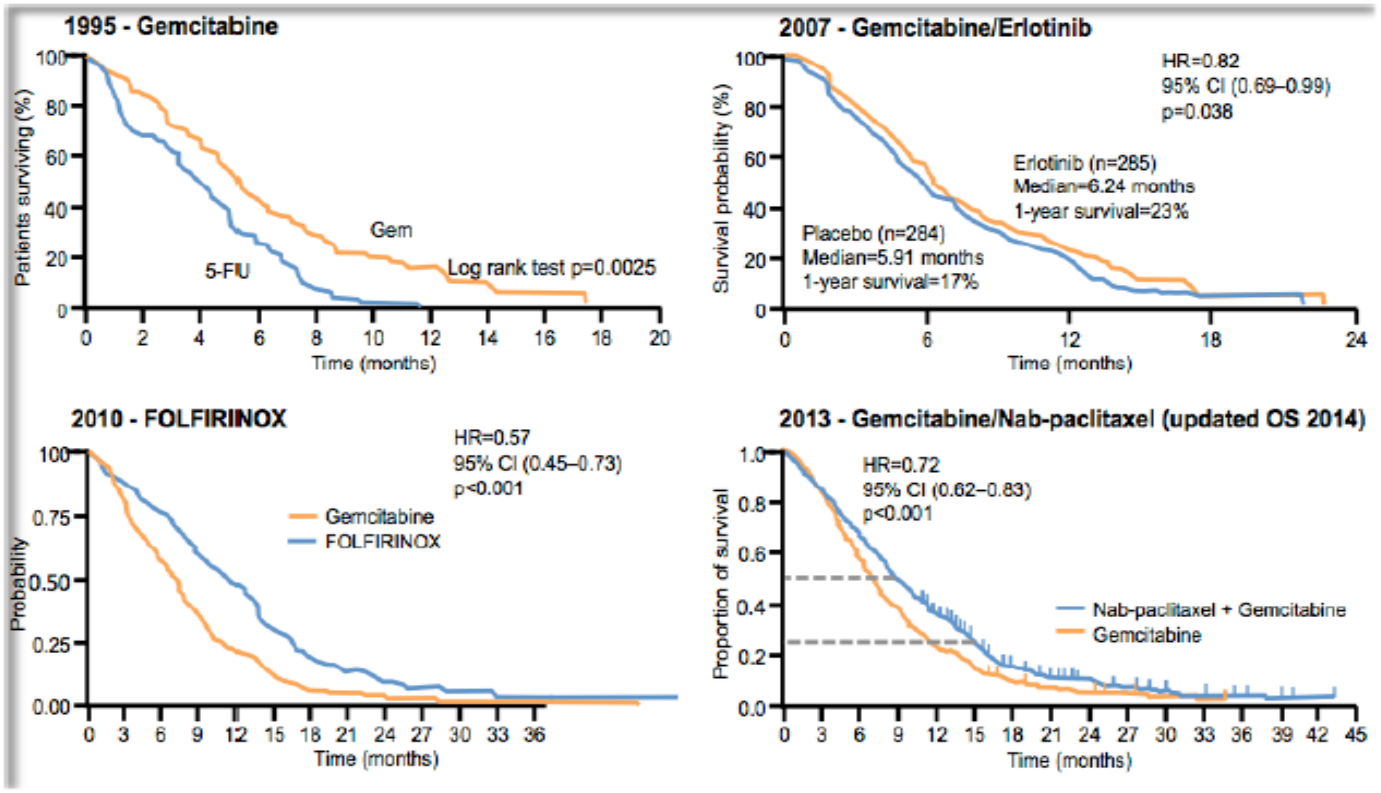
2010 FOLFIRINOX : 11-12 mo

2013 Gemcitabine + Abraxane : 9-10 mo

CECOG ACADEM

First line therapeutic options in 2019

Small incremental benefits with frontline cytotoxic therapies over the last 2 decades



Burris et al JCO, 15:2403-2413, 1997, ; Moore et al, JCO, 25:1960-1966, 2007; Conroy et al, 364:1817-1825, 2011 ; Von Hoff et al, NEJM, 2013,

First line therapeutic options in 2019

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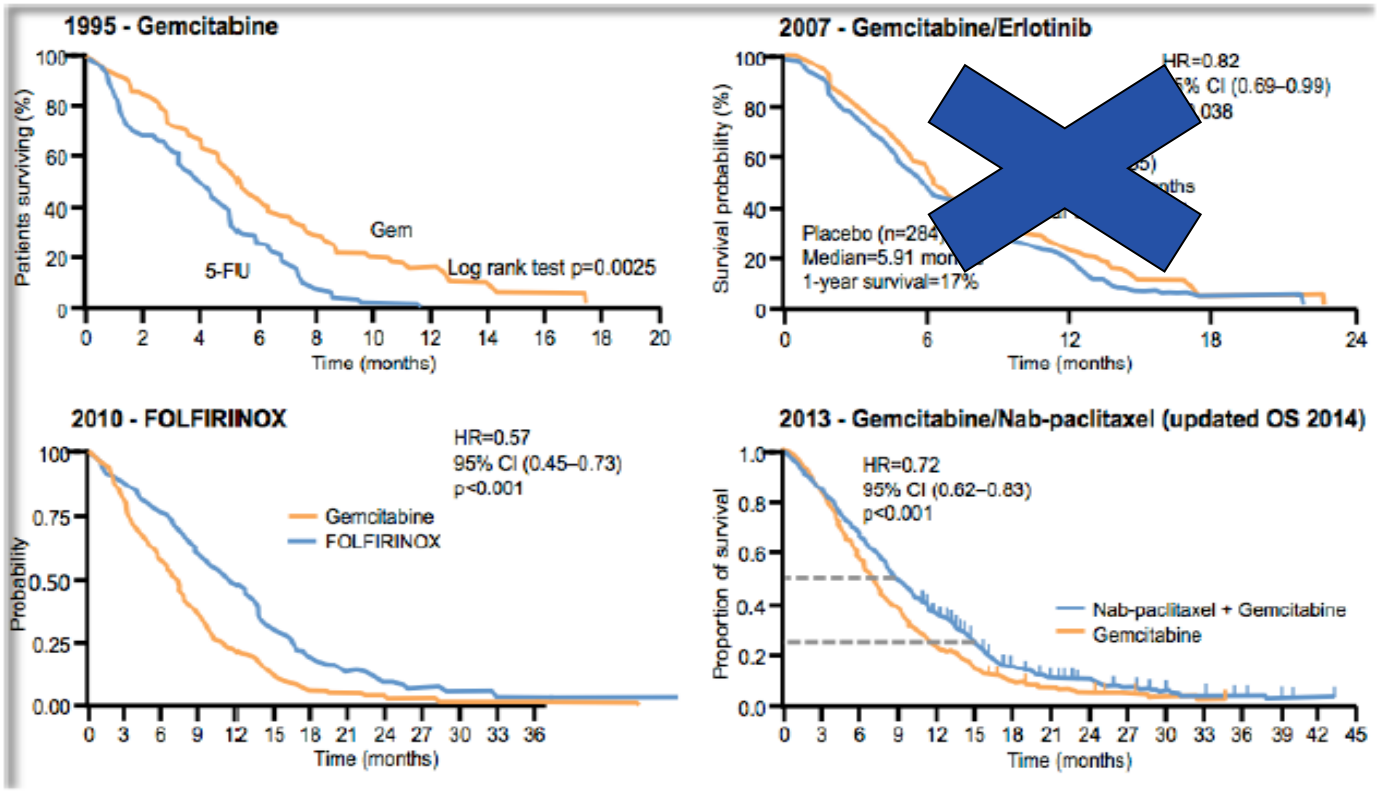
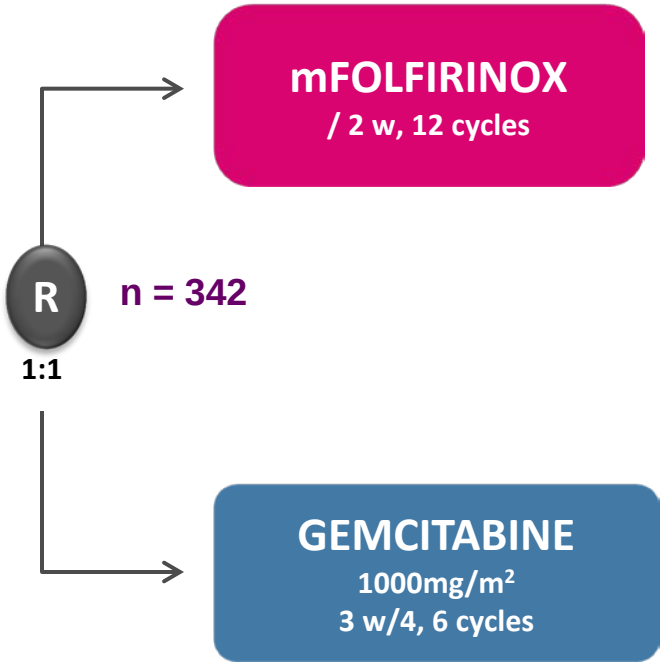


Burris et al JCO, 15:2403-2413, 1997, ; Moore et al, JCO, 25:1960-1966, 2007; Conroy et al, 364:1817-1825, 2011 ; Von Hoff et al, NEJM, 2013,

First line treatment for metastatic disease

FOLFIRINOX the PRODIGE 4 study

- **metastatic**
- **chemotherapy naïve**
- **PS 0 or 1**
- **18-75 year old**
- **Bilirubinemia < 1.5 xN**



Primary Objective : OS

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Conroy et al, *N Engl J Med* 2019

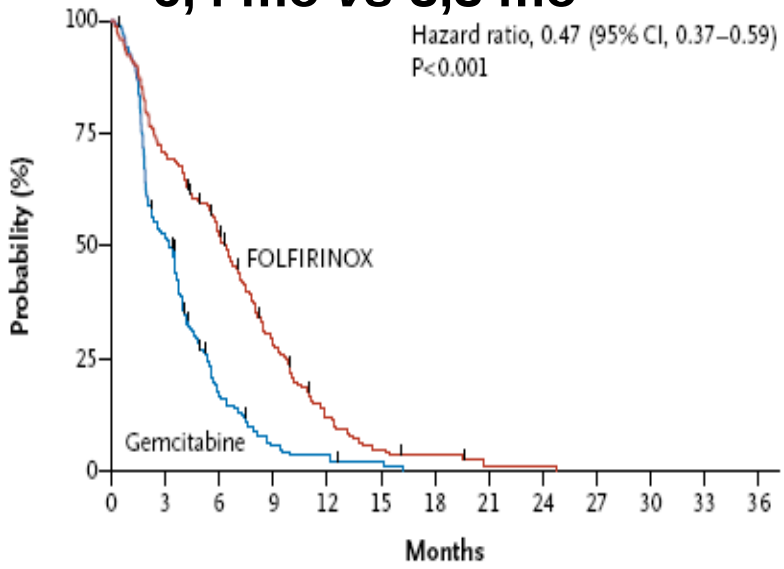
FIRST LINE TREATMENT FOR METASTATIC DISEASE

FOLFIRINOX the PRODIGE 4 study

- ORR= 31% vs 9%- DCR= 70% vs 51%

PFS

6,4 mo *vs* 3,3 mo

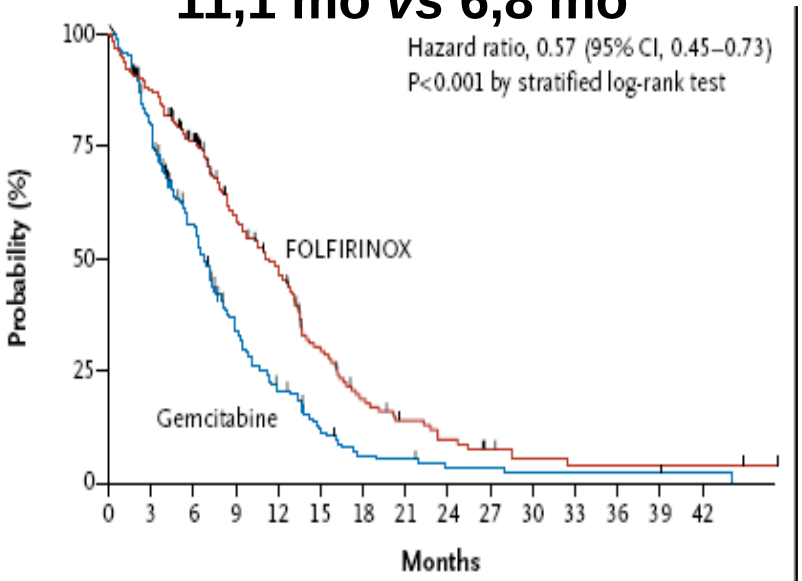


No. at Risk

Gemcitabine	171	88	26	8	5	2	0	0	0	0	0	0	0
FOLFIRINOX	171	121	85	42	17	7	4	1	1	0	0	0	0

