MEDICAL TREATMENT FOR PANCREATIC CANCER (LOCALIZED, LOCALLY ADVANCED AND METASTATIC)

Josep Tabernero, MD PhD

Medical Oncology Department

Vall d'Hebron University Hospital

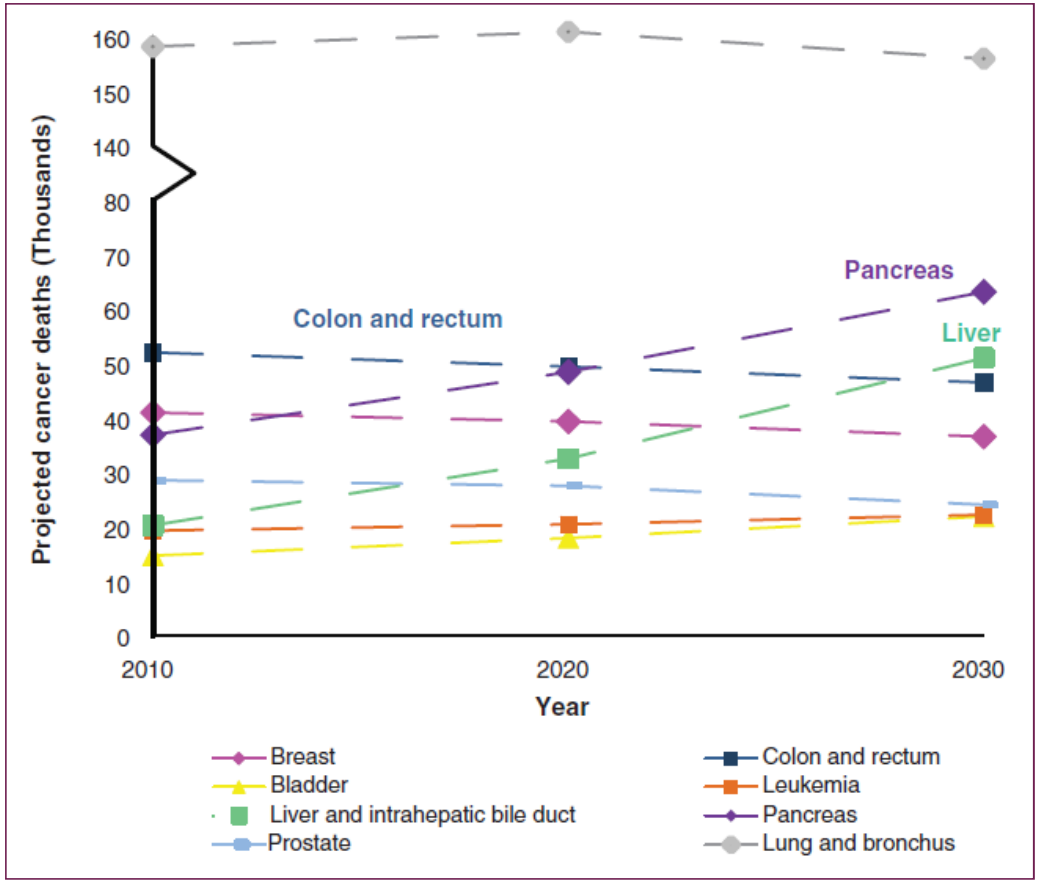
Barcelona, Spain

DECLARATION OF INTERESTS

Josep Tabernero reports personal financial interest in form of scientific consultancy role for Array Biopharma, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Chugai, Genentech, Inc., Genmab A/S, Halozyme, Imugene Limited, Inflection Biosciences Limited, Ipsen, Kura Oncology, Lilly, MSD, Menarini, Merck Serono, Merrimack, Merus, Molecular Partners, Novartis, Peptomyc, Pfizer, Pharmacyclics, ProteoDesign SL, Rafael Pharmaceuticals, F. Hoffmann-La Roche Ltd, Sanofi, SeaGen, Seattle Genetics, Servier, Symphogen, Taiho, VCN Biosciences, Biocartis, Foundation Medicine, HalioDX SAS and Roche Diagnostics.

Josep Tabernero declares institutional financial interest in form of financial support for clinical trials or contracted research for Agendia BV, Amgen SA, Debiopharm International SA, Janssen-Cilag SA, Mologen AG, Novartis Farmacéutica SA, Pharma Mar, Roche Farma SA, Laboratorios Servier SL and Symphogen A/S.

