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ESMO PRECEPTORSHIP ON ADVANCED NON RESECTABLE HEPATOCELLULAR CARCINOMA BILIARY AND PANCREATIC CANCER

6-7 DECEMBER 2019
PARIS, FRANCE

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ESMO wishes to thank the following company for supporting this ESMO Preceptorship Programme

MSD

ESMO

Pancreatic cancer treatment
« Second line and Sequence »

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Sorbonne Paris-Cité, Paris Descartes University
Hopital Européen Georges Pompidou
Inserm U970

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UNIVERSITÉ PARIS DESCARTES

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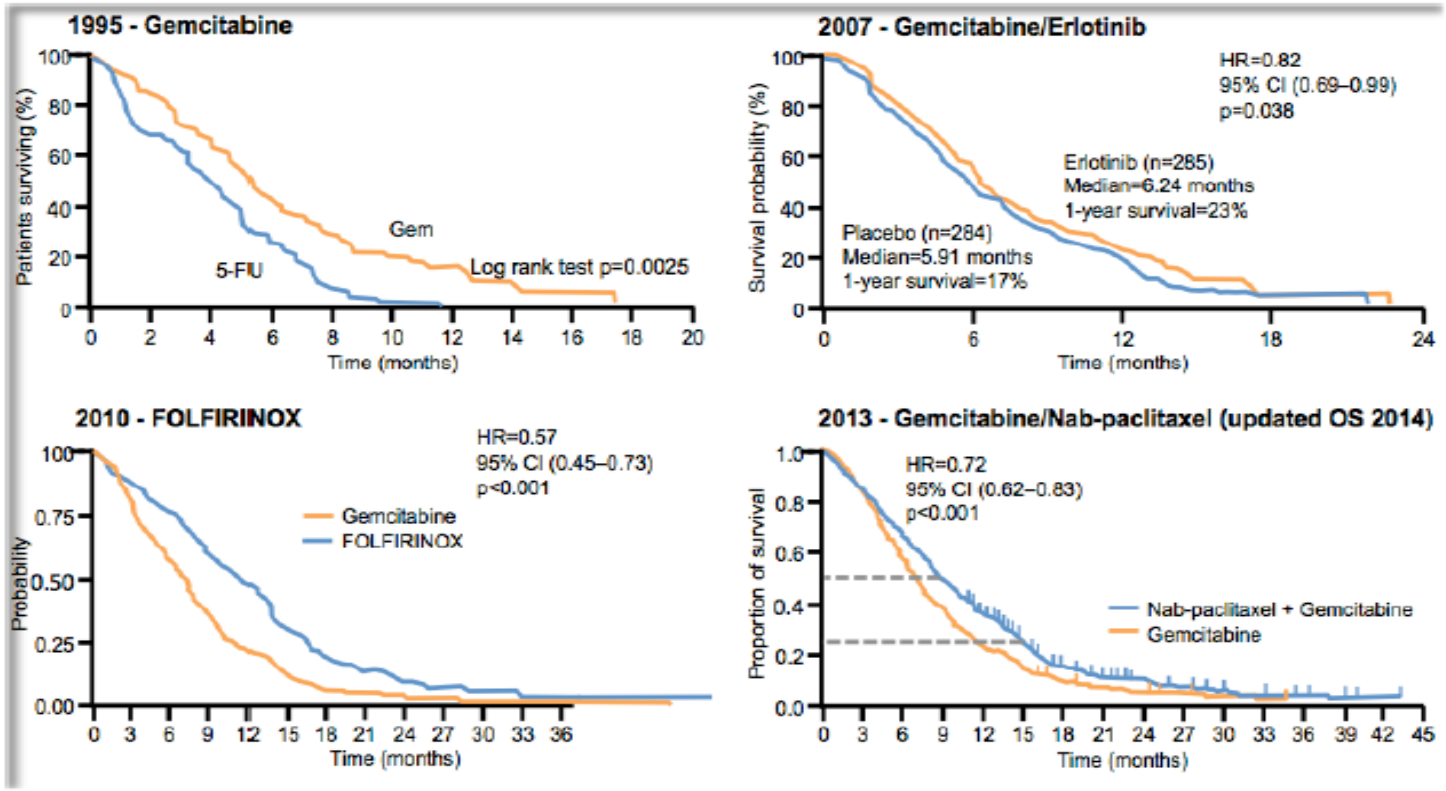
First line therapeutic options in 2019

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,

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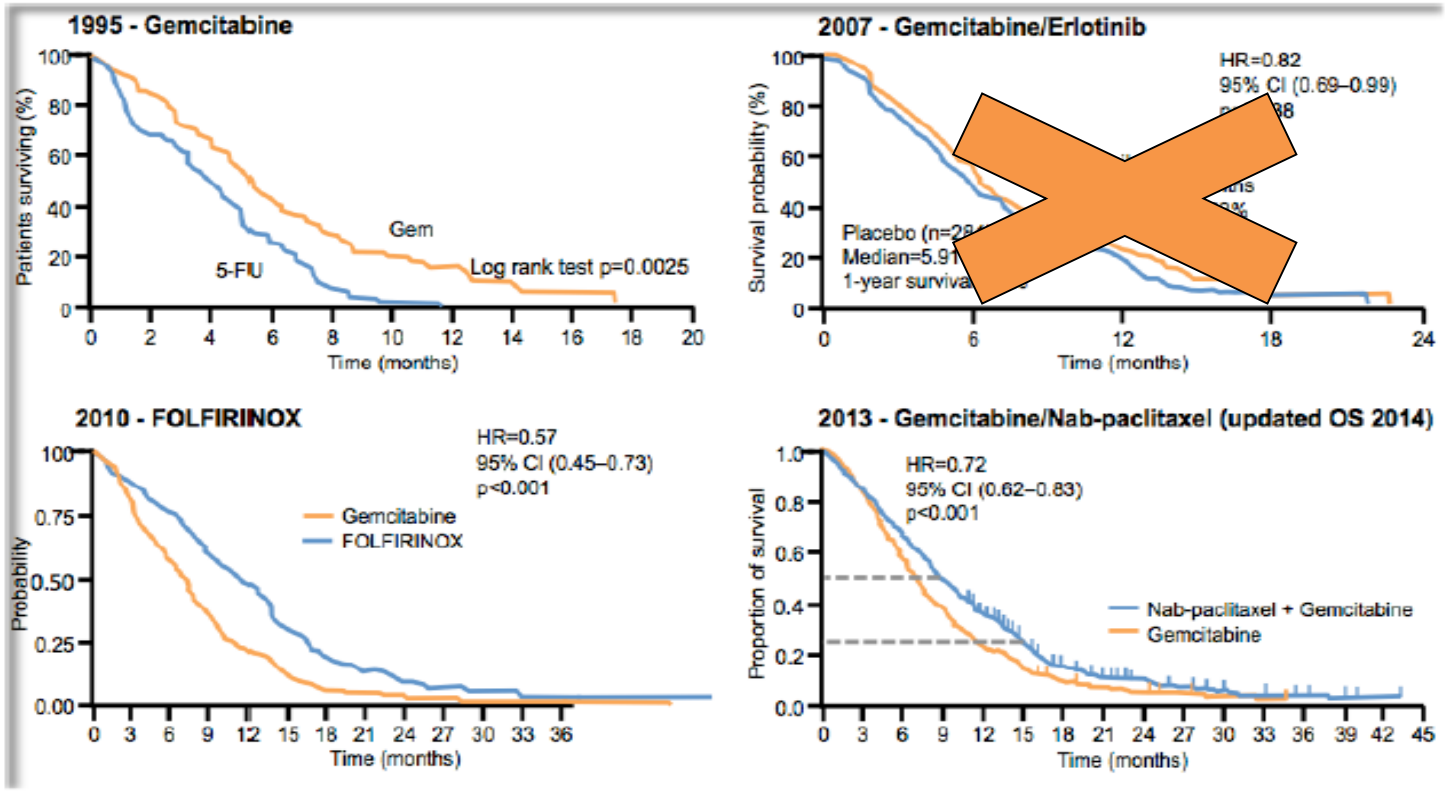

Burris et al JCO, 15:2403-2413, 1997, ; Moore et al, JCO, 25:1960-1966, 2007; Conroy et al, 364:1817-1825, 2011 ; Von Hoff et al, NEJM, 2013,

Second line options

L1 option	FOLFIRINOX*	GEMCITABINE-ABRAXANE *	GEMCITABINE*
	PS0, age <75,bili N	PS 0-1,age >75-80,bili >N	PS 0-2, age > 75,bili>N
L2	NAL-IRI/5FU* ? GEMCITABINE GEMCITABINE-ABX or GEM-CDDP or GEMOX Clinical trials	NAL-IRI/5FU* OXALIPLATIN/5FU* FOLFIRINOX ? or FOLFIRI Clinical trials	NAL-IRI/5FU* Oxaliplatin/5FU* FOLFIRINOX ? or FOLFIRI or Taxanes Clinical trials
L3	Clinical trials	Clinical trials	Clinical trials ?