OS

11,1 mo *vs* 6,8 mo



No. at Risk

Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2

Conroy T et al. N Engl J Med 2011

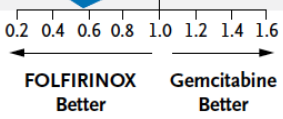
FIRST LINE TREATMENT FOR METASTATIC DISEASE

FOLFIRINOX

the PRODIGE 4 study

The FOLFIRINOX regimen
Was favoured in all subgroups

Subgroup	Gemcitabine	FOLFIRINOX	Hazard Ratio for Death (95% Confidence Interval)
	no. of events/no. of patients		
Age			
≤65 yr	104/121	93/123	0.61 (0.46–0.82)
>65 yr	43/50	33/48	0.48 (0.30–0.77)
Sex			
Male	92/105	81/106	0.57 (0.43–0.78)
Female	55/66	45/65	0.57 (0.38–0.85)
ECOG performance status			
0	52/64	42/63	0.59 (0.39–0.89)
1	95/107	84/108	0.55 (0.40–0.74)
Level of albumin			
Normal	73/84	61/82	0.55 (0.39–0.77)
Abnormal	37/41	43/54	0.48 (0.30–0.77)
Primary tumor location			
Head of pancreas	55/63	49/67	0.57 (0.38–0.84)
Other	92/108	77/104	0.56 (0.41–0.76)
Metastases			
Synchronous	140/161	115/155	0.57 (0.44–0.73)
Metachronous	7/10	10/15	0.61 (0.23–1.62)
No. of metastatic sites			
1	41/47	30/44	0.61 (0.38–0.99)
2	55/59	53/68	0.39 (0.26–0.59)
≥3	51/65	41/57	0.69 (0.46–1.05)
Hepatic metastases			
No	17/21	11/20	0.30 (0.13–0.66)
Yes	130/150	113/149	0.61 (0.48–0.79)
Pulmonary metastases			
No	109/122	101/136	0.56 (0.42–0.73)
Yes	38/49	23/33	0.56 (0.33–0.96)
Level of carbohydrate antigen 19-9			
Normal	17/24	14/23	0.42 (0.20–0.90)
Abnormal	126/142	108/142	0.58 (0.44–0.75)
Biliary stent			
No	130/149	107/144	0.56 (0.43–0.73)
Yes	17/22	18/27	0.66 (0.34–1.28)
Total	147/171	126/171	



Conroy T et al. N Engl J Med 2011

Tolerability

Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

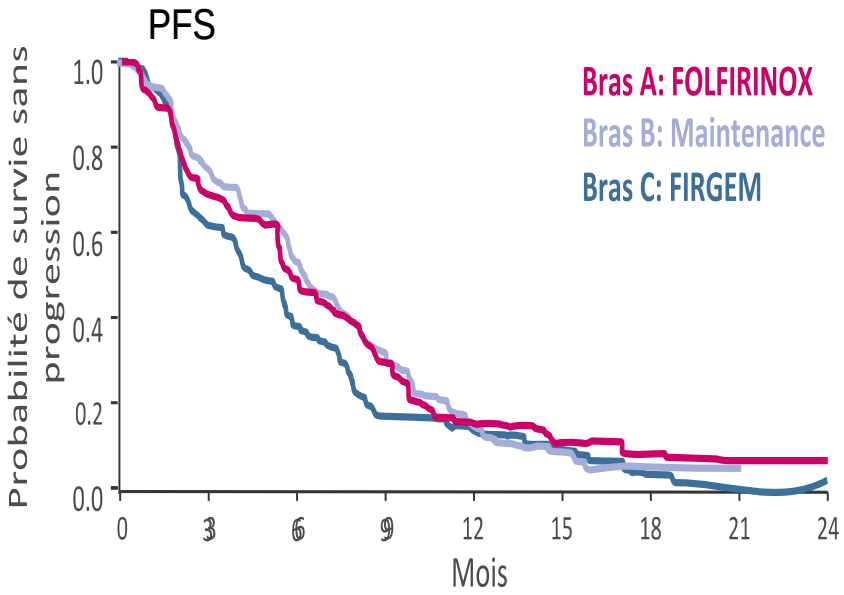
* Events listed are those that occurred in more than 5% of patients in either

IS MAINTENANCE POSSIBLE WITH FOLFIRINOX?

The PRODIGE 35 study

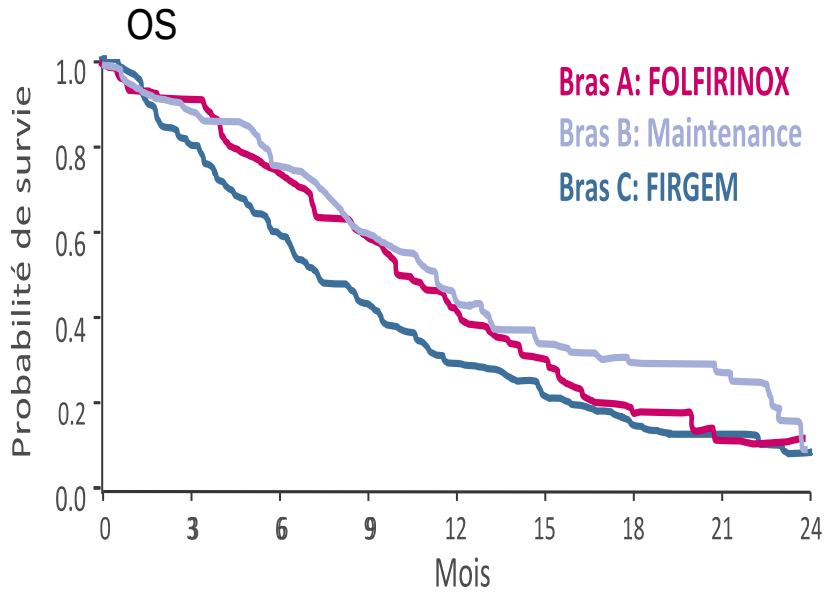
Survie sans progression

Population ITT	Bras A (n = 91)	Bras B (n = 92)	Bras C (n = 90)
SSP (mois) IC 95%	**6,3** 5,3 – 7,6	**5,7** 5,3 – 7,5	**4,5** 3,5 – 5,7
SSP 9 mois (%)	**31,9**	**29,1**	**16,4**
SSP 12 mois (%)	**14,7**	**14,9**	**12,9**



Survie globale

Population ITT	Bras A (n = 91)	Bras B (n = 92)	Bras C (n = 90)
SG (mois) IC 95%	**10,1** 8.5-12.2	**11,0** 8.7-13.1	**7,3** 5,7 – 9,5
SG 9 mois (%)	**73,6**	**75**	**60**
SG 12 mois (%)	**43,3**	**44,1**	**28,5**



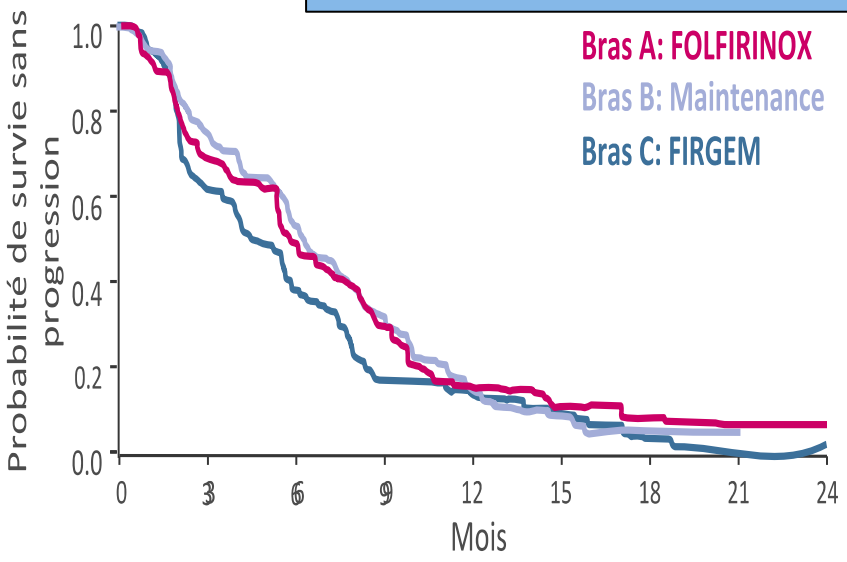
*Dahan L et al, **ASCO 2018**, Abs #4000*

IS MAINTENANCE POSSIBLE WITH FOLFIRINOX?

The PRODIGE 35 study

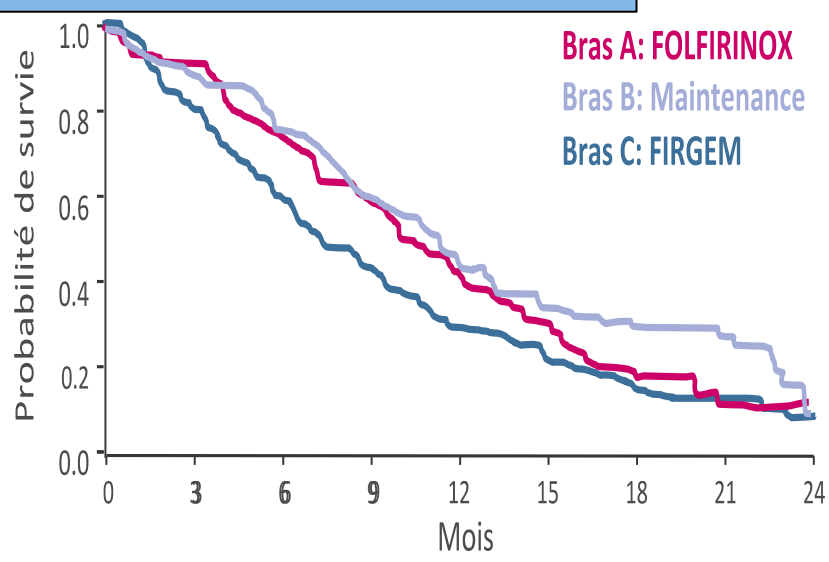
Survie sans progression

Population ITT	Bras A (n = 91)	Bras B (n = 92)	Bras C (n = 90)
SSP (mois)	6,3	5,7	4,5
IC 95% PFS			5,7 – 9,5
SSP 9 mois (%)			60
SSP 12 mois (%)			28,5



Survie globale

Population ITT	Bras A (n = 91)	Bras B (n = 92)	Bras C (n = 90)
SG (mois)	10,1	11,0	7,3



De-escalation, « stop & go » is feasible, safe and good for our patients QoL

*Dahan L et al, **ASCO 2018**, Abs #4000*

First line treatment for metastatic disease

Gem+ Nab-paclitaxel the MPACT study

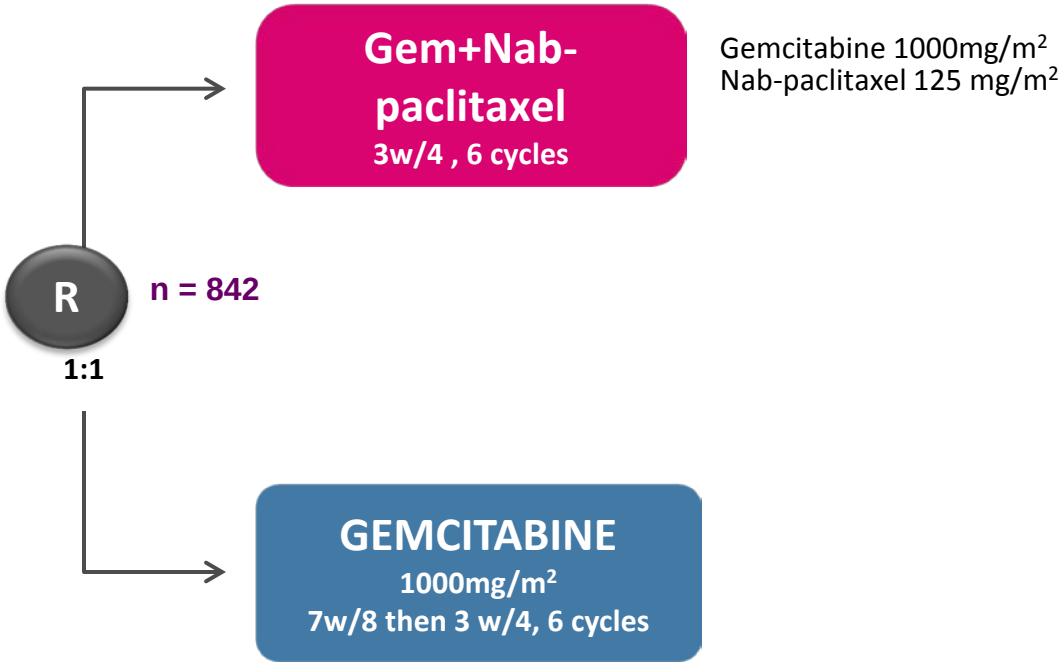
- **metastatic**
- **chemotherapy naive**
- **KPS ≥70**
- **measurable tumor**
- **Bilirubinemia normal**