PROJECTING CANCER INCIDENCE AND DEATHS TO 2030

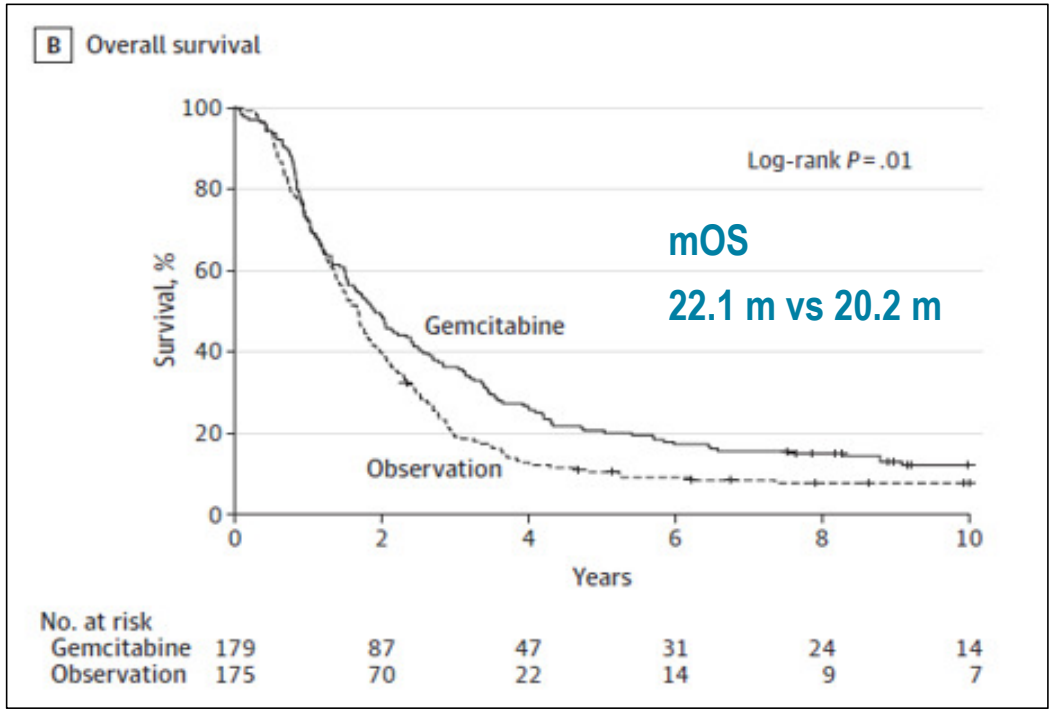


Rahib et al, Cancer Res 2014

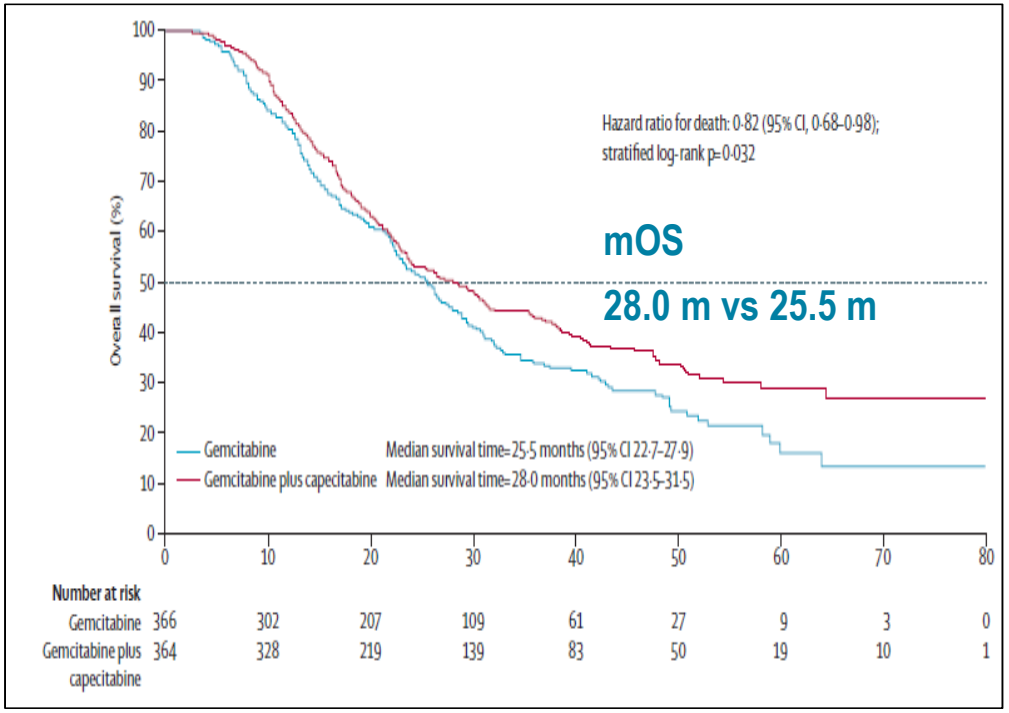
LOCALIZED PDAC

ADJUVANT TREATMENT IN PDAC

CONKO[1]: Gemcitabine vs Observation



ESPAC-4[2]: Gemcitabine + Capecitabine vs Gemcitabine



1.Oettle H, et al. JAMA 2013. 2. Neoptolemos JP, et al. Lancet 2017

ADJUVANT TREATMENT IN PDAC

Resected PDCA