*=phase III trial

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European Society for Medical Oncology

How many patients from L1 phase III trials are eligible for L2?

- Dahan L et al, Gut 2010 (FFCD0301)
  68% LV5FU2+ Cisplatine arm ; 55% gemcitabine arm

- Conroy T et al, N Engl J Med 2011
  47% FOLFIRINOX arm ; 50% gemcitabine arm

- Von Hoff DD et al, N Engl J Med 2013
  38% gemcitabine+nab-paclitaxel arm ; 42% gemcitabine arm

At least 40% to 50%

L2 and L3 in clinical practice

117 patients ; 1997 à 2006
90 synchronous et 27 Metachronus

Treatment line	1	2	3
N patient	**99 (85%)**	**53 (45%)**	**24 (21%)**
Chemo regimen - 5FU + platinum - Gem + platinum - Gem mono - Other	 18 (18%) 30 (30%) 50 (51%) 1 (1%)	 11 (21%) 17 (32%) 23 (43%) 2 (4%)	 9 (38%) 2 (8%) 5 (21%) 8 (33%)
ORR - PR - SD - PD - NE	 22 - 22% 25 - 25% 30 - 30% 22 - 22%	 5 - 10% 15 - 28% 23 - 43% 10 - 19%	 4 - 16% 6 - 25% 8 - 33% 6 - 25%
PFS	2.9 (2.0 – 3.5)	2.3 (1.8 – 3.4)	2.5 (1.5 – 4.5)

Bachet JB et al, Gastroenterol Clin Biol 2009

Retrospective and phase II studies
Oxaliplatin - Irinotecan

Author, year	chemo L1	chemo L2	N patients	ORR (%)	SD (%)	PFS (mo)	OS (mo)
Kozuch, 2001	Gem B	G-FLIP	34	24	21	3.9	10.3
Cantore, 2004	Gem B	CPT11-Ox	30	10	23	4.1	5.9
Tsavaris, 2005	Gem	5FU-Ox	30	23	30	5.1	5.8
Gebbia, 2007	Gem B	5FU-Ox	42	14	38	4.0	6.7
Xiong, 2008	Gem B	CapOX	39	3	21	-	5.8
Yoo, 2009	Gem B	mFOLFOX mFOLFIRI.3	30 31	7 0	10 23	1,5 2,1	3,7 4,2
Assaf, 2011	Gem B	FOLFIRINOX	22	19	44	5,4	8,5
Zaniboni, 2012	Gem B	FOLFIRI	50	8	28	3,2	5,0
Neuzillet, 2012	**Gemox**	**FOLFIRI**	**63**	**8**	**32**	**3,0**	**6,6**
Lee, 2013	Gem B	FOLFIRINOX	18	28	28	2,8	8,4
Ko, 2013	Gem B	Nal-Iri	40	7	43	2,4	5,2
Zaanan, 2014	**Gem B**	**FOLFOX**	**27**	**0**	**36**	**1,7**	**4,3**

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Yoo, 2009	Gem B					1,5 2,1	3,7 4,2
Assaf, 2011	Gem B					5,4	8,5
Zaniboni, 2012	Gem B					3,2	5,0
Neuzillet, 2012	**Gemox**					**3,0**	**6,6**
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Zaanan, 2014	**Gem B**	**FOLFOX**	**27**	**0**	**36**	**1,7**	**4,3**

Overall

⇒ ORR: 0 to 28%

⇒ DCR: 36 to 63%

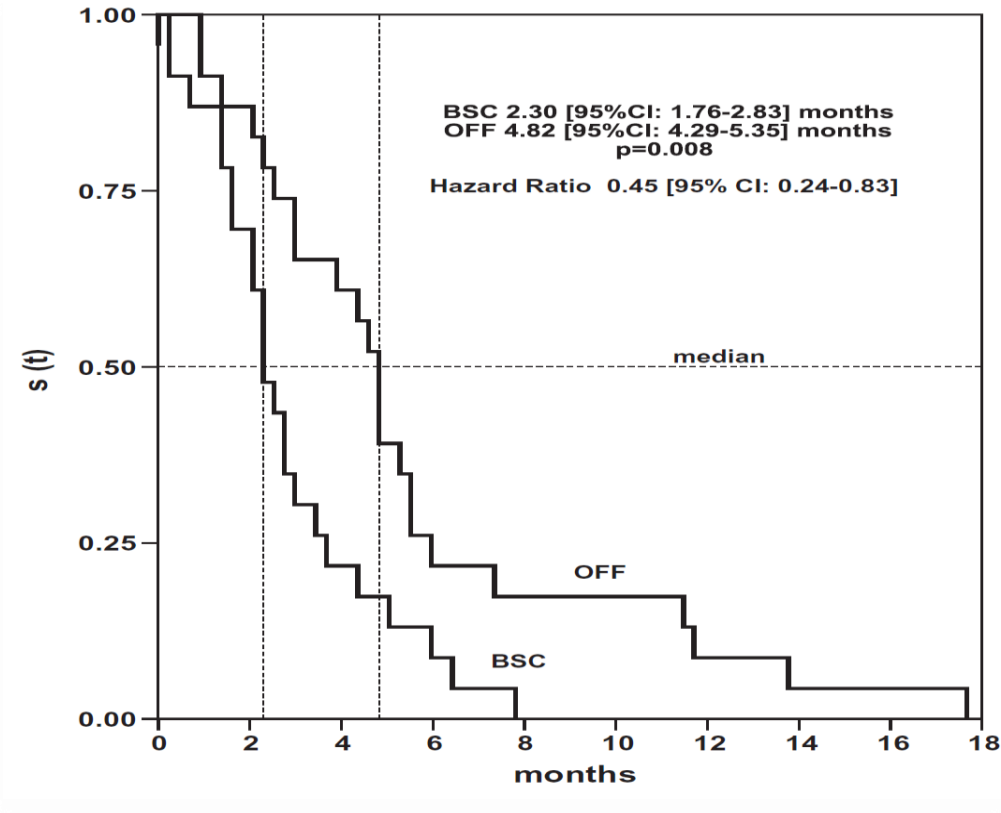
⇒ PFS: 1.5 to 5.1 mo

⇒ OS: 3.7 to 10.3 mo

Is it relevant ? Any randomized data?

Phase III trial:

- **5FU+oxaliplatin and BSC *vs* BSC 46 patients**
- **Stopped prematurely because of poor accrual**
- **Median 2nd line survival: 4.82 *vs* 2.30 months (*p*=0.008)**
- **Median Overall Survival: 9.09 *vs* 7.90 months (*p*=0.031)**



Pelzer U et al, Eur J Cancer 2011

Randomized data for L2

Author, year	treatment	n	PFS (mo)		OS (mo)	
Oettle et al, J Clin Oncol 2014	5FU	84	2,0	HR=0,68 *p*=0,019	3,3	HR=0,66 *p*=0,010
	5FU+Oxali	76	2,9		5,9	
Von Hoff et al, WCGIC 2014	5FU	398	1,5	HR=0,56 *p*<0,001	4,2	HR=0,67 *p*=0,012
	5FU+MM-398		3,1		6,1	
	MM-398		2,7		4,9	
Gill et al, 2014	5FU FOLFOX		2.9 3.1	NS	9.1 6.1	NS
Yoo et al, 2009	FOLFOX FOLFIRI.3		2 1.5	NS	4.2 3.7	NS