Stratification:

PS

Liver metastases

Country



Primary Objective : OS

Von Hoff et al., N Engl J Med 2013

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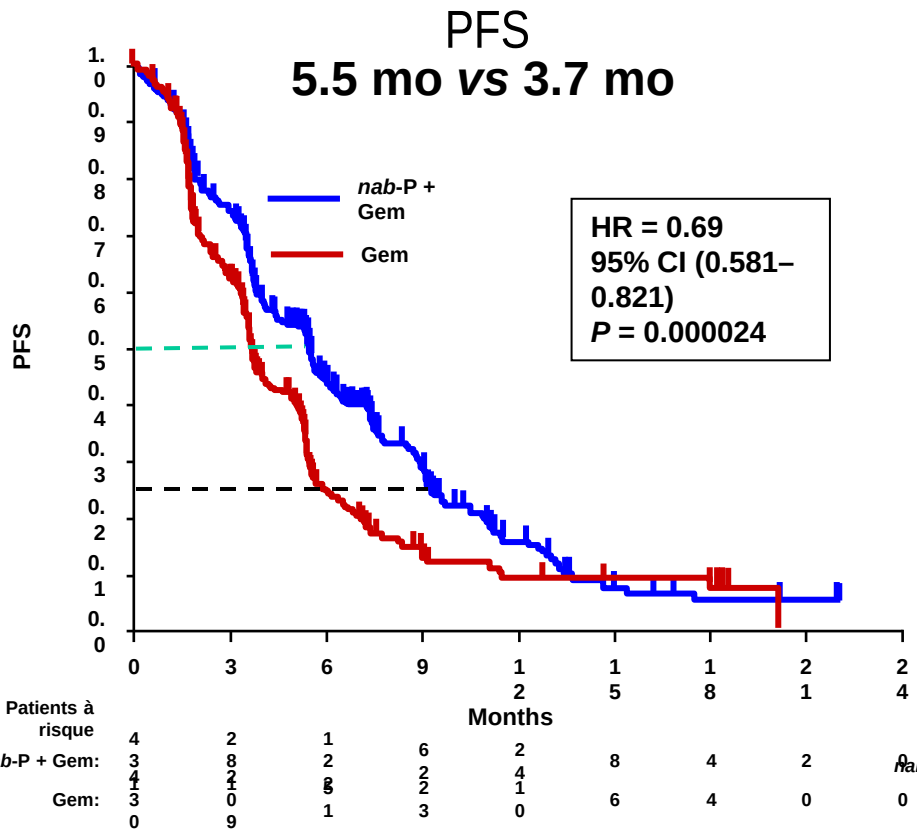
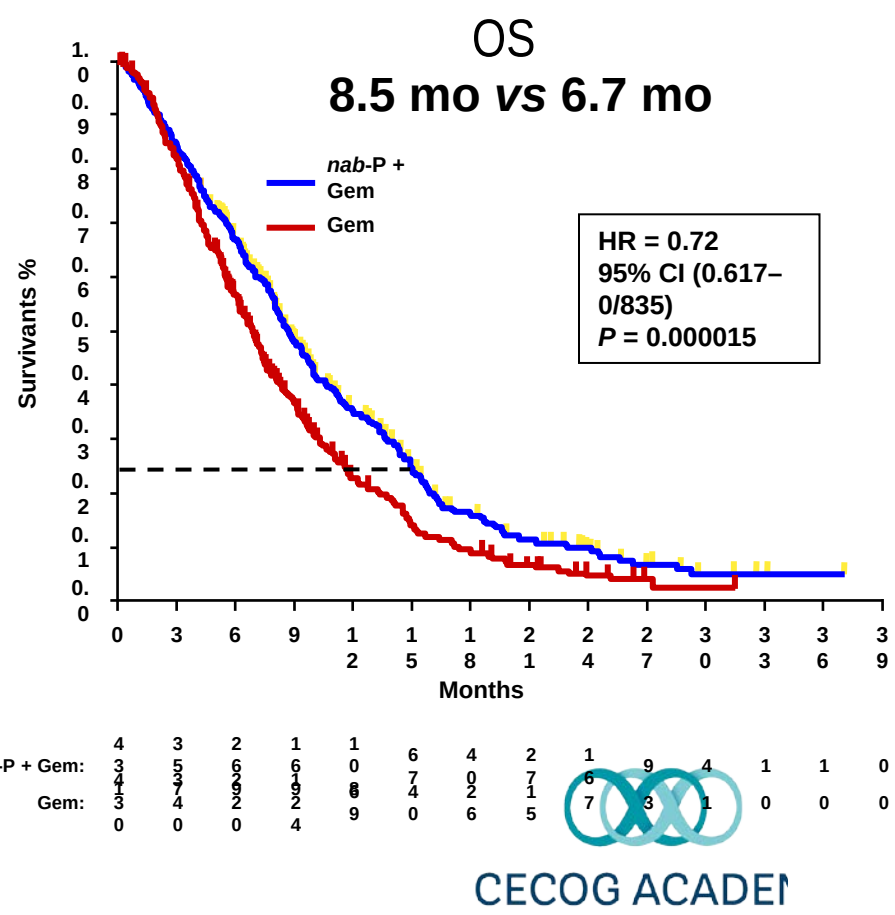
FIRST LINE TREATMENT FOR METASTATIC DISEASE

Gem+ Nab-paclitaxel the MPACT study

- ORR= 29% vs 8%- DCR= 48% vs 33%



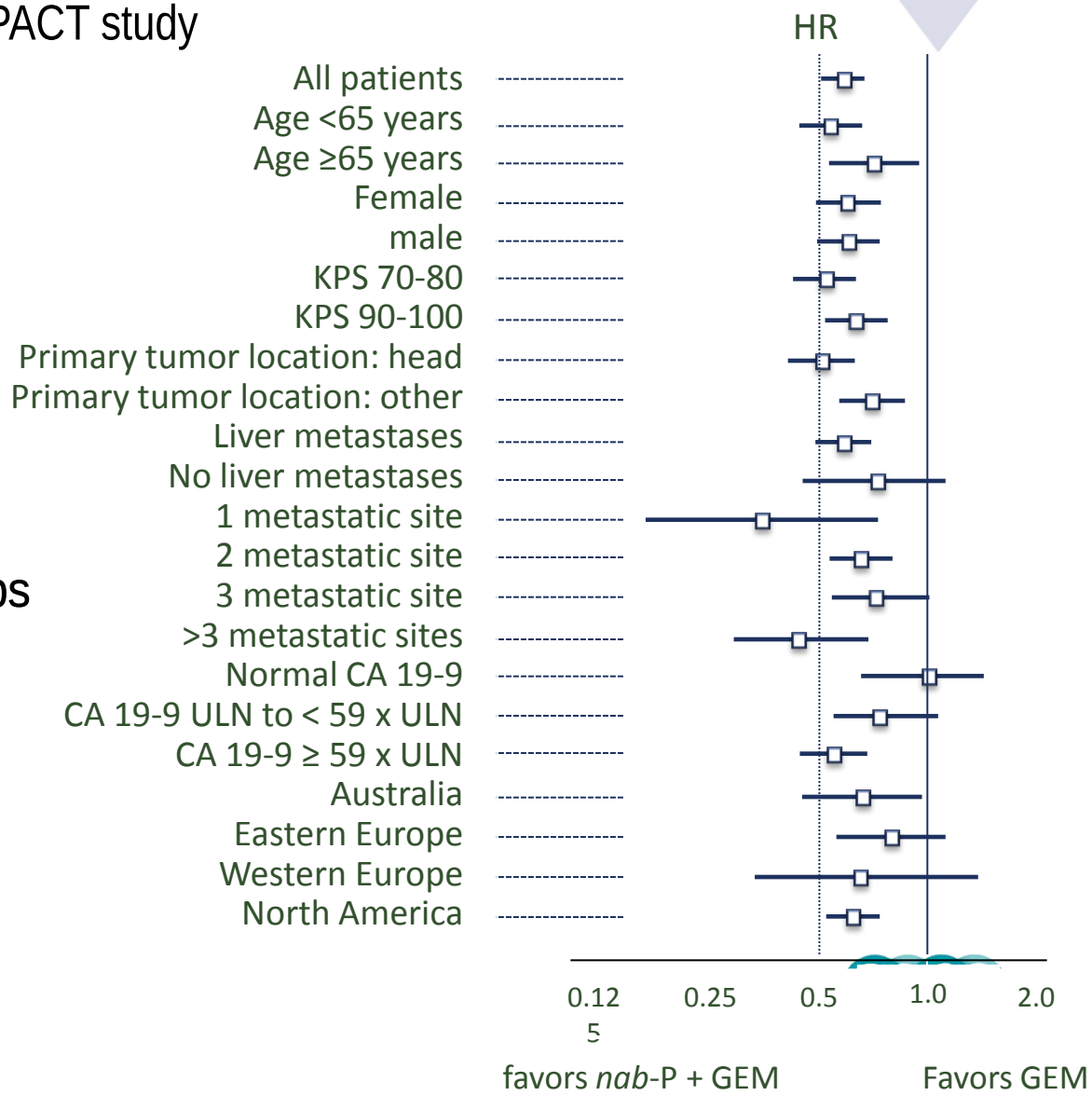


Von Hoff et al., N Engl J Med 2013

FIRST LINE TREATMENT FOR METASTATIC DISEASE

Gem+ Nab-paclitaxel the MPACT study

The combination
Gem+ Nab-paclitaxel
Was favoured in all subgroups
Except normal CA 19.9



Von Hoff et al., N Engl J Med 2013

Tolerability

Table 3. Common Adverse Events of Grade 3 or Higher and Growth-Factor Use.*

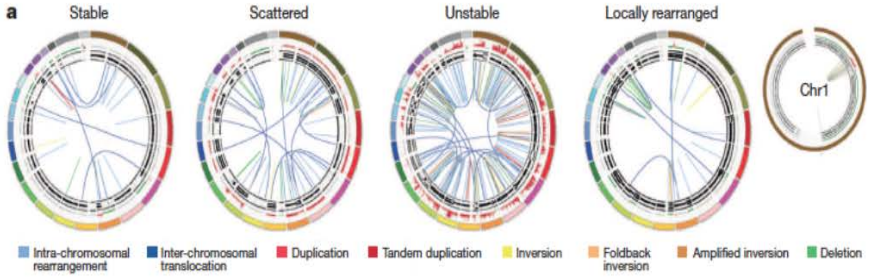
Event	nab-Paclitaxel plus Gemcitabine (N=421)	Gemcitabine Alone (N=402)
Adverse event leading to death — no. (%)	18 (4)	18 (4)
Grade ≥3 hematologic adverse event — no./total no. (%)†		
Neutropenia	153/405 (38)	103/388 (27)
Leukopenia	124/405 (31)	63/388 (16)
Thrombocytopenia	52/405 (13)	36/388 (9)
Anemia	53/405 (13)	48/388 (12)
Receipt of growth factors — no./total no. (%)	110/431 (26)	63/431 (15)
Febrile neutropenia — no. (%)‡	14 (3)	6 (1)
Grade ≥3 nonhematologic adverse event occurring in >5% of patients — no. (%)‡		
Fatigue	70 (17)	27 (7)
Peripheral neuropathy§	70 (17)	3 (1)
Diarrhea	24 (6)	3 (1)
Grade ≥3 peripheral neuropathy		
Median time to onset — days	140	113
Median time to improvement by one grade — days	21	29
Median time to improvement to grade ≤1 — days	29	NR