n= 1088

RANDOMIZE

Gemcitabine
n = 193

S1
n = 192

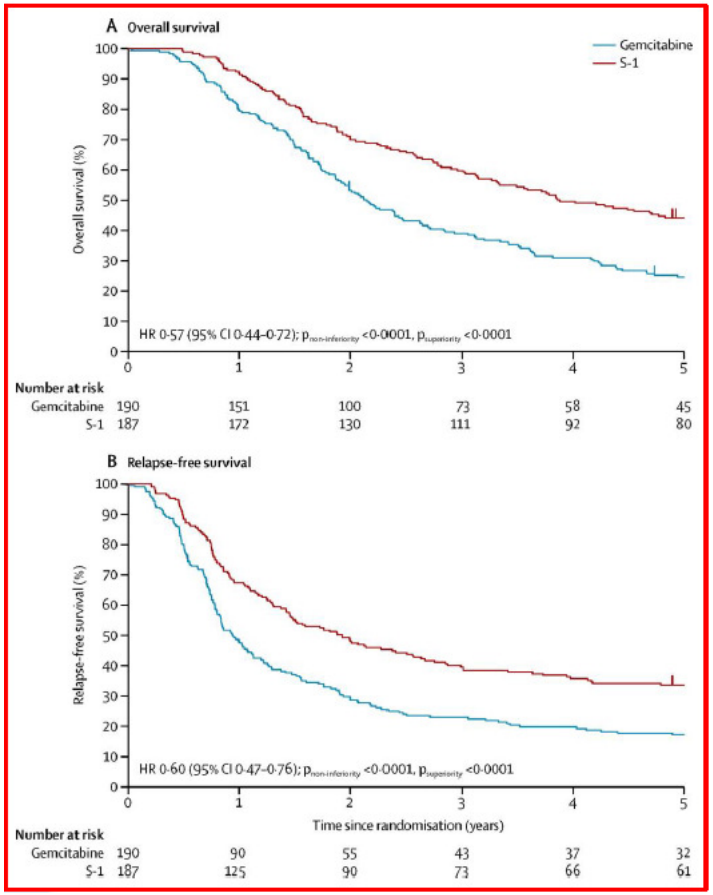
Randomization 1: 1
Stratification: Institution; R0 vs R1, N status

Primary Endpoint: Overall survival

	3-Year	5-Year	Med OS
Gemcitabine	38.8 %	24.4%	25.5 mo
S1	59.7%	44.1 %	46.5 mo
HR= 0.57 (CI 0.44- 0.72), p< 0.0001			

- ✓ N = 385
- ✓ S1 40-60 mg 2x/d for 4 / 6 weeks
- ✓ G3/4 toxicity in favour of S1