Mainly in the era of gem-based first line treatments

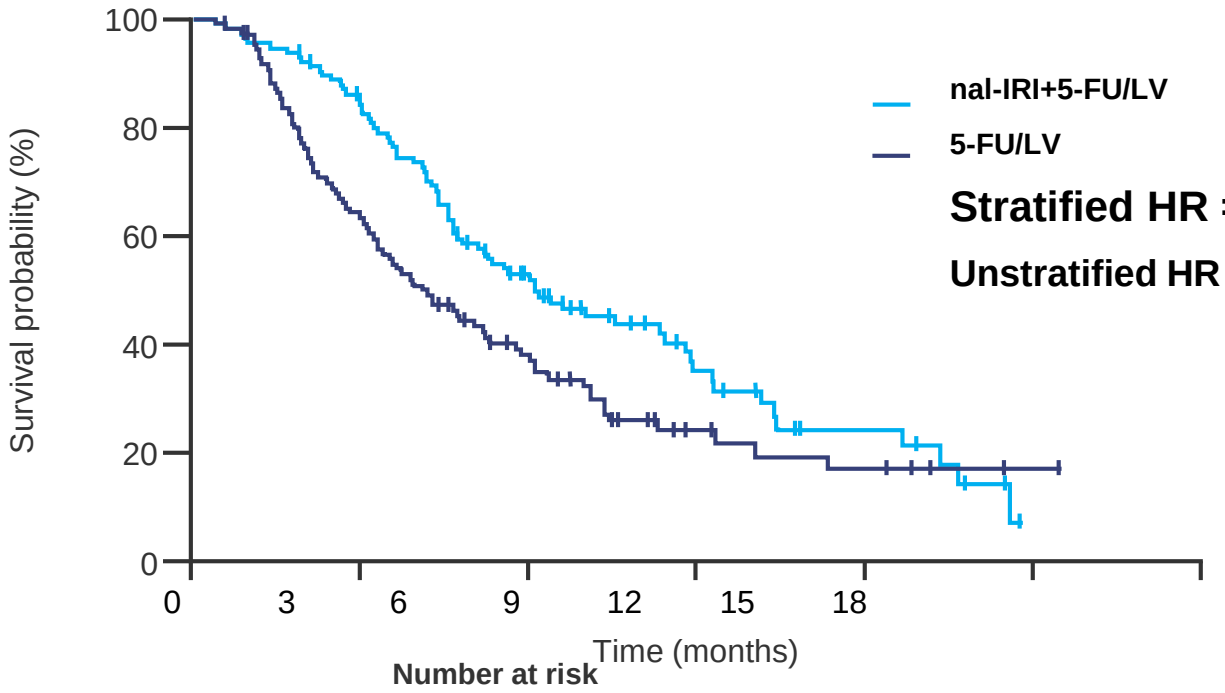
5FU based after Gem-based in clinical practice?

RECIST v1.1 criteria	5FU regimens N=61	FOLFOX N= 24	FOLFIRI 1/3 N=21	FOLFIRINOX N=16	p
Best Response					
Complete response	0	0	0	0	0.17
Partial response	3 (4.92)	0	2 (9.52)	1 (6.25)	
Stable disease	25 (40.98)	7 (29.17)	11 (52.38)	7 (43.75)	
Progressive disease	30 (49.18)	16 (66.67)	8 (38.10)	6 (37.50)	
Not assessable	3 (4.92)	1 (4.17)	0	2 (12.5)	
Disease control rate	28 (45.9)	7 (29.17)	13 (61.9)	8 (50)	
Survivals Median: months 95% CI (min-max)					
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 (4-8)	3.5 (2.3-6)	9.7 (4.5-11.2)	6.1 (2.8-8.8)	0.13

Pointet et al. ASCO GI 2018 (in press)

NAPOLI-1: 1.9 month (45%) increase in median OS with nal-IRI+5-FU/LV

nal-IRI+5-FU/LV combination therapy vs. 5-FU/LV



	Median, mo (95% CI)
nal-IRI+5-FU/LV	6.1 (4.8–8.9)
5-FU/LV	4.2 (3.3–5.3)

Stratified HR = 0.57 (0.41–0.80)

Unstratified HR = 0.67 (0.49–0.92)

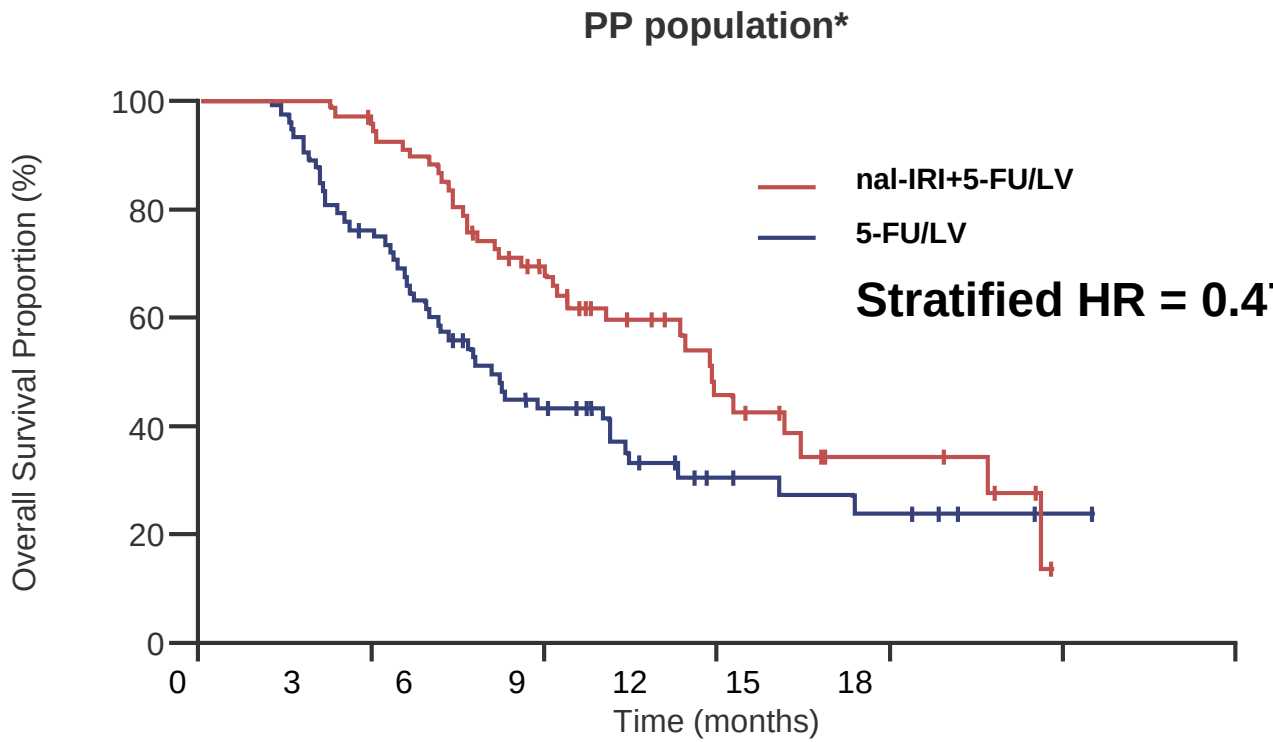
P = 0.012

Number at risk

nal-IRI+5-FU/LV	117	97	51	20	8	0	0
5-FU/LV	119	68	34	11	6	1	0

Survival analysis after 313 deaths on Feb 14th, 2014; Wang-Gillam A, et al. Lancet 2016;387:545; Chen LT, et al. J Clin Oncol 2015;33(S3):abstract 234 (and presentation)

NAPOLI-1: significant OS benefit with nal-IRI+5-FU/LV for the PP population in a pre-specified extended analysis



	Median, mo (95% CI)
nal-IRI+5-FU/LV	8.9 (6.4–10.5)
5-FU/LV	5.1 (4.0–7.2)

Stratified HR = 0.47 (0.29–0.77)

P = 0.0018

Number at risk

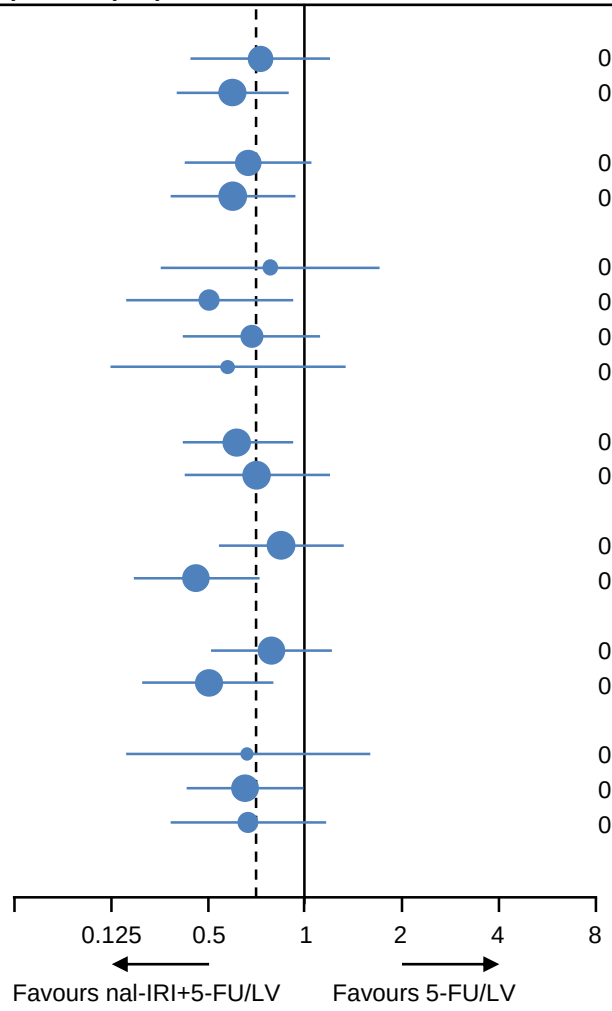
nal-IRI+5-FU/LV	66	63	38	16	6	0	0
5-FU/LV	71	52	25	10	6	1	0

*Per-protocol (PP) population: eligible patients who received ≥80% dose intensity of the protocol-defined treatment during the first 6 weeks of treatment.