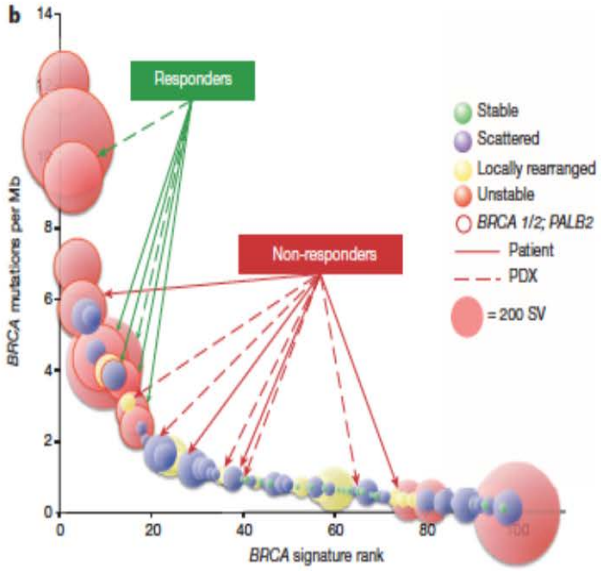
METASTATIC PANCREATIC CANCER

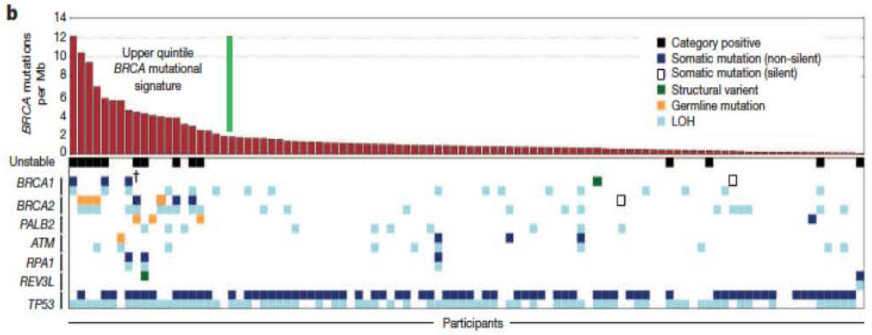
Rare subtypes: BRCAness

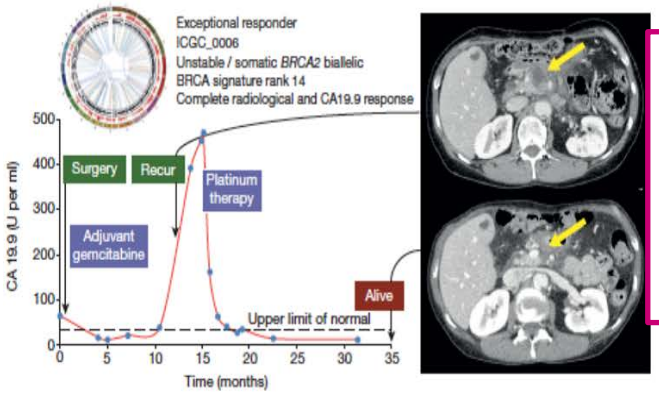
ARTICLE Waddell et al, *Nature* 2015
doi:10.1038/nature14169

Whole genomes redefine the mutational landscape of pancreatic cancer





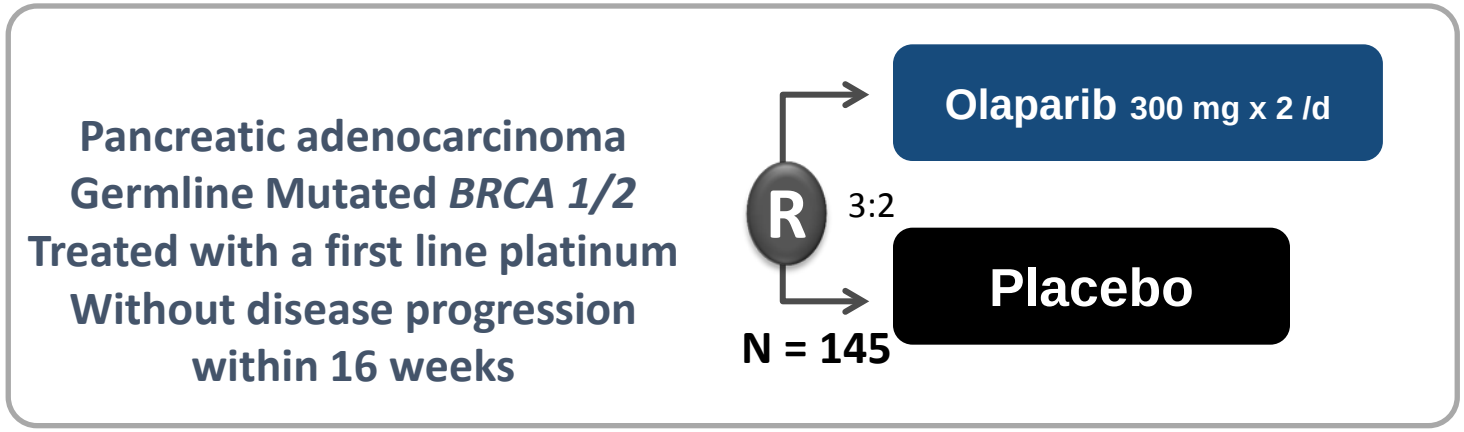




POLO study
NCT02184195
Phase III
Maintenance
Olaparib

GERMLINE BRCA2 MUTATED PANCREATIC CANCER

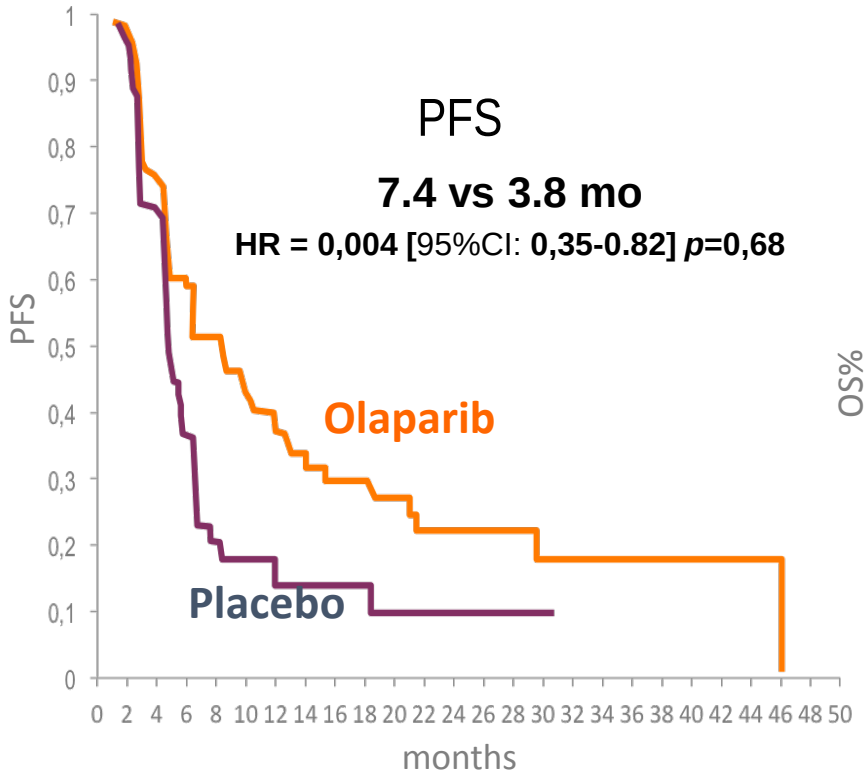
The POLO study

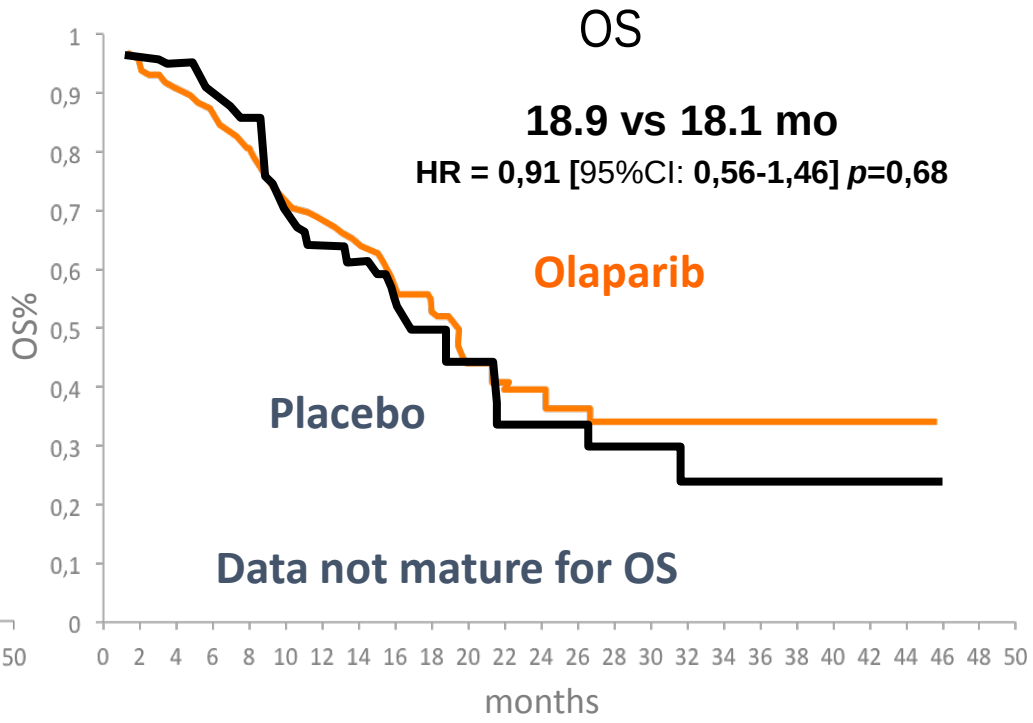


Primary objective: Progression free survival

GERMLINE BRCA2 MUTATED PANCREATIC CANCER

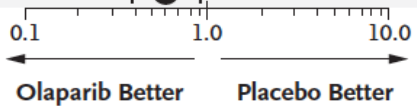
The POLO study





GERMLINE BRCA2 MUTATED PANCREATIC CANCER

Subgroup	Olaparib	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no. (%)		
All patients	60/92 (65.2)	44/62 (71.0)	0.53 (0.35–0.82)
Previous chemotherapy			
FOLFIRINOX variants	50/79 (63.3)	35/50 (70.0)	0.54 (0.35–0.84)
Other	8/10 (80.0)	6/8 (75.0)	0.76 (0.27–2.32)
Absence of biliary stent	59/91 (64.8)	40/58 (69.0)	0.54 (0.36–0.82)
Type of previous chemotherapy			
Doublet chemotherapy	12/15 (80.0)	8/10 (80.0)	0.59 (0.24–1.50)
Triplet chemotherapy	45/73 (61.6)	33/46 (71.7)	0.51 (0.32–0.82)
Duration of first-line treatment before randomization			
16 wk to 6 mo	42/61 (68.9)	29/40 (72.5)	0.69 (0.43–1.12)
>6 mo	18/30 (60.0)	15/21 (71.4)	0.35 (0.17–0.72)
Best response with first-line treatment			
Partial or complete response	30/46 (65.2)	20/30 (66.7)	0.62 (0.35–1.12)
Stable disease	30/45 (66.7)	24/31 (77.4)	0.50 (0.29–0.87)
Disease at baseline			
Measurable	53/78 (67.9)	39/52 (75.0)	0.57 (0.37–0.88)
Not measurable or no evidence of disease	7/13 (53.8)	5/6 (83.3)	0.45 (0.14–1.57)
Germline *BRCA* mutation type (determined by BRACAnalysis CDx test)			
BRCA1	20/29 (69.0)	12/16 (75.0)	0.40 (0.20–0.85)
BRCA2	38/59 (64.4)	32/45 (71.1)	0.63 (0.39–1.02)
Age at randomization			
<65 yr	39/64 (60.9)	37/49 (75.5)	0.45 (0.28–0.72)
≥65 yr	21/28 (75.0)	7/13 (53.8)	1.02 (0.45–2.60)
Sex			
Male	33/53 (62.3)	23/31 (74.2)	0.46 (0.27–0.80)
Female	27/39 (69.2)	21/31 (67.7)	0.66 (0.37–1.19)
White race	55/82 (67.1)	41/59 (69.5)	0.59 (0.39–0.90)