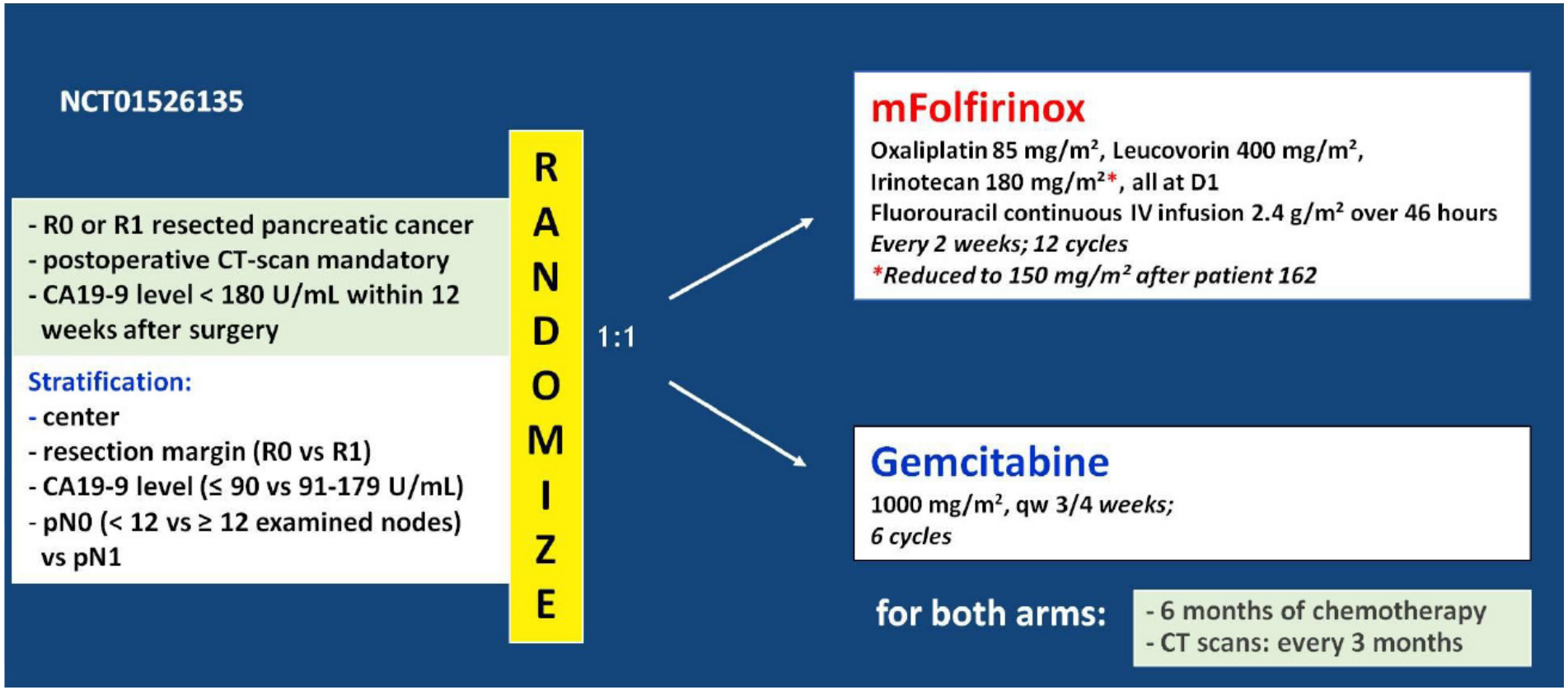
JASPAC-01: Gemcitabine vs S-1



Uesaka et al. Lancet 2016

ADJUVANT TREATMENT IN PDAC

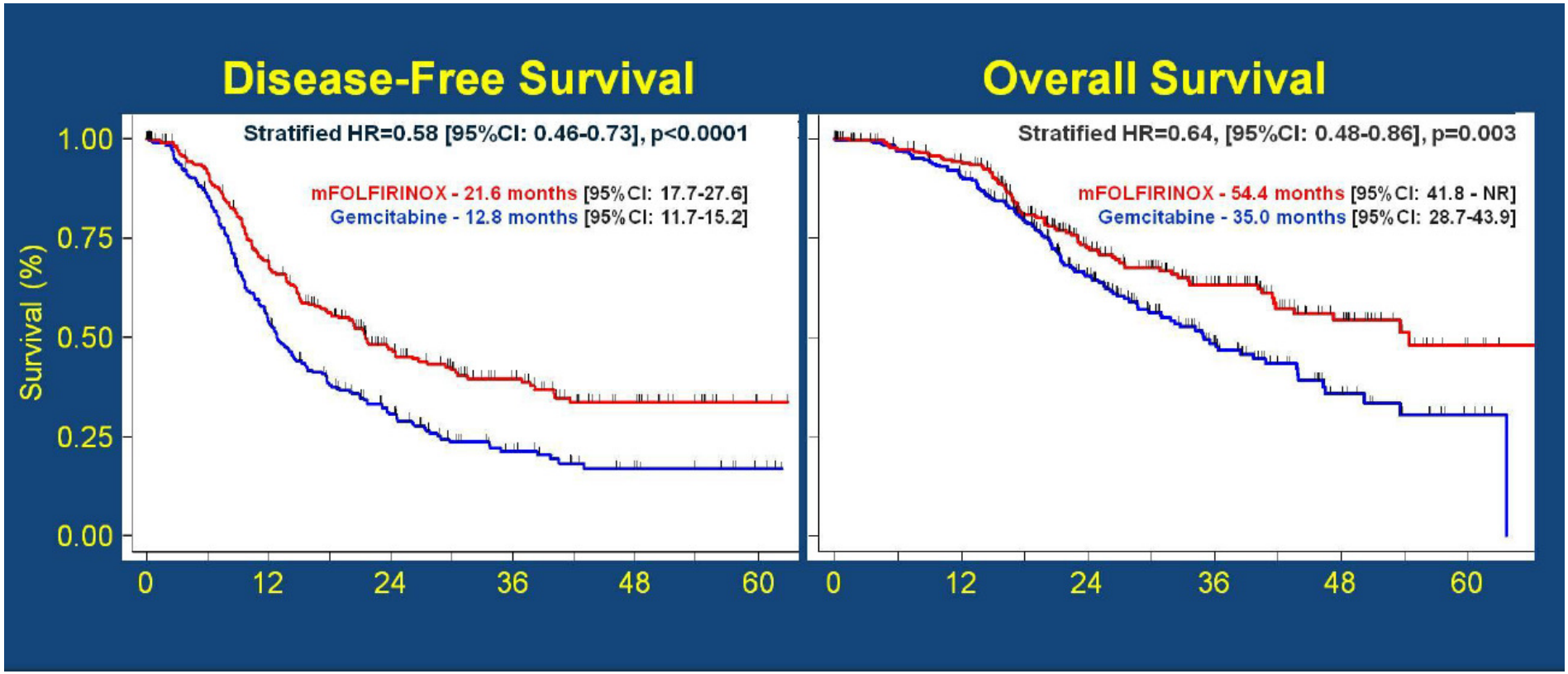
Phase III PRODIGE 24/CCTG PA.6 Trial



Conroy T et al, J Clin Oncol 2018

ADJUVANT TREATMENT IN PDAC

Phase III PRODIGE 24/CCTG PA.6 Trial



Conroy T et al, J Clin Oncol 2018

ADJUVANT TREATMENT IN PDAC

Phase III PRODIGE 24/CCTG PA.6 Trial

Hematological toxicity

Grade 3-4 adverse events, % per patient	mFolfirinox N=238	Gemcitabine N=243	p
Anemia	0.0%	0.4%	1.00
Neutropenia	28.4 %	26.0 %	0.56
G-CSF use	59.9 %	3.7 %	<0.001
Febrile neutropenia	2.9 %	3.7 %	0.65
Lymphopenia	1.3 %	2.9 %	0.34
Thrombocytopenia	1.3 %	4.5 %	0.03

Conroy T et al, J Clin Oncol 2018

ADJUVANT TREATMENT IN PDAC

Phase III PRODIGE 24/CCTG PA.6 Trial

Non- Hematological toxicity

AE, % per patient	mFolfirinox N=238		Gemcitabine N=243		p-value all grades
	All grades	Grade 3/4	All grades	Grade 3/4	
Diarrhea	84.4 %	18.6 %*	49 %	3.7 %	< 0.001
Sensory peripheral neuropathy	61.2 %	9.3 %	8.7 %	-	< 0.001
Fatigue	84 %	11 %	77.6 %	4.6 %	0.003
Vomiting	46 %	5 %	29 %	1.2 %	< 0.001
Mucositis	33.8 %	2.5 %	14.9 %	0 %	< 0.001
Alopecia	27 %	-	19.5 %	-	0.07
Hand-foot syndrome	5 %	0.4 %	0.8 %	-	0.023