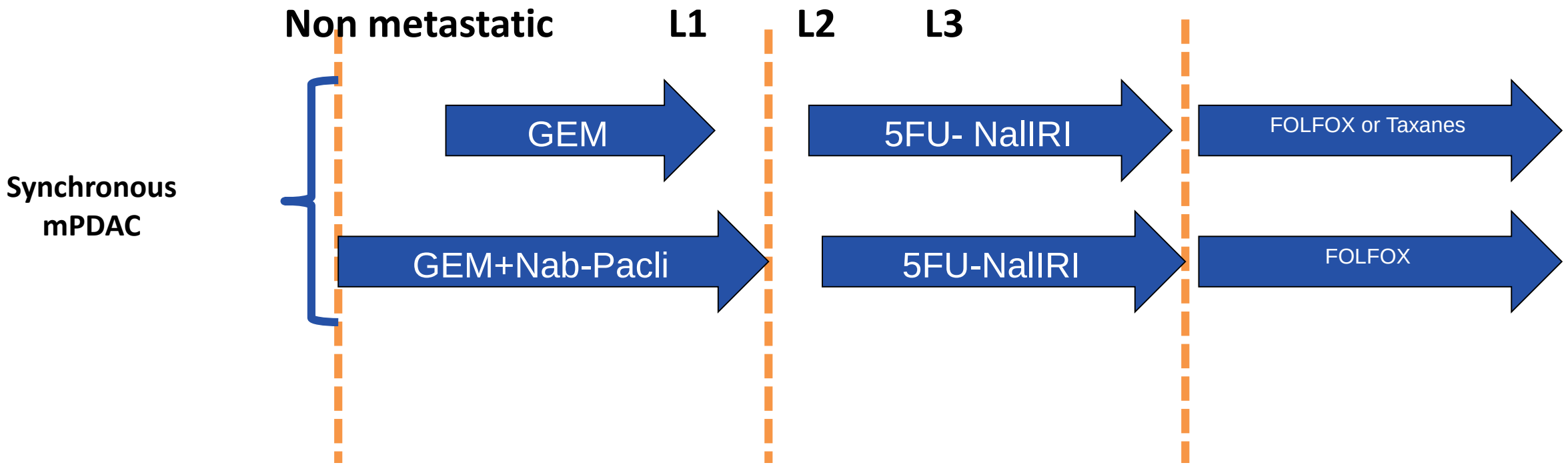
Chen LT, et al. J Clin Oncol 2015;33(S3):abstract 234 (and presentation)

NAPOLI-1: survival benefit of nal-IRI+5-FU/LV was homogeneous across most subgroups (II)

	Combination therapy nal-IRI+5-FU/LV Events/patients (n/N)	Combination therapy control 5-FU/LV Events/patients (n/N)	Hazard ratio for death (95% CI)
Sex			
Women	30/48	33/52	0.74 (0.45–1.22)
Men	45/69	47/67	0.60 (0.40–0.91)
BMI			
≥Median	36/58	39/58	0.68 (0.43–1.07)
<Median	39/59	41/61	0.60 (0.38–0.95)
Region			
North America	14/19	11/19	0.79 (0.36–1.75)
Asia	23/34	24/35	0.51 (0.28–0.93)
Europe	28/47	34/49	0.69 (0.42–1.14)
Other	10/17	11/16	0.58 (0.24–1.38)
Stage at diagnosis			
Stage IV	46/61	51/62	0.63 (0.42–0.94)
Other	28/55	28/55	0.72 (0.42–1.21)
Time since diagnosis			
≥Median	38/62	38/60	0.86 (0.55–1.34)
<Median	37/55	42/57	0.46 (0.29–0.73)
Time since metastatic diagnosis			
≥Median	42/61	41/58	0.80 (0.52–1.23)
<Median	32/55	39/60	0.50 (0.31–0.81)
Previous lines of metastatic therapy			
0	10/15	1/15	0.68 (0.28–1.64)
1	40/62	47/67	0.66 (0.43–1.00)
≥2	25/40	23/37	0.68 (0.38–1.20)



Wang-Gillam A, et al. Lancet 2016;387:545



- **With a gem based first line the second line standard is 5FU+ Nal-Iri**

- **FOLFOX or taxane (if nab-paclitaxel has not been used) can be used later for eligible patients**

And after FOLFIRINOX?

- Available agents :
  - gemcitabine
  - taxanes (docetaxel, paclitaxel)
  - nab-paclitaxel

- What are the published data ?

Gemcitabine in L2

- After L1 5FU : 63 patients,
  ORR:10,5%; DCR:40,5%
  PFS: 2,5 mo; OS:3,8 mo
  Rothenberg et al, Ann Oncol 1996
- After L1 5FU+ Cisplatin : 69 patients
  ORR: 10%; DCR: 38%
  Dahan L et al, Gut 2010
- After L1 FOLFIRINOX : 85 patients
  gem monotherapy 82,5% or gem-based 12,5%,
  OS: 4,4 mois
  Conroy T et al, NEJM 2011

Taxanes in L2

Author, year	Chemo L1	Chemo L2	N patients	ORR (%)	SD (%)	PFS (mo)	OS (mo)
Oettle, 2000	Gem B	Paclitaxel	18	6	28	-	4.0
Ignatiadis, 2006	Gem B	Docetaxel-Gefitinib	26	0	19	2.1	2.9
Saif, 2010	Gem B	Docetaxel	17	6	31	2	4
Hosein, 2012	Gem B	nab-paclitaxel	19	5	32	1,7	7,3
Soares, 2014	Gem B	Capecitabine-Docetaxel	43	14	59	3,7	5,3
Ettrick, 2015	Gem	Docetaxel-Oxaliplatine	44	16	32	1,6	9,2

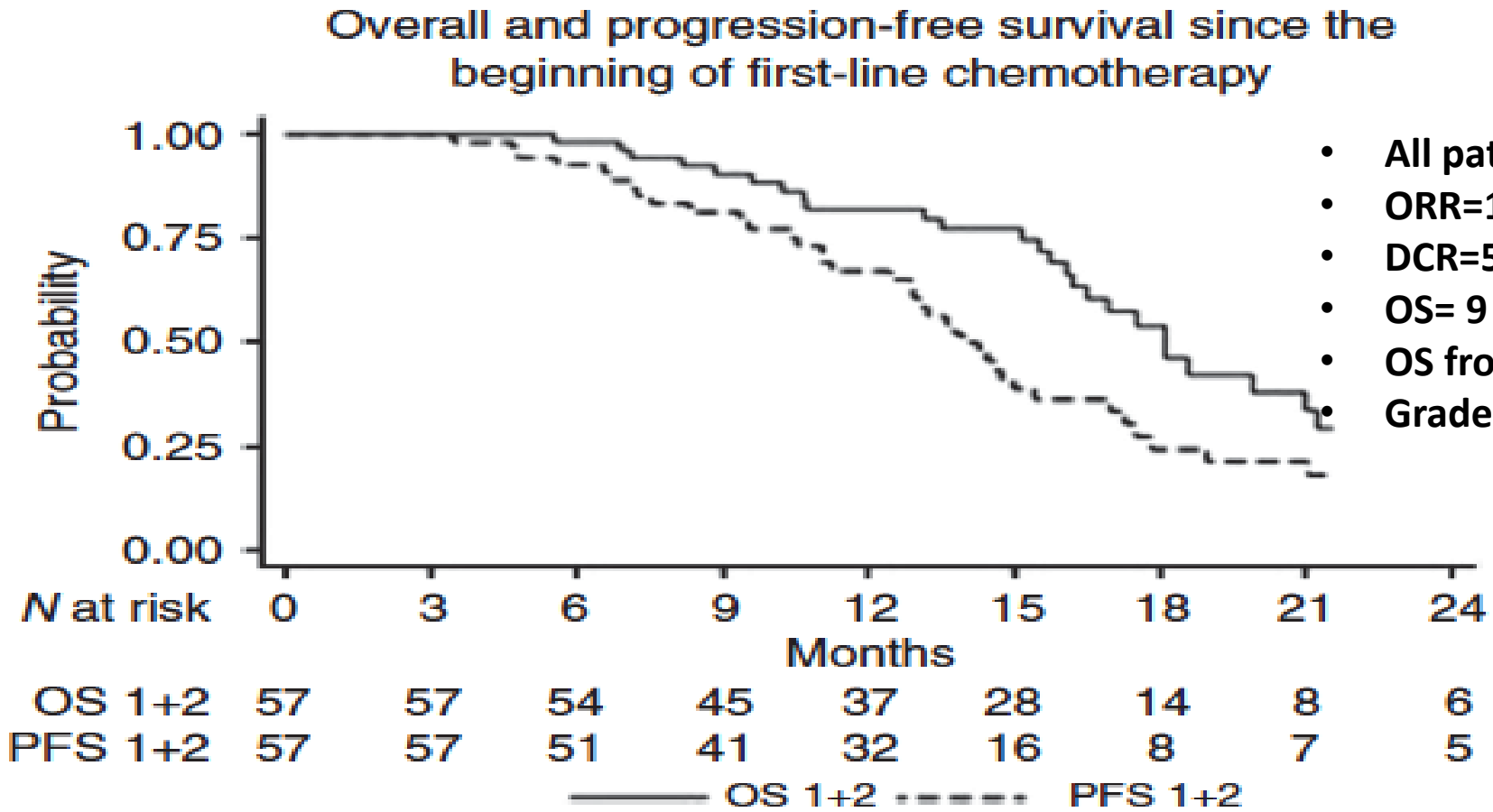
What about Gem and Taxanes in L2?