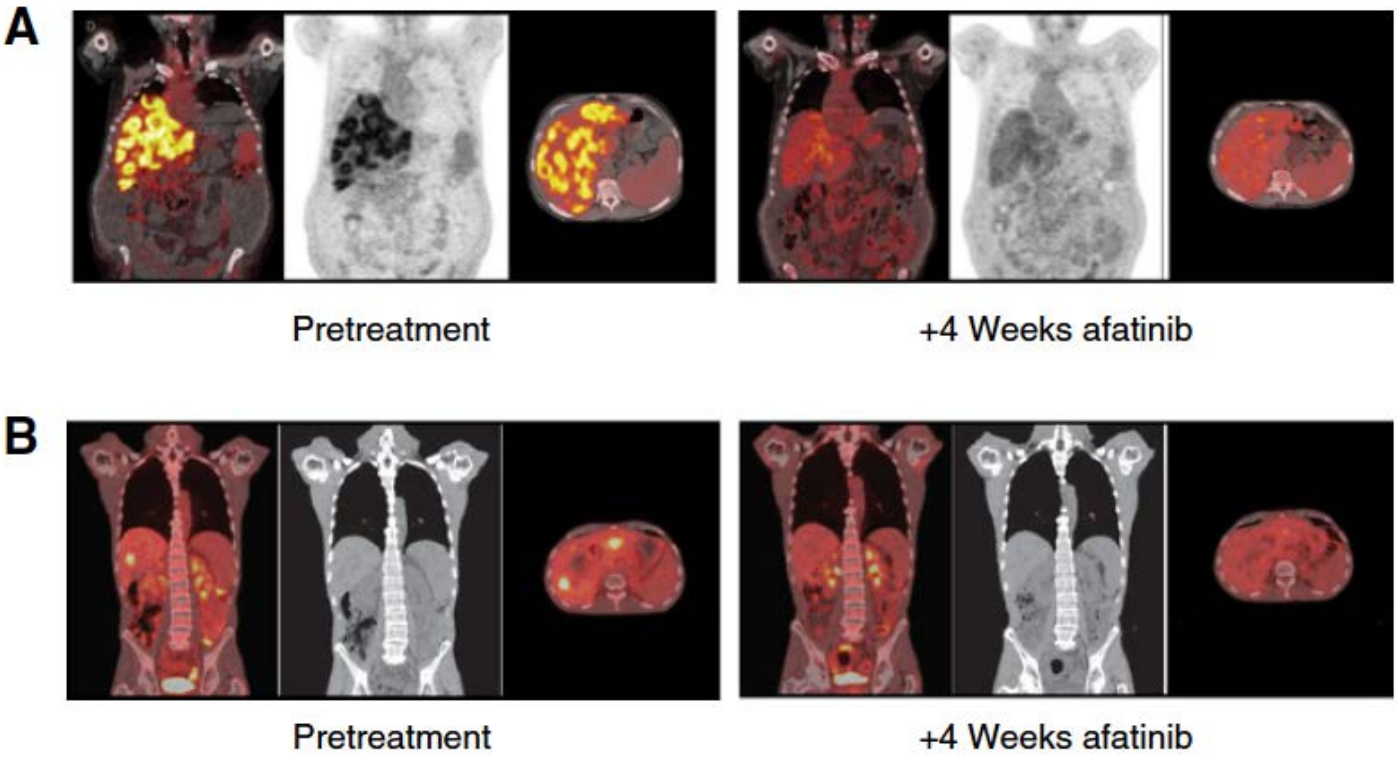
Golan, NEJM 2019

NRG1 Gene Fusions Are Recurrent, Clinically Actionable Gene Rearrangements in *KRAS* Wild-Type Pancreatic Ductal Adenocarcinoma

Clin can res 2019

Martin R. Jones[1], Laura M. Williamson[1], James T. Topham[2], Michael K.C. Lee[3],

Occurrence not well documented but <5%



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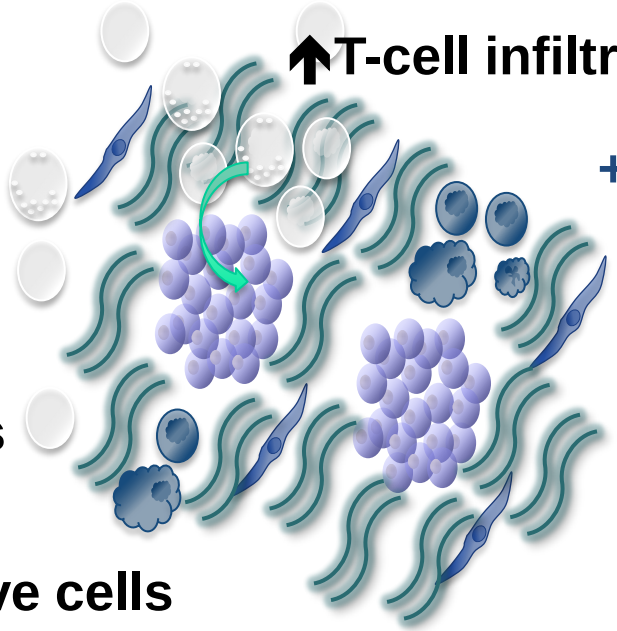
Immune checkpoint inhibitors (PD(L)1): a way to improve ?

Currently some small patients cohort MSI+ with positive results
Otherwise:

TGFβ inhibitor



⬆T-cell infiltration

+ anti-PD(L)1

⬇fibrosis

⬇immunosuppressive cells

Combinations with Vaccines

CECOG ACADEMY

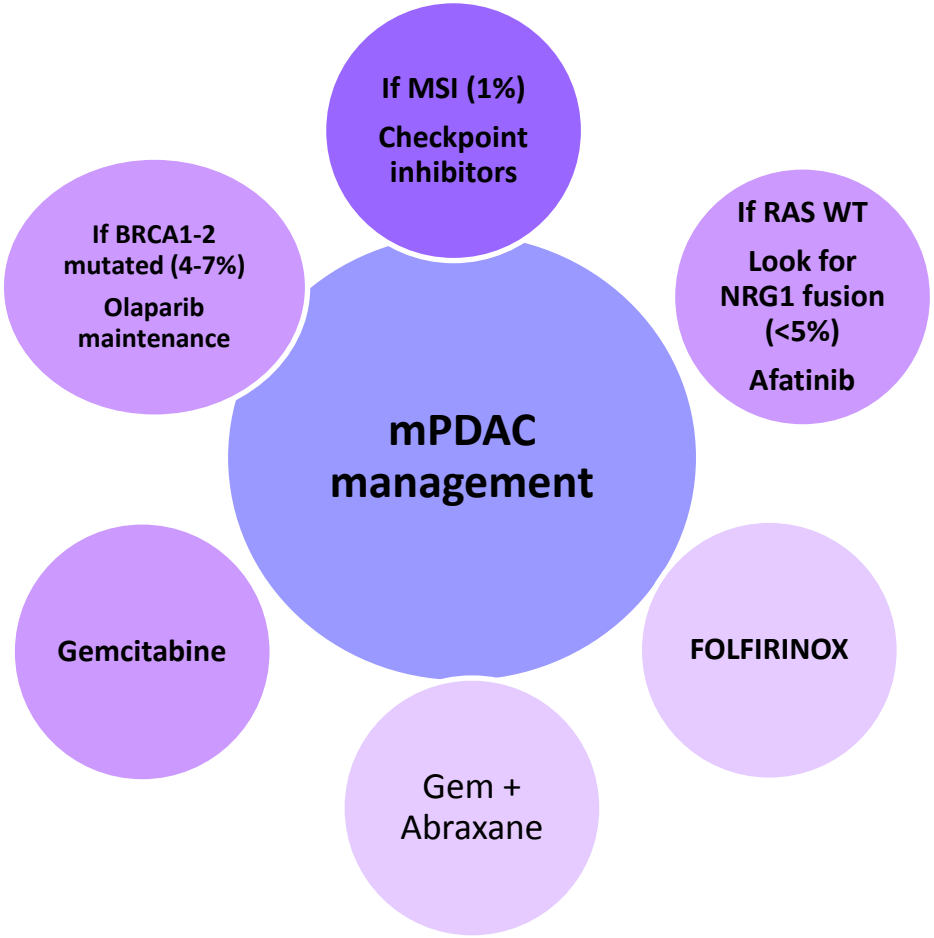
Courtesy : C. Neuzillet

How can we chose the best treatment for each individual patient?

CECOG ACADEMY

In an expert center

Molecular profiling



CECOG ACADEMY

FOLFIRINOX VS GEM+ NAB-PACLITAXEL

Efficacy

	FOLFIRINOX	Gem+NP
PS	PS2 < 1%	KPS 70-80: 40%
ORR	31,6%	29%
DCR	70%	50%
PFS	6.4 mo	5.5 mo
OS	11.1 mo	8.5 mo
OS with gem	6.8 mo	6.7 mo
2nd line Ttt	38%	47%

Conroy T et al. N Engl J Med 2011 *Von Hoff et al., N Engl J Med 2013*

FOLFIRINOX VS GEM+ NAB-PACLITAXEL

Safety

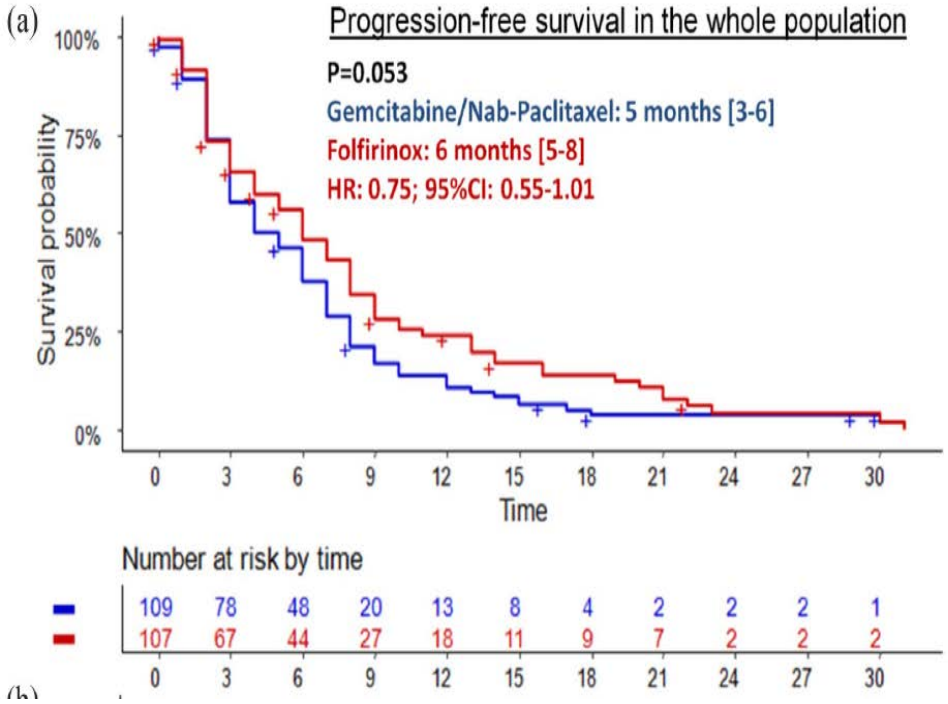
	FOLFIRINOX	Gem+NP
Plt	9.1%	13%
PMN	45%	38%
febrile	3%	5.4%
Anemia	8%	13%
Neuropathy	9%	17%
DIarrhea	13%	6%
Alopecia	11%	50%

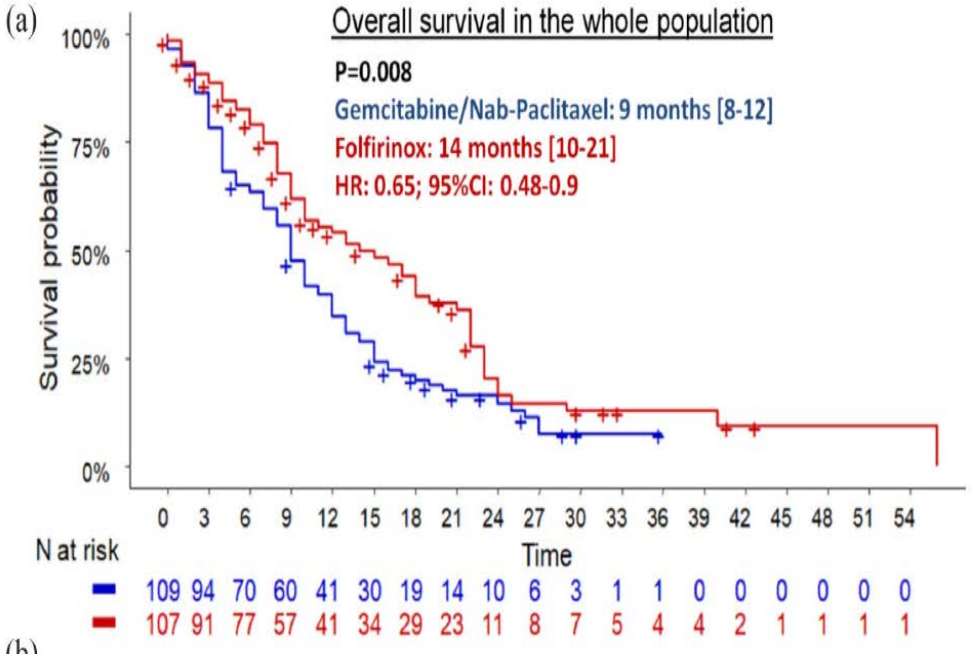
Conroy T et al. N Engl J Med 2011 *Von Hoff et al., N Engl J Med 2013*

Folfirinox *versus* gemcitabine/nab-paclitaxel as first-line therapy in patients with metastatic pancreatic cancer: a comparative propensity score study