Conroy T et al, J Clin Oncol 2018

ADJUVANT TREATMENT IN PDAC

Ongoing Phase III Adjuvant studies

Study	Treatment	Planned N
RTOG 0848 (NCT01013649)	Gemcitabine/combination ± CRT; erlotinib randomization removed Primary endpoint: OS	545 (accrual complete)
APACT (NCT01964430)	Gemcitabine ± nab-paclitaxel Primary endpoint: DFS	800 (accrual complete)
Italy GIP-2 (NCT02355119)	FOLFOXIRI vs gemcitabine Primary endpoint: DFS	310

Clinicaltrials. gov

ADJUVANT TREATMENT IN PDAC

Limits of Adjuvant Strategies in PDAC

- R0-resection rate for resectable PDAC is around 70%.
- Administration of planned adjuvant chemotherapy may be limited by post-operative complications and early relapse (25-50%).
- Available data about neoadjuvant strategy in PDAC:
  - Mainly retrospective and single arm prospective studies
  - Heterogeneous population, definition of R0, chemotherapy, radiotherapy…
  - Recently: introduction of FOLFIRINOX and gemcitabine/nap-paclitaxel, but some of these trials used radiotherapy.

Versteijne E et al. BJS 2018, Tzeng CW et al. J Gastrointest Surg 2014; Aloia TA et al. J Am Coll Surg 2007, Mayo SC et al. J Am Coll Surg 2012, Katz et al. JAMA Surg, 2016; Yoo et al. Oncotarget, 2017; Murphy et al. JAMA Oncol 2018, Ielpo et al. Eur J Surg Oncol 2016

LOCALLY ADVANCED PDAC

Chemotherapy as First Choice: Which Drug or Regimen?

UNRESECTABLE PDAC: WHICH CHEMOTHERAPEUTIC REGIMEN?

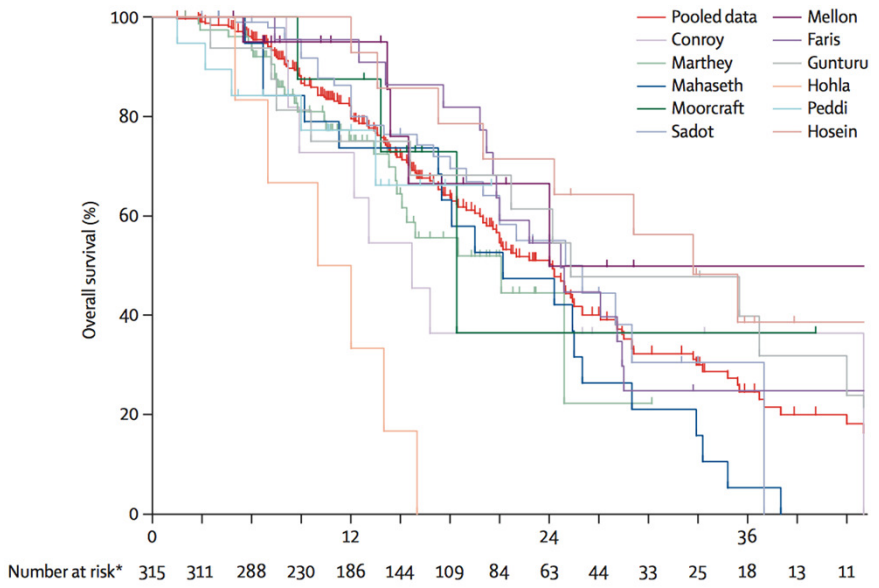
...but, ***some concerns about a combination chemotherapy:***

Only phase II trials and unconvincing meta-analyses, but no randomized trials

FOLFIRINOX for Locally Advanced Pancreatic Cancer: A Systematic Review and Patient-Level Meta-Analysis

Background: 35% of patients with pancreatic cancer have unresectable locally advanced disease at diagnosis