BJC

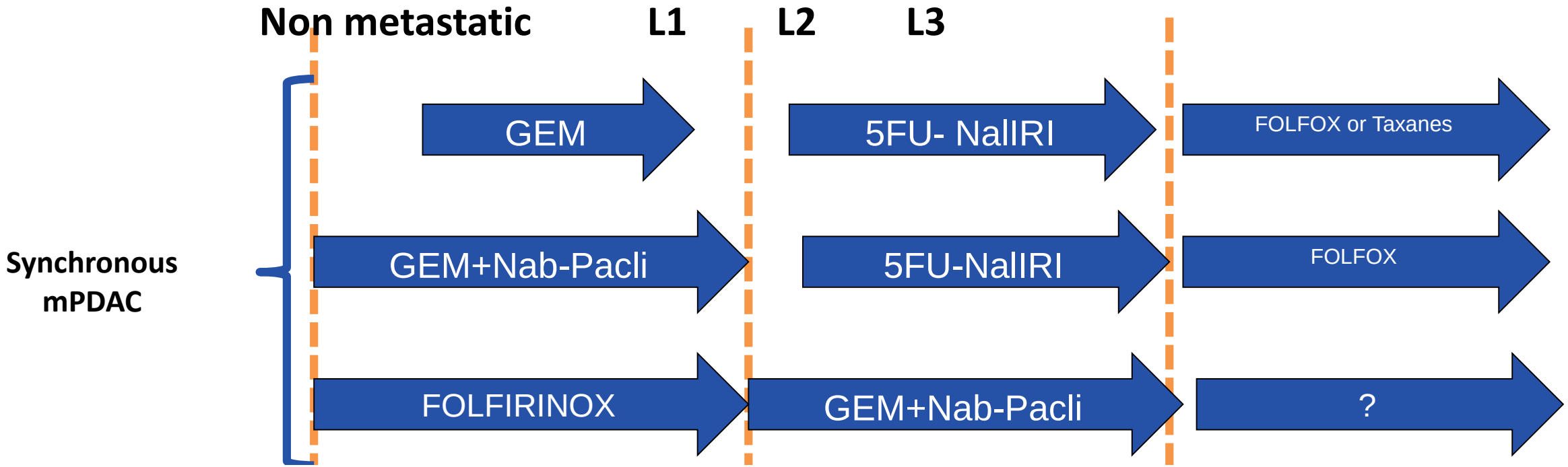
Keywords: metastatic pancreatic car

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%



- **After FOLFIRINOX, gem+nab-paclitaxel seems to give promising results in good condition patients though randomized data are still lacking**

- **Issue : access to nab-paclitaxel L2**

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

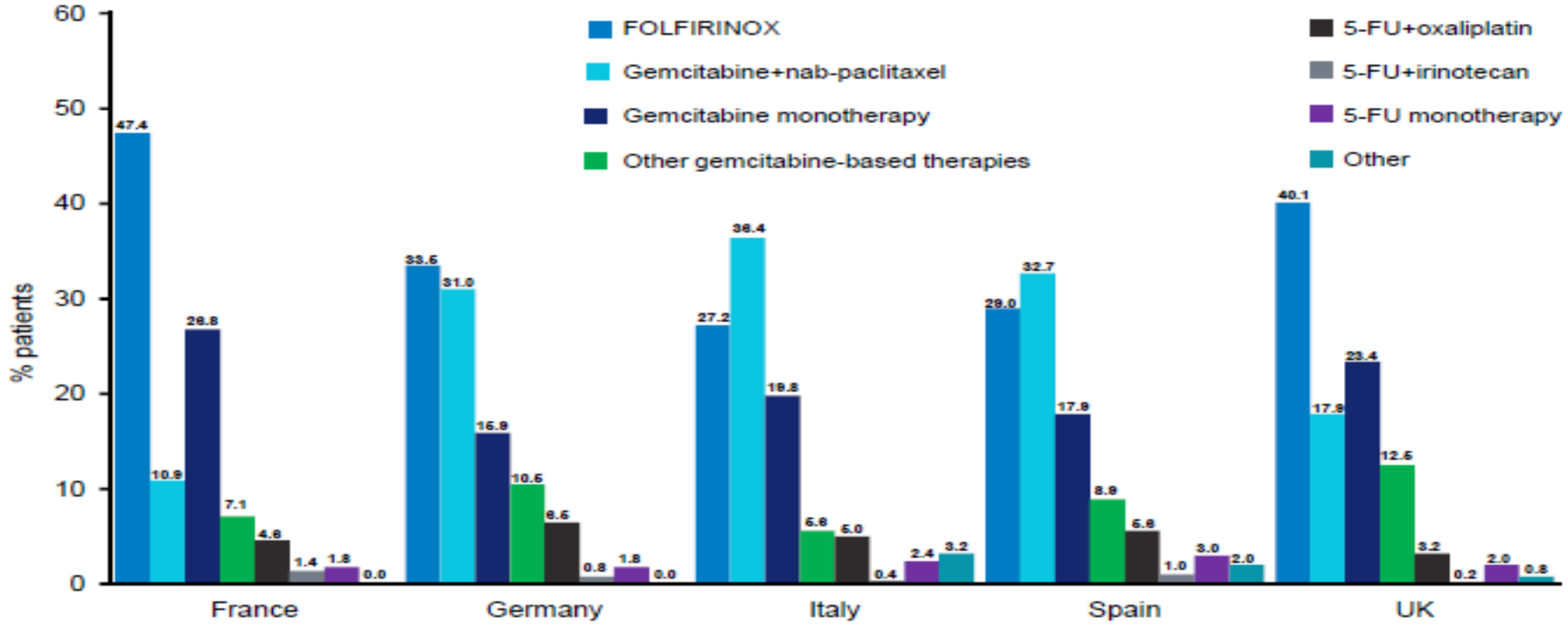
- General disease information and patient characteristics
- Disease characteristics at diagnosis
- Initial treatment for pancreatic cancer
- Details of first/second/third-line treatment

*University and general hospitals, cancer and reference centres, office-based specialists.
mPAC, metastatic pancreatic adenocarcinoma