Nicolas Williet, Angélique Saint, Anne-Laure Pointet, David Tougeron, Simon Pernot, Astrid Pozet, Dominique Bechade, Isabelle Trouilloud, Nelson Lourenco, Vincent Hautefeuille, Christophe Locher, Jérome Desrame, Pascal Artru, Anne Thirot Bidault, Bertrand Le Roy, Denis Pezet, Jean-Marc Phelip and Julien Taieb

Williet et al. ther adv in gastroenterol 2019





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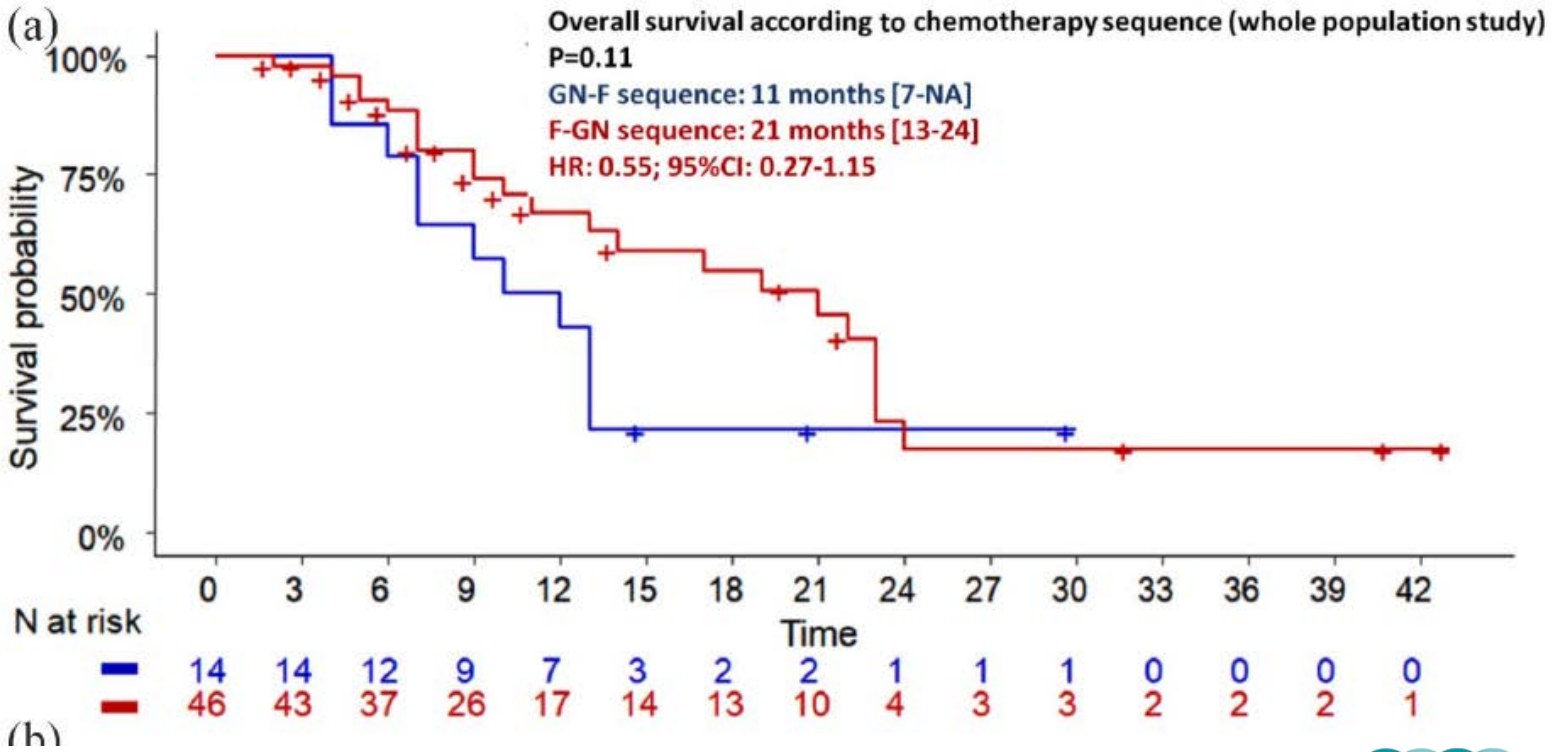
Folfirinox *versus* gemcitabine/nab-paclitaxel as first-line therapy in patients with metastatic pancreatic cancer: a comparative propensity score study

Nicolas Williet, Angélique Saint, Anne-Laure Pointet, David Tougeron, Simon Pernot, Astrid Pozet, Dominique Bechade, Isabelle Trouilloud, Nelson Lourenco, Vincent Hautefeuille, Christophe Locher, Jérome Desrame, Pascal Artru, Anne Thirot Bidault, Bertrand Le Roy, Denis Pezet, Jean-Marc Phelip and Julien Taieb

The good sequence? FFX=> GN or GN=> FFX?



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European Chart review

Physicians recruited from nine European countries





Grouped as "North" region

Recruitment from different regions and clinical settings* to ensure a balanced selection

Inclusion criteria

Completed first-line treatment for mPAC between July 2014 and January 2016; age ≥18 years

Patient record

- General disease information and patient characteristics
- Disease characteristics at diagnosis
- Initial treatment for pancreatic cancer
- Details of first/second/third-line treatment

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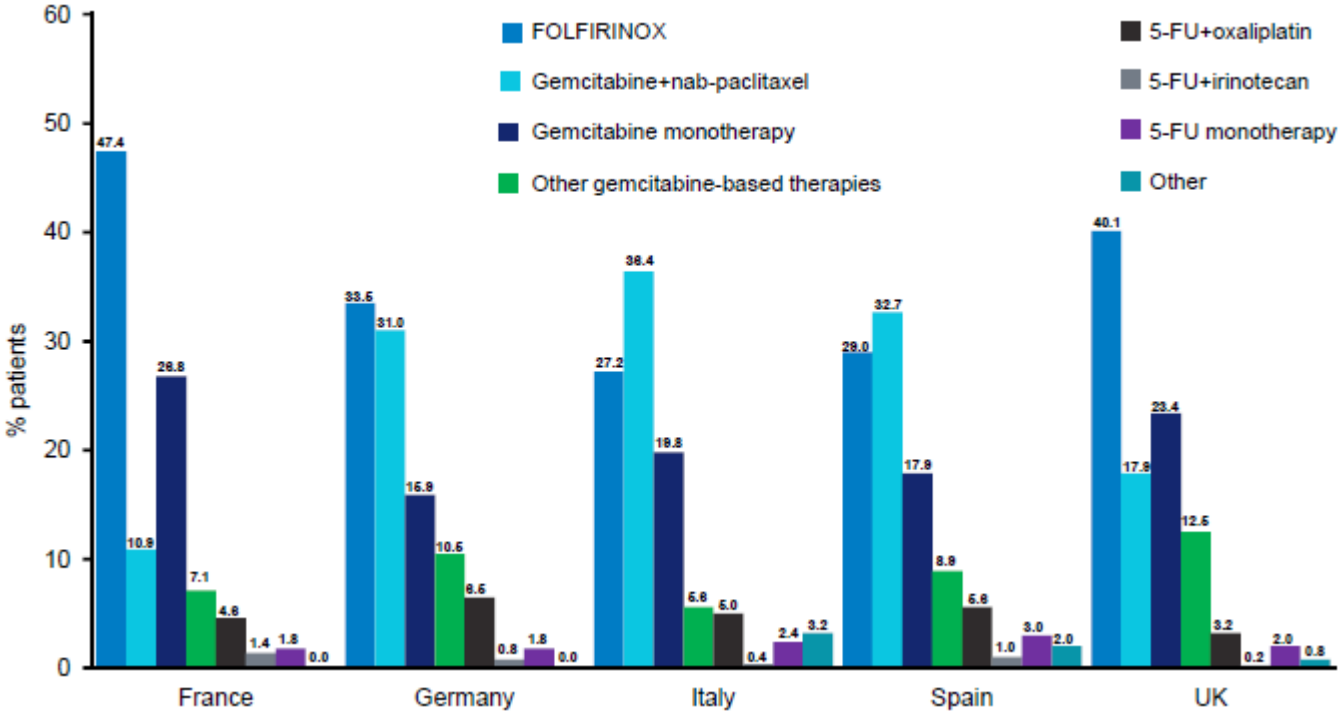
*University and general hospitals, cancer and reference centres, office-based specialists.

mPAC, metastatic pancreatic adenocarcinoma

Taieb et al. ESMO OPEN 2019

European Chart review

> 2500 patients



More than 70% received a second line (but biased)

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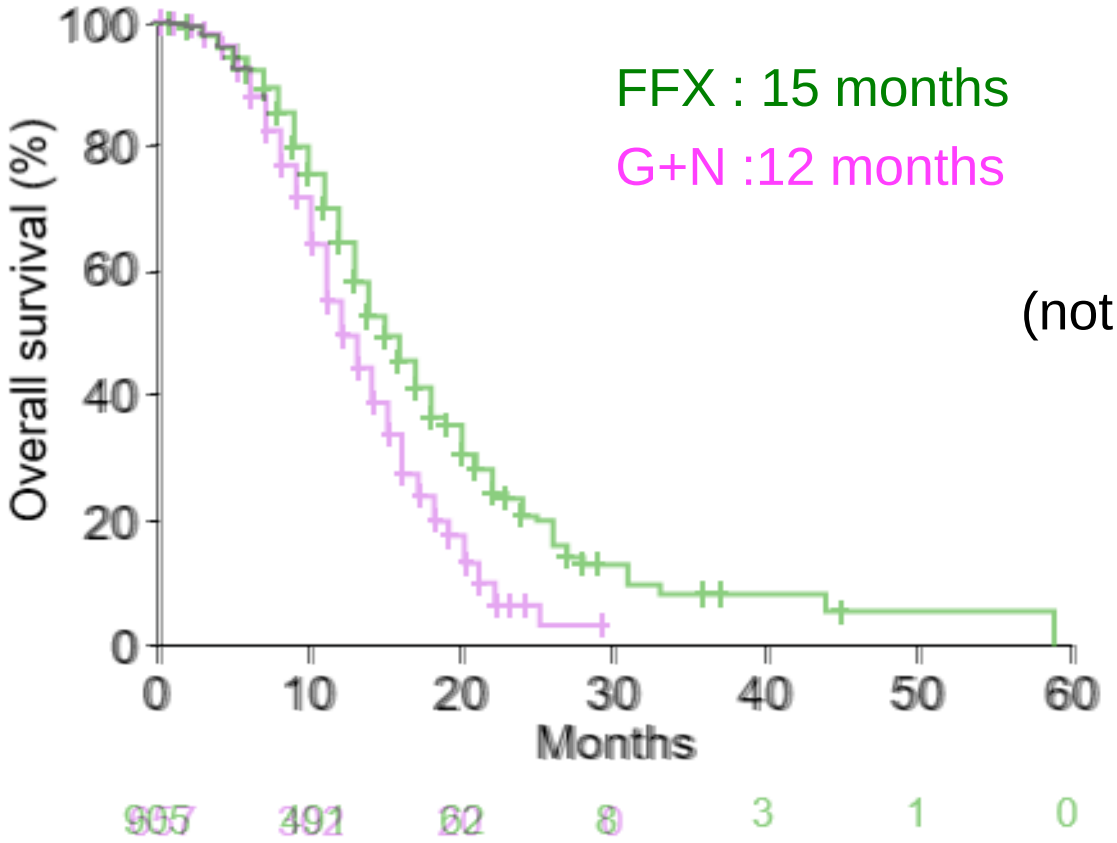
Taieb et al. ESMO Open 2019

European Chart review



FFX : 15 months

G+N :12 months

(not randomized)