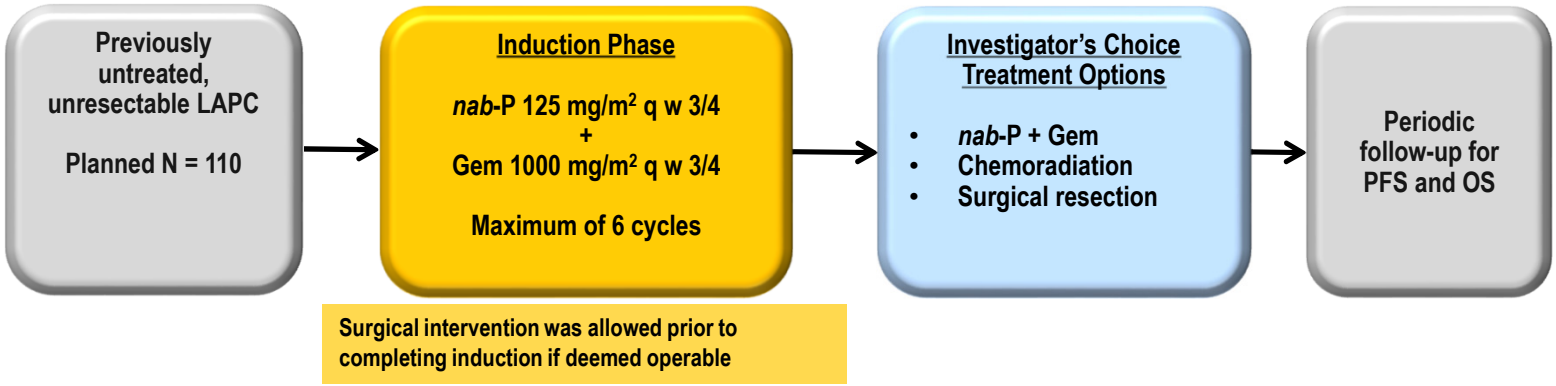
	Number of patients	Radiotherapy or chemoradiotherapy	Resection	R0 resection
Boone[22]	10	5 (50%)	2 (20%)	1 (50%)
Conroy[12]	11	NR	0	NA
Faris[21]	22	20 (91%)	5 (23%)	5 (100%)
Gunturu[24]	16	NR	2 (13%)	NR
Hohla[18]	6	2 (33%)	2 (33%)	NR
Hosein[23]	14	9 (64%)	6 (43%)	5 (83%)
Mahaseth[19]	20	10 (50%)	4 (20%)	3 (75%)
Marthey[25]	77	24 (31%)	28 (36%)	25 (89%)
Mellon[28]	21	21 (100%)	5 (24%)	5 (100%)
Moorcraft[26]	8	NR	2 (25%)	NR
Peddi[20]	19	NR	4 (21%)	NR
Sadot[29]	101	63 (62%)	31 (31%)	16 (52%)
Total	325	154 (57%)	91 (28%)	60 (74%)



mOS 24.2 (10-32.7) months

Suker M, et al. Lancet Oncol. 2016

nab-Paclitaxel Plus Gemcitabine for Patients With Locally Advanced Pancreatic Cancer: Interim Efficacy and Safety Results From the Phase II **LAPACT Trial**



LAPC

- Unresectable pancreatic cancer:
  - Occlusion, thrombosis, or encasement of the superior mesenteric vein and portal vein
  - Tumor abutment >180° or thrombosis of superior mesenteric artery
  - Abutment or encasement of the celiac axis
  - Lymph node involvement

Key Exclusion Criteria

- Endocrine/mixed-origin pancreatic tumors
- Prior anticancer therapy for pancreatic carcinoma
- Borderline resectable disease

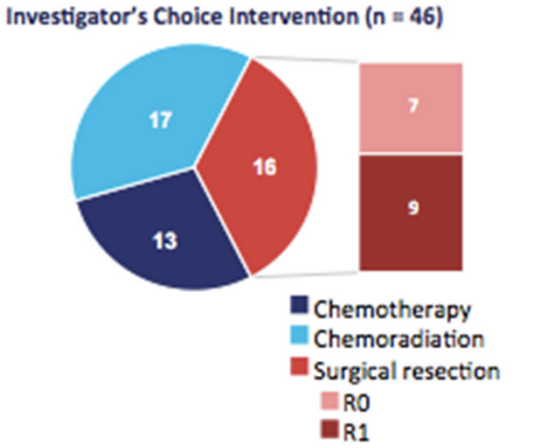
- **Primary Endpoint: Time to treatment failure**—time from first dose of study therapy to treatment failure
- **Secondary Endpoints:** DCR (after 6 cycles of therapy; CR, PR, and SD), ORR, PFS, OS, safety, and QoL (EORTC QLQ-C30 and QLQ-PAN26)

CR, complete response; DCR, disease control rate; EORTC, European Organisation for Research and Treatment of Cancer; LAPC, locally advanced pancreatic cancer; ORR, overall response rate; PR, partial response; QoL, quality of life; SD, stable disease