Taieb et al. ESMO GI 2018

European Chart review

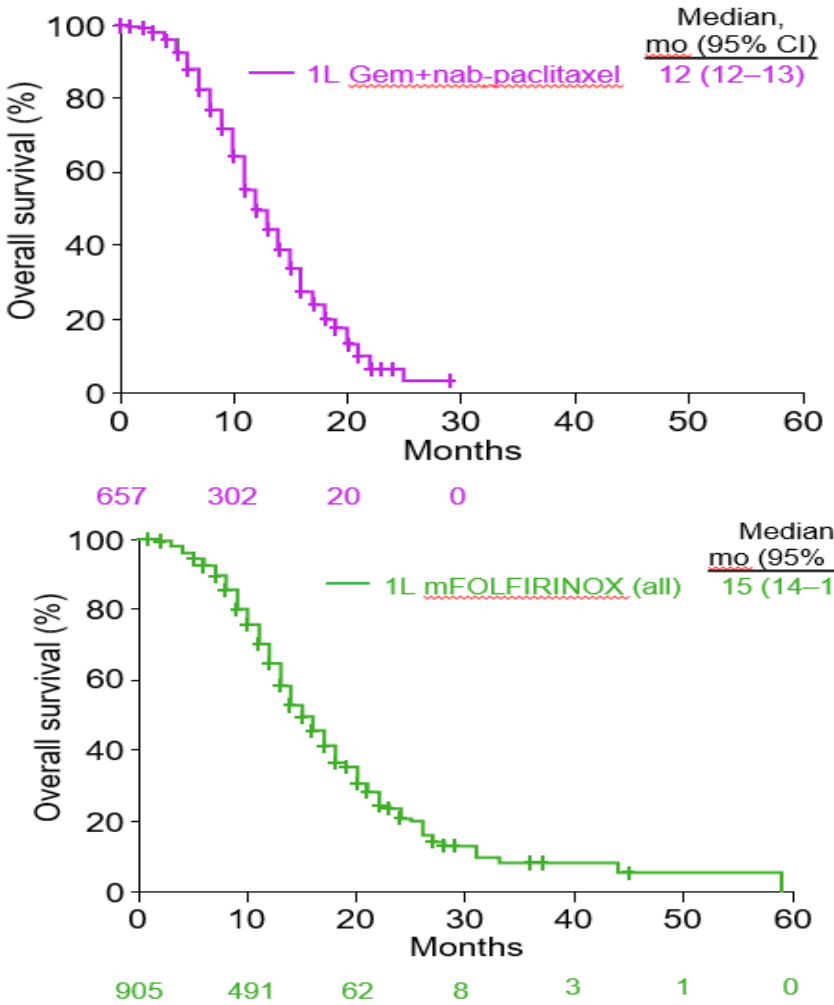
> 2500 patients

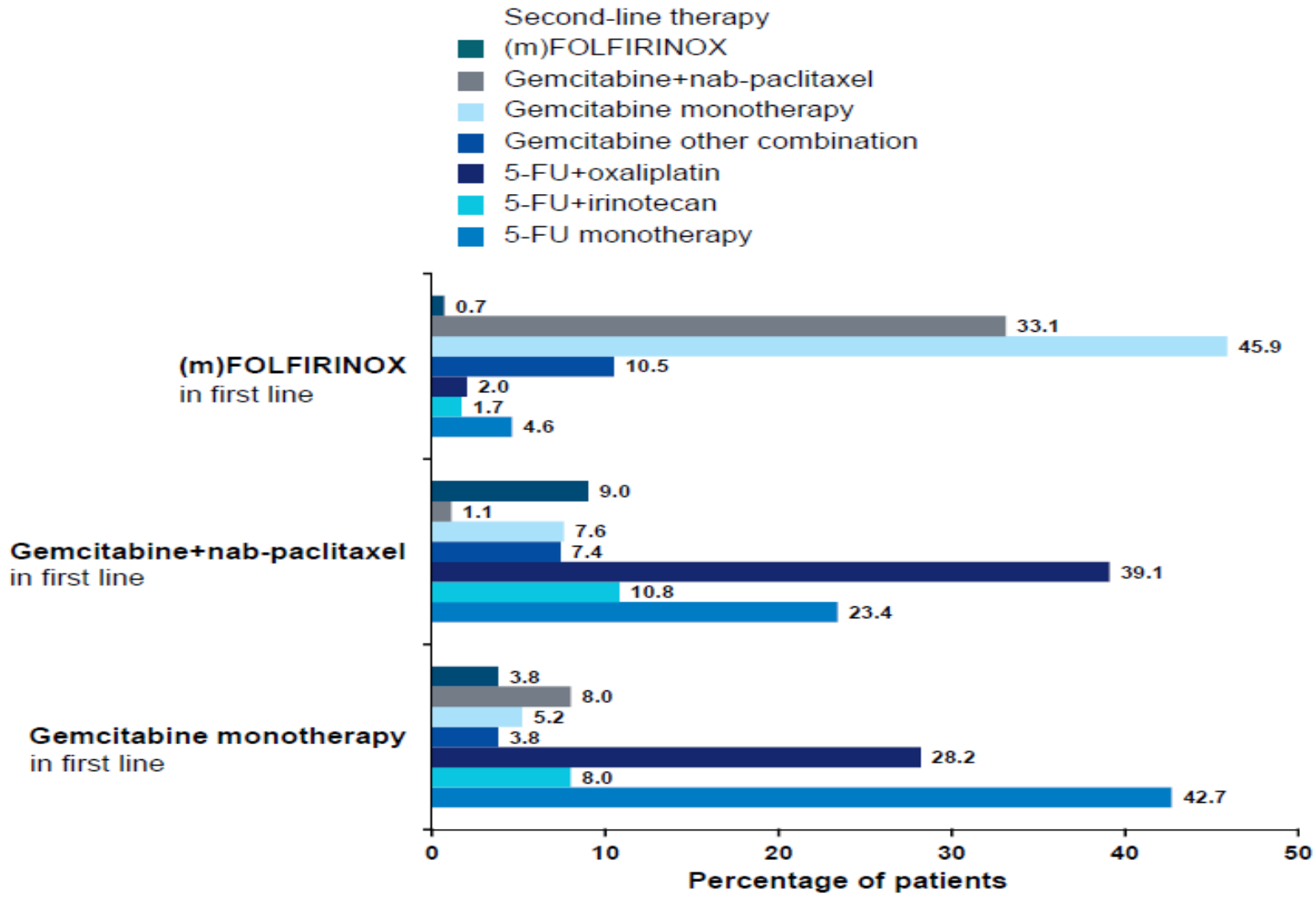


More than 70% received a second line (but biased)