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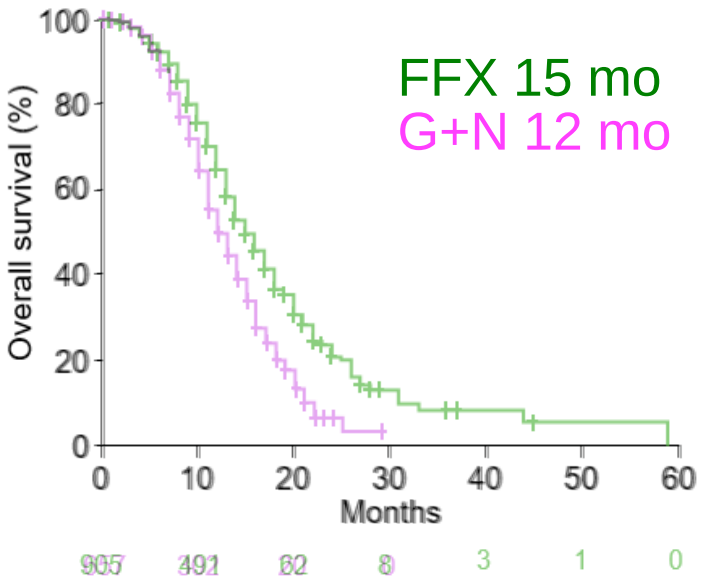
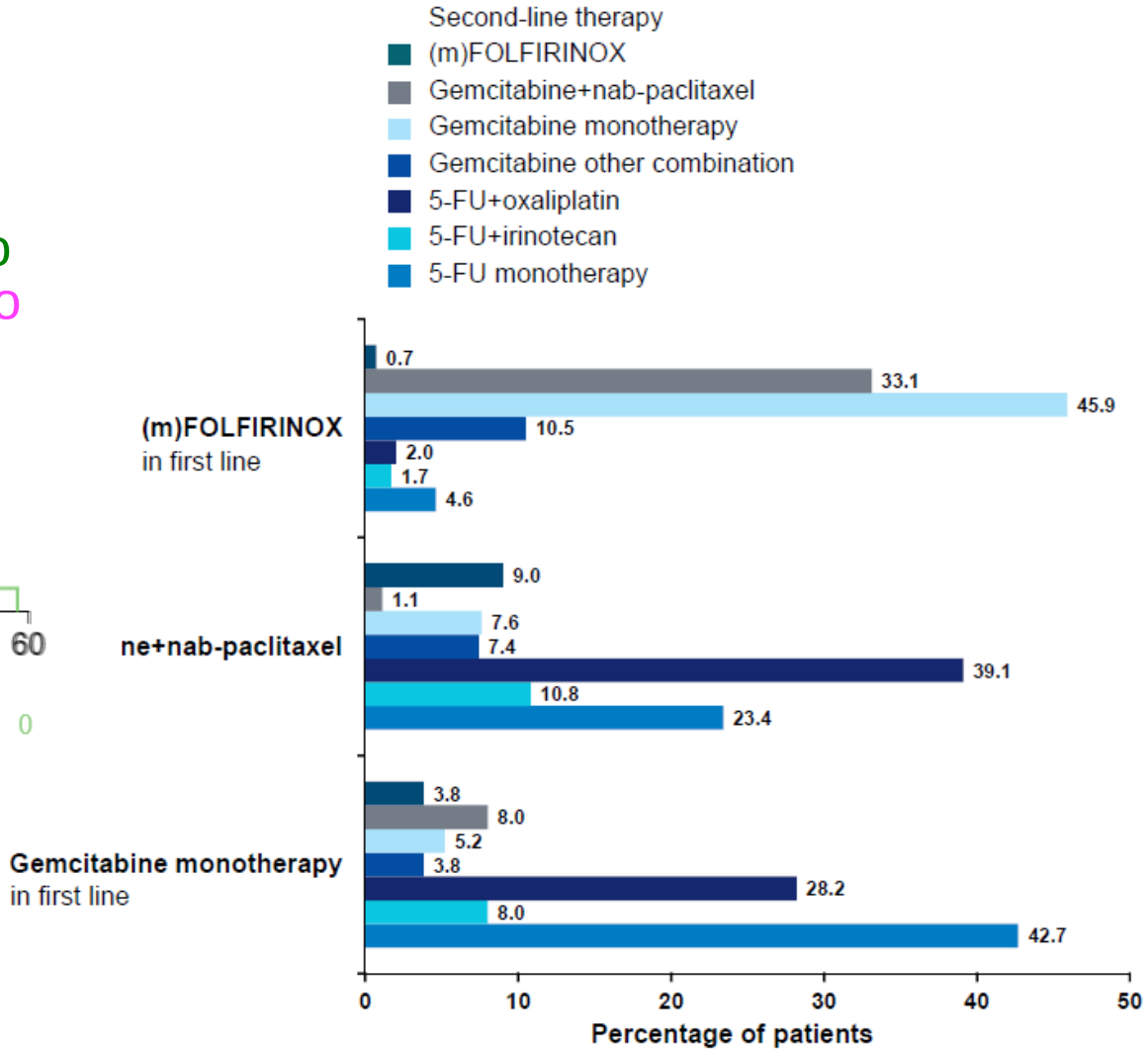
European Chart review



FFX 15 mo
G+N 12 mo



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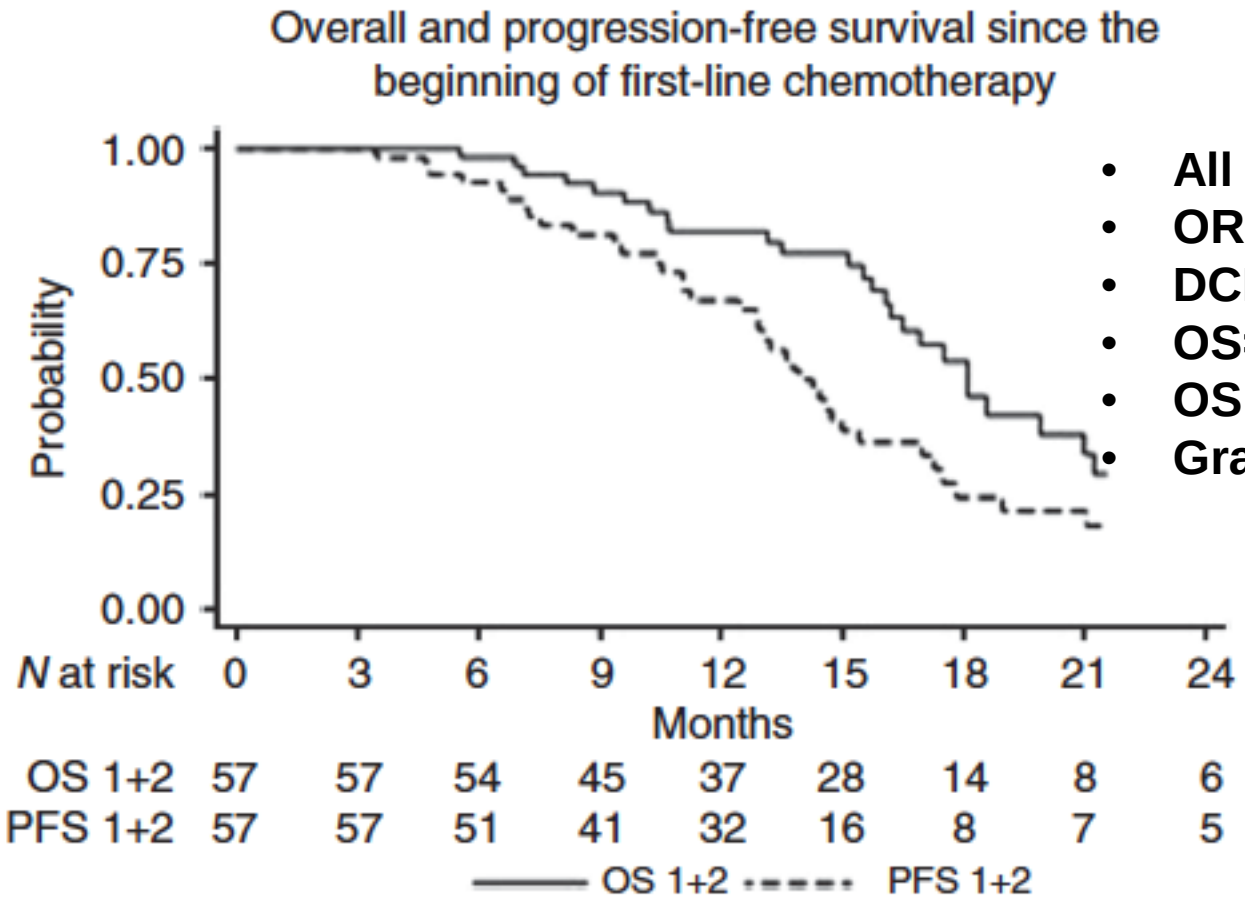
Taieb et al. ESMO OPEN 2019

BJC
Keywords: metastatic pancreatic car

Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after Folfirinox failure: an AGEO prospective multicentre cohort

Alix Portal[1,14], Simon Pernot[1,14], David Tougeron[2], Claire Arbaud[3], Anne Thirot Bidault[4], Christelle de la Fouchardière[5], Pascal Hammel[6], Thierry Lecomte[7], Johann Dréanic[8], Romain Coriat[8], Jean-Baptiste Bachet[9], Olivier Dubreuil[9], Lysiane Marthey[10], Laetitia Dahan[11], Belinda Tchoundjeu[12], Christophe Locher[13], Céline Lepère[1], Franck Bonnetain[3] and Julien Taieb*[,1,14]



- All patients eligible for L2
- ORR=17%
- DCR=58%
- OS= 9 mo
- OS from L1 = 18 mo
- Grade 3-4 AE = 40%

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Clinics and Research in Hepatology and Gastroenterology (2019) xxx, xxx–xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Pointet et al. CLINRE 2019

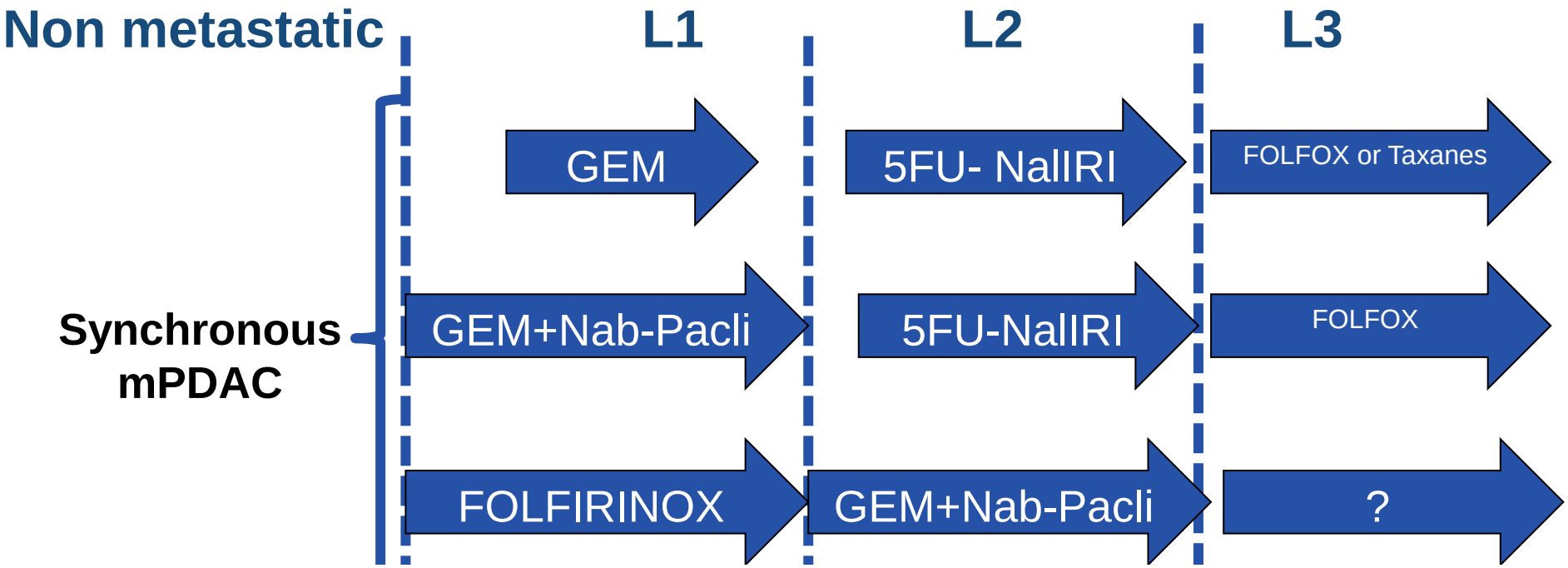
ORIGINAL ARTICLE

Three fluoropyrimidine-based regimens in routine clinical practice after nab-paclitaxel plus gemcitabine for metastatic pancreatic cancer: An AGEO multicenter study