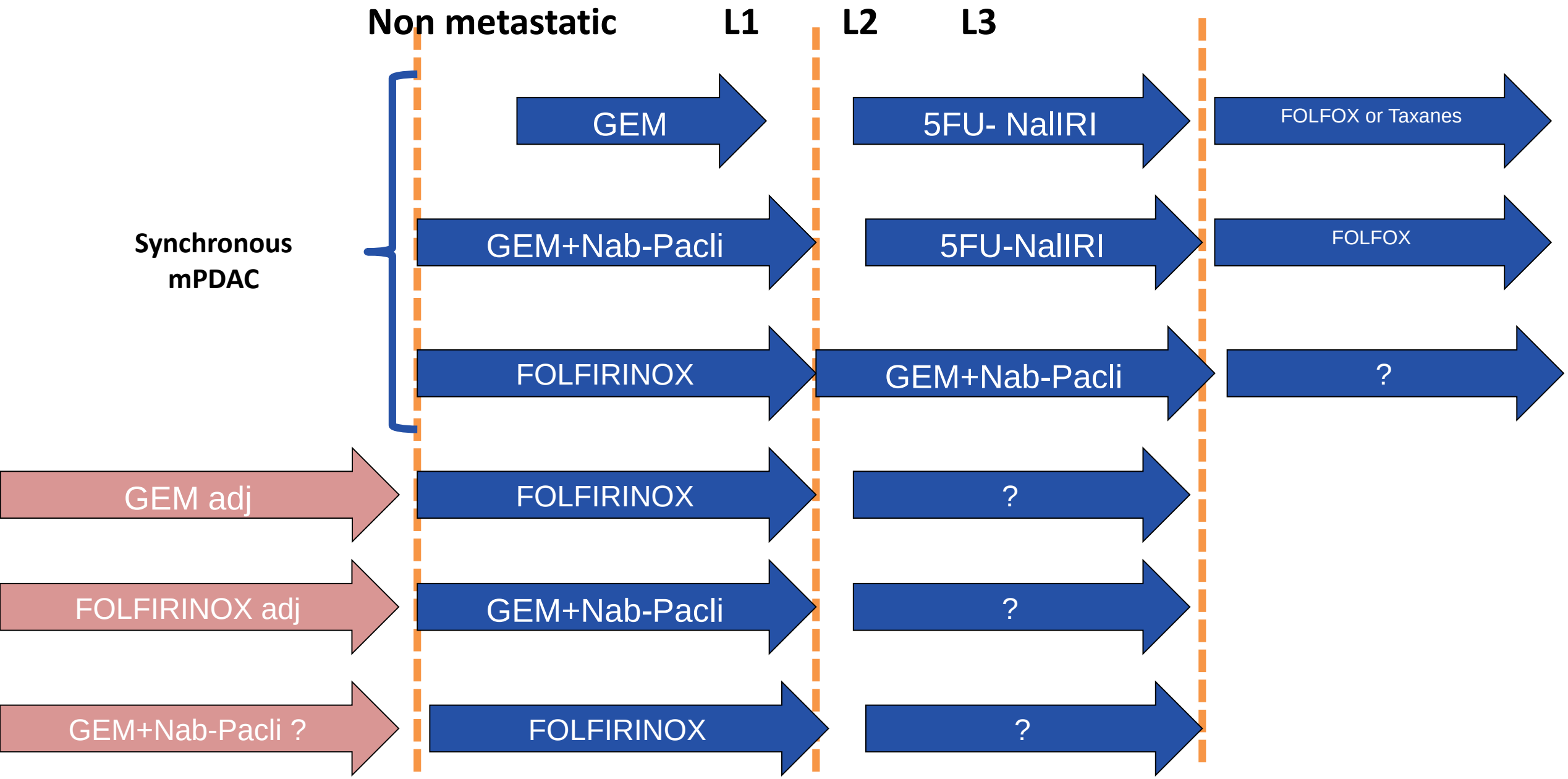
Taieb et al. ESMO GI 2018

European Chart review





Taieb et al. ESMO GI 2018

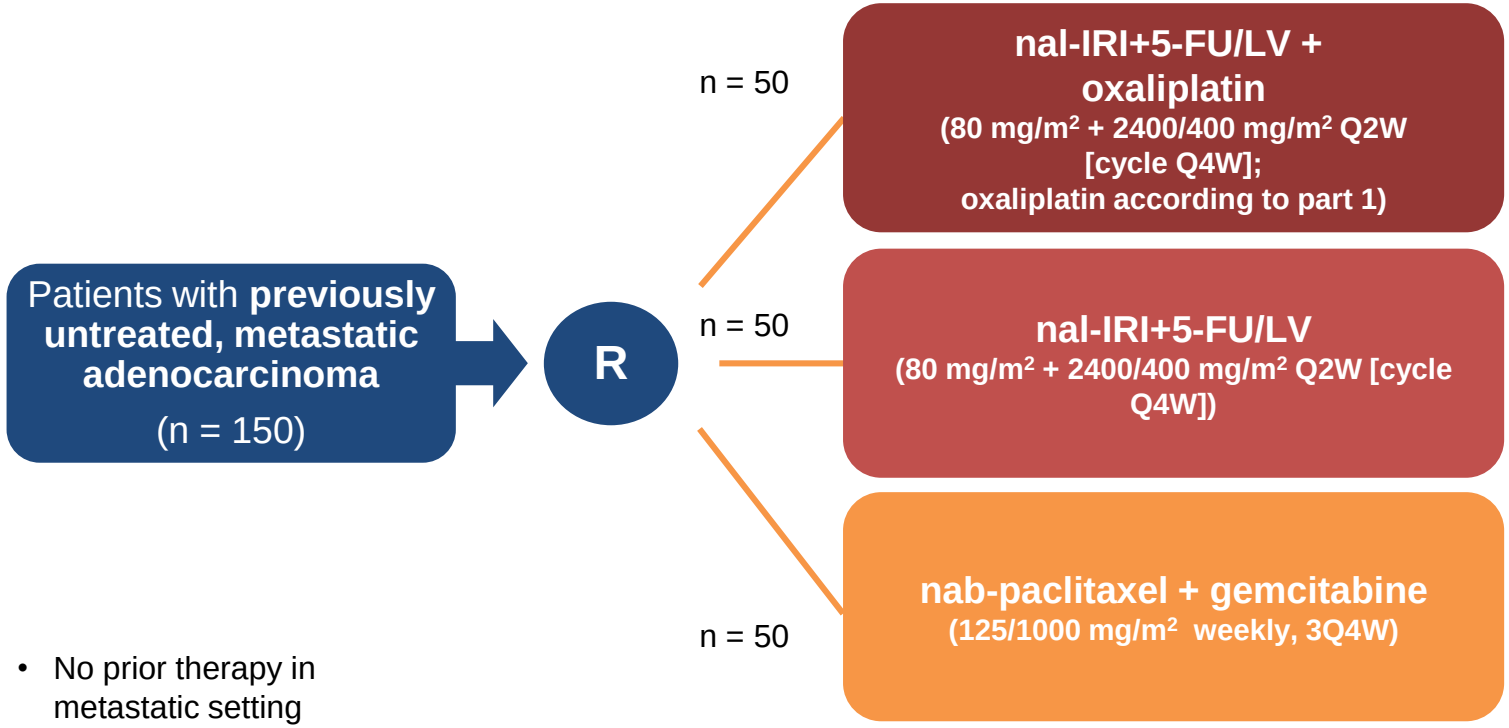

Non metastatic
L1
L2
L3
Synchronous mPDAC
GEM
5FU- NalIRI
FOLFOX or Taxanes
GEM+Nab-Pacli
5FU-NalIRI
FOLFOX
FOLFIRINOX
GEM+Nab-Pacli
?
GEM adj
FOLFIRINOX
?
FOLFIRINOX adj
GEM+Nab-Pacli
?
GEM+Nab-Pacli ?
FOLFIRINOX
?

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

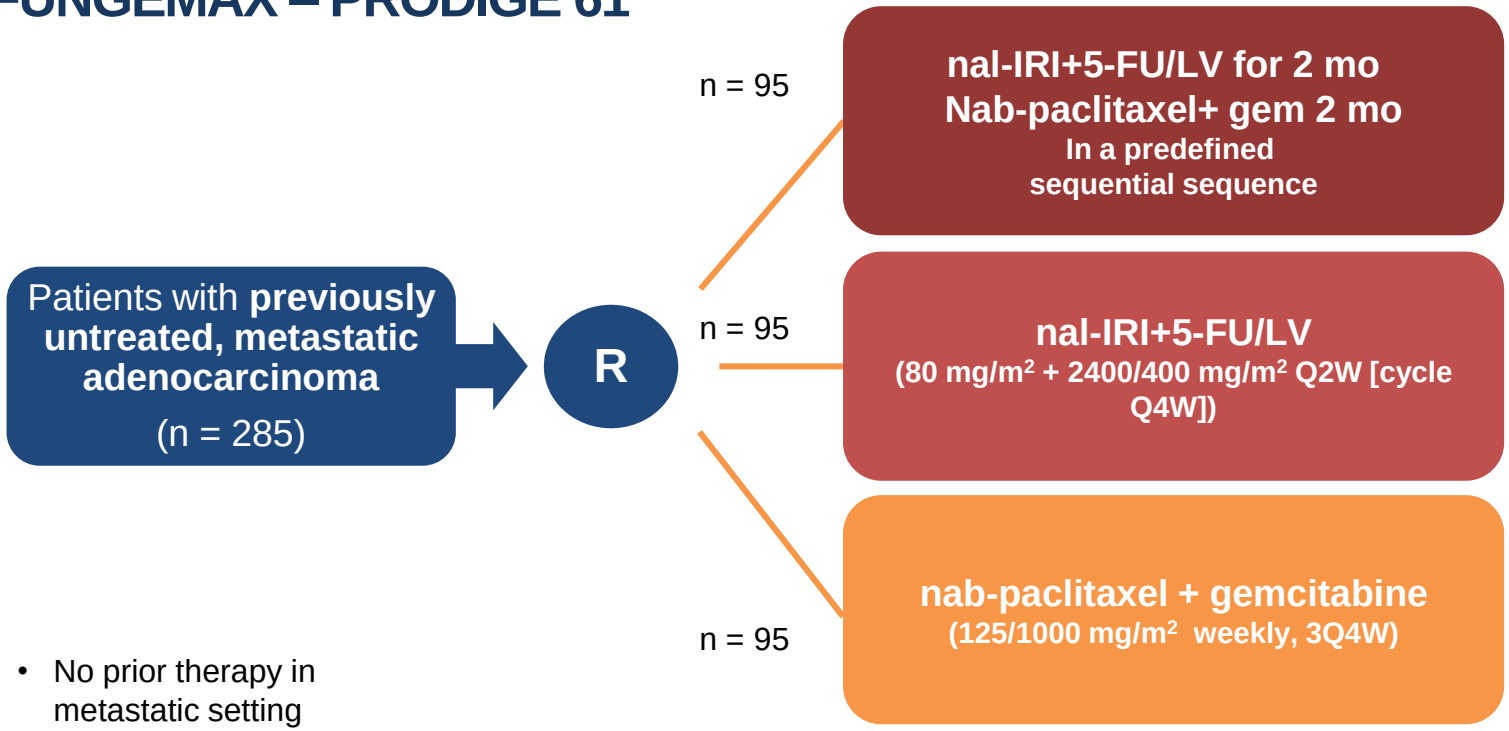


- No prior therapy in metastatic setting
- ECOG PS 0 or 1
- Aged ≥18 years

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

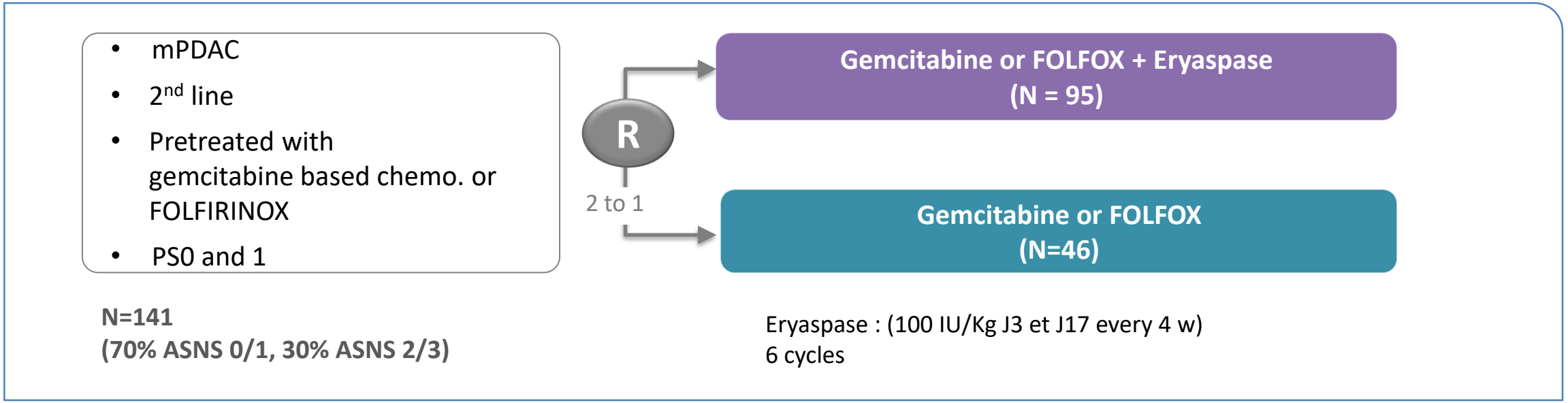
FUNGEMAX – PRODIGE 61

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



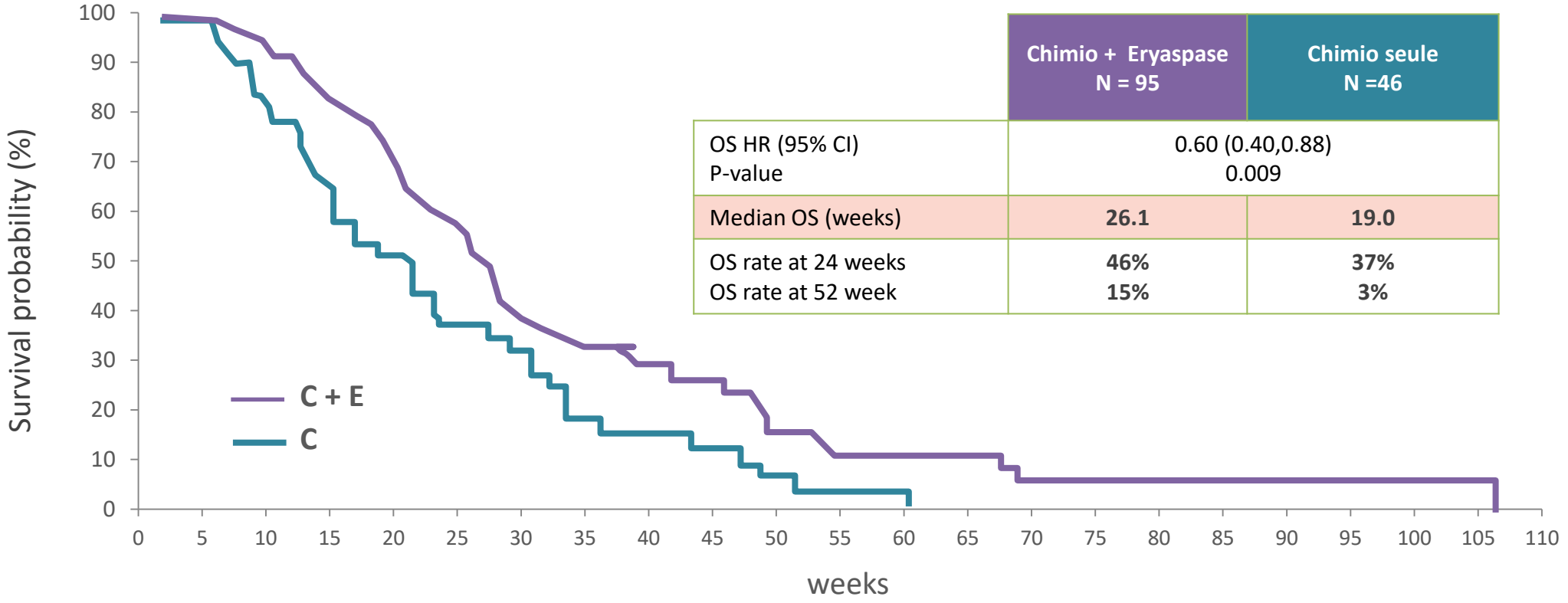
- No prior therapy in metastatic setting
- ECOG PS 0 or 1
- Aged ≥18 years
- Normal bilirubine level

GRASPANC : **design**



- Primary Objective:
  - PFS and OS in pts with no or weak ASNS expression (0/1+ in IHC)
  - Target HR < 0.85 for PFS or OS
- Secondary Objectives : PFS, OS, ORR and tolerability in all patients

GRASPANC : OS in all patients



	Chimio + Eryaspase N = 95	Chimio seule N =46
OS HR (95% CI) P-value	0.60 (0.40,0.88) 0.009	
Median OS (weeks)	**26.1**	**19.0**
OS rate at 24 weeks OS rate at 52 week	**46%** **15%**	**37%** **3%**

C+E	95	89	82	71	58	46	32	25	22	19	12	8	6	4	2	2	2	1	1	1	1	1	0
C	46	40	34	25	19	15	10	6	5	4	2	1	1										

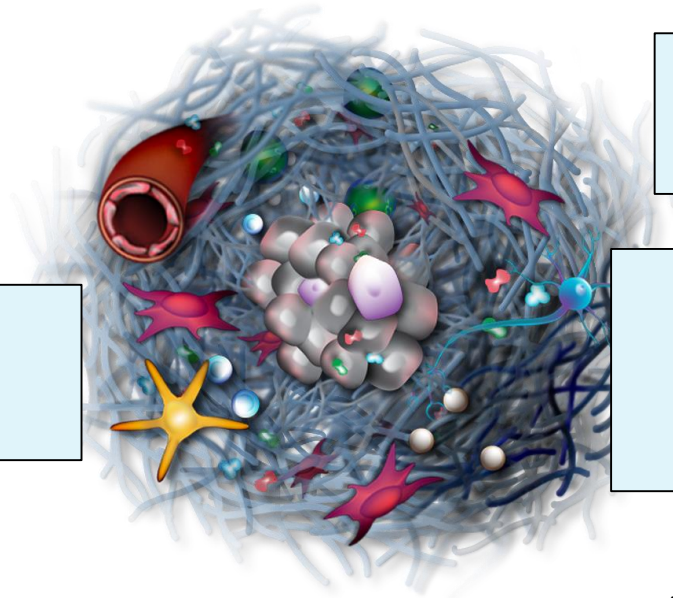
Hammel P *et al.* - ESMO 2017 - Abs. 621PD

- Target Cancer Stemcell (Napabucasin)
- Target BRCAness
- Target Ras or interaction domains with binding partners

- TGF-β (evofosamide)
- Notch/DDL4 (demcizumab)
- Wnt/B-catenin (OMP-54F28)
- Lysyl-oxidase inhibitors (simtuzumab)
- Recombinant human hyalorunidase

Other

Stroma



Metabolism

Immunity/ Inflammation

- Metformin
- L-asparaginase
- Hydroxychloroquin
- Physical activity

- Gvax /CRS207
- Anti-CLTA4, Anti-PD1/PDL1 + CCR2 targeting or anti-TGFb or other co treatments

Adapted from Neuzillet C, Pharmacol Ther 2015

Conclusion

- **Second line treatment of mPDAC depends of first-line choices (and adjuvant?)**
- **The landscape of mPDAC treatment is moving, changing second line possibilities**
- **5FU+ Nal-IRI has the highest level of evidence currently after a gem based first-line treatment**
- **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**
- **If not done in first line think about rare subtypes (MSI, BRCA2 …) for specific treatments/trials.**

Thank you for your attention !