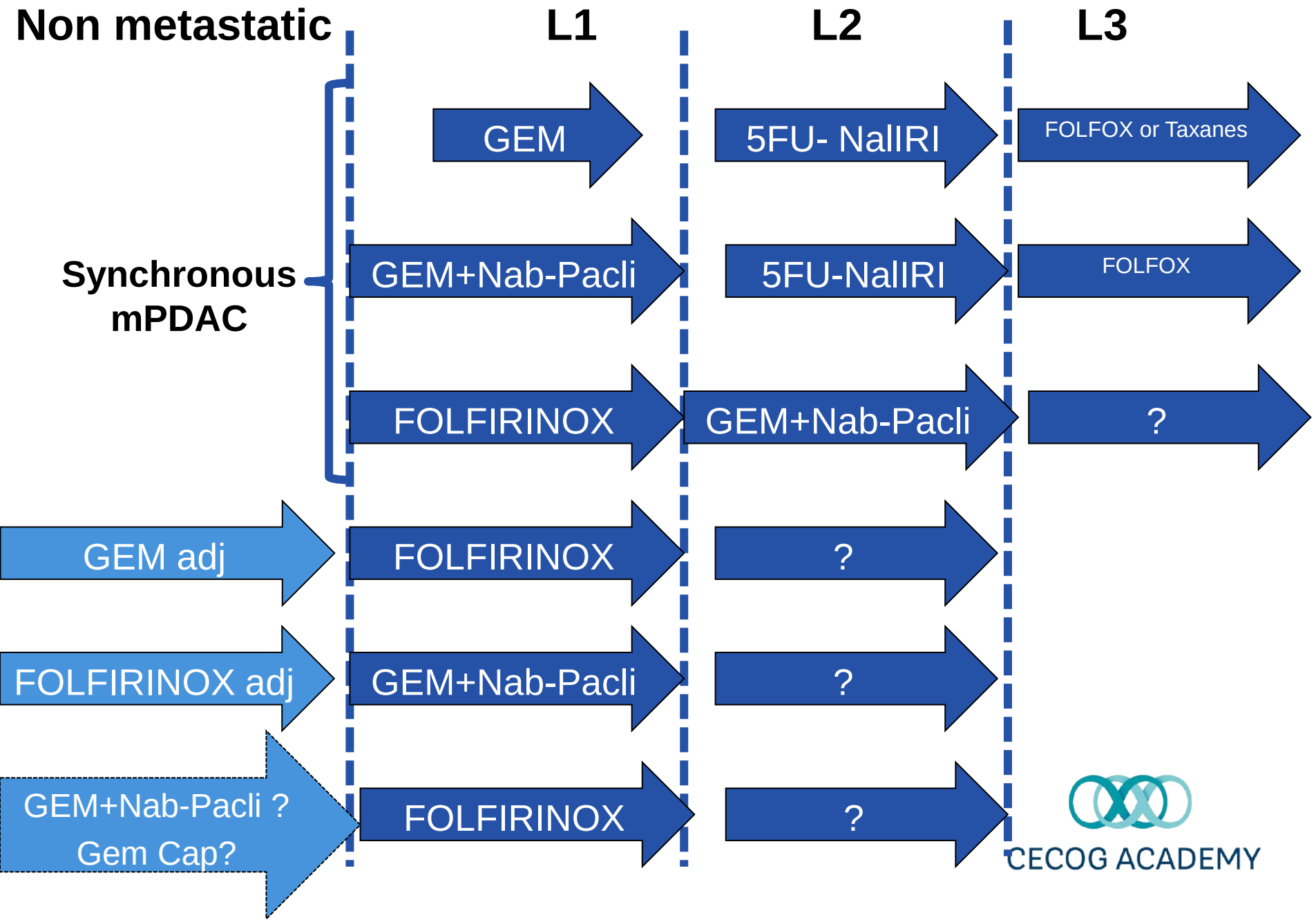
Anne-Laure Pointet[a,*], David Tougeron[b], Simon Pernot[a], Astrid Pozet[c], Dominique Béchade[d], Isabelle Trouilloud[e], Nelson Lourenco[f], Vincent Hautefeuille[g], Christophe Locher[h], Nicolas Williet[i], Jérôme Desrame[j], Pascal Artru[j], Emilie Soularue[k], Bertrand Le Roy[l], Julien Taieb[a]

Table 3 Patient survival and tumor response rate.

	Overall population $n=61$	FOLFOX $n=24$	FOLFIRI 1/3 $n=21$	FOLFIRINOX $n=16$	P
Best Response (RECIST v1.1 criteria) (n, %)					
Complete response	0	0	0	0	0.17
Partial response	3 (4.9)	0	2 (9.5)	1 (6.3)	
Stable disease	25 (40.9)	7 (29.2)	11 (52.4)	7 (43.8)	
Progressive disease	30 (49.2)	16 (66.7)	8 (38.1)	6 (37.5)	
Not assessable	3 (4.9)	1 (4.2)	0	2 (12.5)	
Disease control rate	28 (45.9)	7 (29.2)	13 (61.9)	8 (50.0)	
Survival (median, 95% CI) (months)					
PFS 1	6.0 (4.1-6.8)	5.5 (2.8-6.6)	6.8 (6.0-9.0)	4.2 (2.9-8)	0.10
OS 1	12.7 (10.4-15.1)	10.4 (7.6-14.5)	18.4 (11.7-24.1)	12.3 (6.8-15.7)	0.02
PFS 2	2.95 (2.3-5.4)	2 (1.5-2.3)	6.6 (2.5-9.4)	3.4 (2-6.9)	0.08
OS 2	5.97 (4.0-8.0)	3.5 (2.3-6)	9.7 (4.5-11.2)	6.1 (2.8-8.8)	0.13



- **After FOLFIRINOX, gem+nab-paclitaxel seems to give promising results in good condition patients though randomized data are still lacking**
- **After Gem+nab-paclitaxel FOLFIRINOX is rarely feasible**
- **Issue : access to nab-paclitaxel L2**


Non metastatic
L1
L2
L3
GEM
5FU- NalIRI
FOLFOX or Taxanes
Synchronous mPDAC
GEM+Nab-Pacli
5FU-NalIRI
FOLFOX
FOLFIRINOX
GEM+Nab-Pacli
?
GEM adj
FOLFIRINOX
?
FOLFIRINOX adj
GEM+Nab-Pacli
?
GEM+Nab-Pacli ?
Gem Cap?
FOLFIRINOX
?
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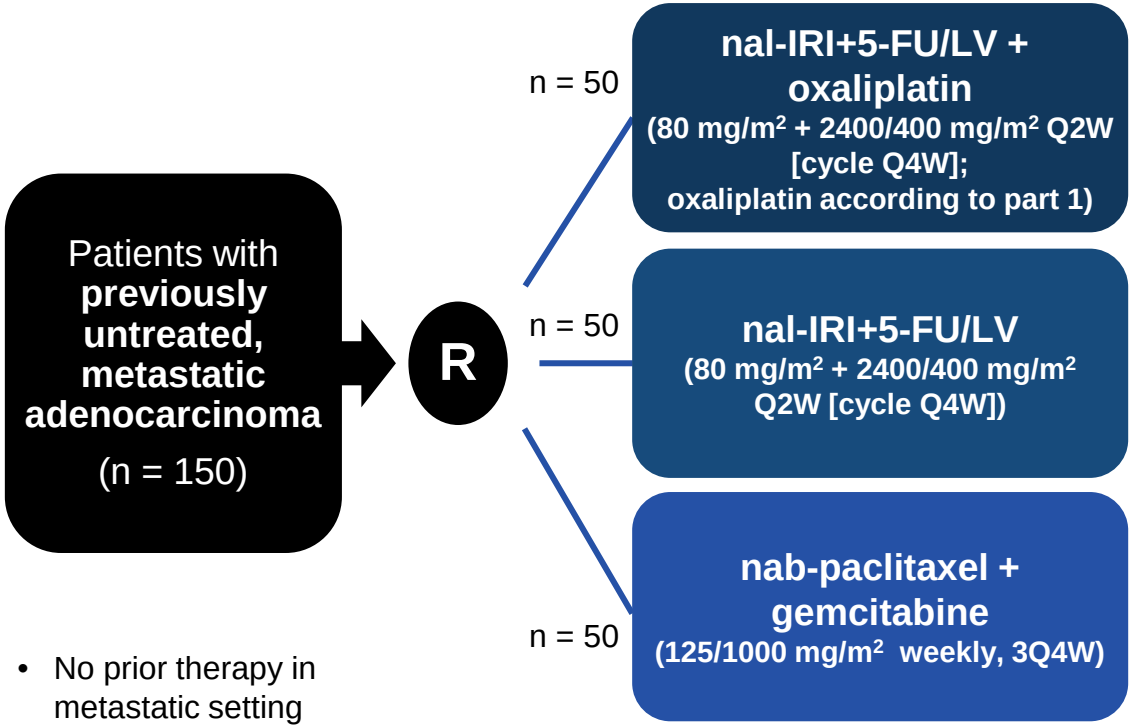
A randomised, open-label phase II study of 1st-line nal-IRI-containing regimens vs. nab-paclitaxel + gemcitabine in metastatic pancreatic cancer

Study endpoints: HR PFS (1°), OS, PFS, ORR, CA19-9 response, HRQoL, safety and toxicity

2-part study:

1. Safety run-in of nal-IRI+5-FU/LV + oxaliplatin
2. Randomised efficacy/safety study of nal-IRI+5-FU/LV ± oxaliplatin vs. nab-paclitaxel + gemcitabine



- No prior therapy in metastatic setting
- ECOG PS 0 or 1
- Aged ≥18 years

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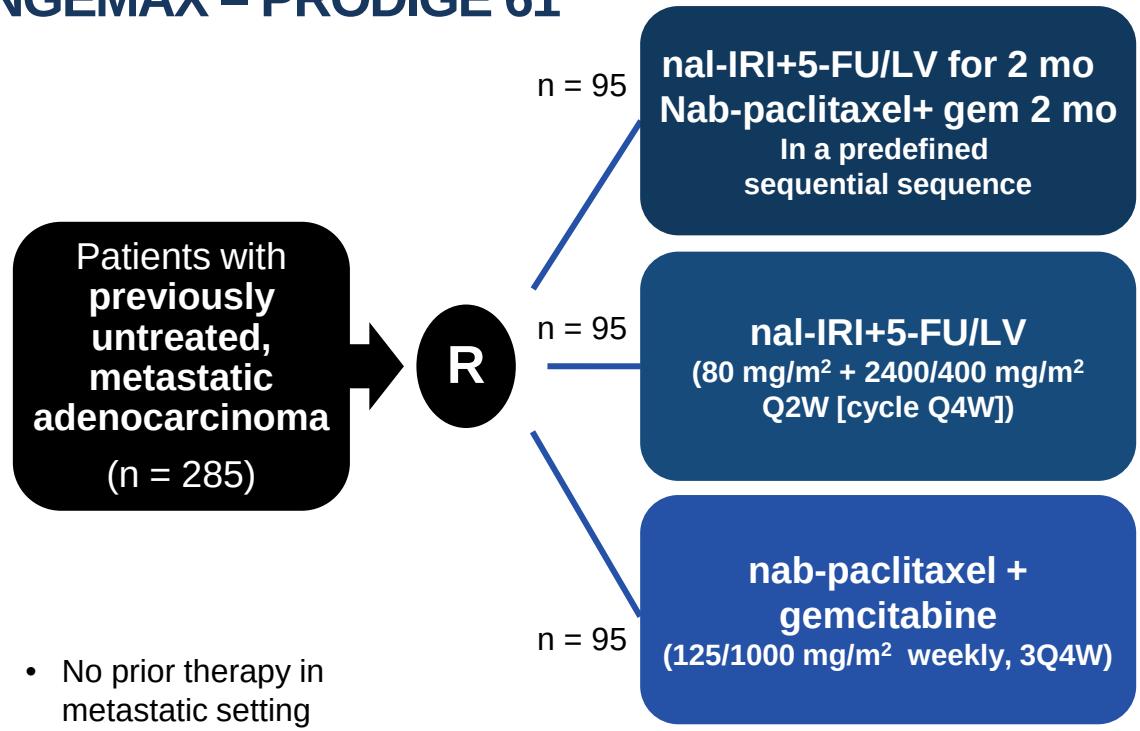
A randomised, open-label phase II study of 1st-line nal-IRI-containing regimens vs. nab-paclitaxel + gemcitabine in metastatic pancreatic cancer

FUNGEMAX – PRODIGE 61

Study endpoints: HR PFS (1°), OS, PFS, ORR, CA19-9 response, HRQoL, safety and toxicity



- No prior therapy in metastatic setting
- ECOG PS 0 or 1
- Aged ≥18 years
- Normal bilirubine level

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Conclusion

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- **First line treatment of mPDAC depends mainly on patients conditions and drugs availability in different countries**
- **Both FOLFIRINOX and G+N are standards but no ransomized comparative trials available**
- **The landscape of mPDAC treatment is moving, with second line options that may be influenced by L1 choices**
- **Gem or Gem+ nab-paclitaxel are good options after FOLFIRINOX (registration issues?)**
- **Sequencial trials are now mandatory to move forward and give patients the best sequence to improve their OS**
- **Think about rare subtypes (MSI, BRCA2, fusion …) for specific treatments/trials.**

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Thank you for your attention !

and thanks to Pascal, Cindy, Jean Luc and Jean Baptiste for their help/slides ;)

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