Philip PA, et al. Ann Oncol. 2017

nab-Paclitaxel Plus Gemcitabine for Patients With Locally Advanced Pancreatic Cancer: Interim Efficacy and Safety Results From the Phase II **LAPACT Trial**

Best Response By RECIST v1.1, n (%)	ITT Population (N = 107)
Complete Response	0
Partial Response	36 (33.6)
All stable disease	61 (57.0)
SD ≥16 weeks	47 (43.9)
SD ≥24 weeks	35 (32.7)
Disease control rate (90% CI)	
SD ≥16 weeks + CR + PR	83 (77.6 [70.3-83.5])
SD ≥24 weeks + CR + PR	71 (66.4 [58.5-73.4])
Progressive disease	5 (4.7)
Not evaluable	1 (0.9)
No post-baseline assessment	4 (3.7)



Grade ≥3 TEAEs in ≥5% of Patients During Induction

TEAE, n (%)	*nab*-Paclitaxel + Gemcitabine (n = 106) All-Grade	Grade ≥ 3
Patients with ≥1 adverse event	105 (99.1)	85 (80.2)
Neutropenia[a]	61 (57.5)	43 (40.6)
Anemia	50 (47.2)	12 (11.3)
Fatigue	53 (50.0)	11 (10.4)
Asthenia	37 (34.9)	8 (7.5)
Hyperglycemia	12 (11.3)	7 (6.6)
Thrombocytopenia	44 (41.5)	7 (6.6)
Alanine aminotransferase increased	20 (18.9)	6 (5.7)

ITT, intent-to-treat; RECIST, Response Evaluation Criteria in Solid Tumors; TEAEs, treatment emergent adverse events

ESMO

Philip PA, et al. Ann Oncol. 2017

Any role for curative-intent resection?

RESECTION AFTER CHEMOTHERAPY

Group	Complete Response	Partial Response	Stable Disease	Progressive Disease	Explored/ All	Resected/ All	R0/ Resected	Resected/ Explored
All patients	3.9% [3.0%–4.9%] $I^2 = 44.7\%$ [28.1%–57.5%] ($n = 82$)	29.1% [24.5%–34.0%] $I^2 = 86.9\%$ [84.2%–89.1%] ($n = 75$)	43.9% [37.9%–50.0%] $I^2 = 87.7\%$ [85%–89.9%] ($n = 63$)	20.8% [17.3%–24.6%] $I^2 = 81.4\%$ [77.3%–84.8%] ($n = 78$)	69.5% [62.1%–76.4%] $I^2 = 95.5\%$ [94.9%–96%] ($n = 88$)	50.7% [44.0%–57.4%] $I^2 = 95.2\%$ [94.6%–95.7%] ($n = 111$)	79.6% [74.8%–83.9%] $I^2 = 81.3\%$ [77.4%–84.6%] ($n = 86$)	77.9% [72.4%–82.9%] $I^2 = 89\%$ [87%–90.6%] ($n = 88$)
Tumor resectable before treatment (group 1)	3.6% [2.0%–5.5%] $I^2 = 53.9\%$ [29.3%–70%] ($n = 28$)	30.6% [20.7%–41.4%] $I^2 = 90.3\%$ [86.7%–92.9%] ($n = 23$)	42.1% [30.5%–54.1%] $I^2 = 91.4\%$ [88.4%–93.6%] ($n = 23$)	20.9% [16.9%–25.3%] $I^2 = 66.9\%$ [51.2%–77.5%] ($n = 29$)	88.1% [82.9%–92.4%] $I^2 = 86.2\%$ [81.5%–89.7%] ($n = 32$)	73.6% [65.9%–80.6%] $I^2 = 90.1\%$ [87.3%–92.3%] ($n = 35$)	82.1% [73.1%–89.6%] $I^2 = 89.3\%$ [85.5%–92%] ($n = 26$)	85.7% [78.9%–91.2%] $I^2 = 88.6\%$ [85%–91.4%] ($n = 32$)
Tumor non-resectable before treatment (group 2)	4.8% [3.5%–6.4%] $I^2 = 33.9\%$ [3.4%–54.8%] ($n = 42$)	30.2% [24.5%–36.3%] $I^2 = 81.8\%$ [75.9%–86.2%] ($n = 40$)	41.6% [34.6%–48.7%] $I^2 = 75\%$ [64.2%–82.6%] ($n = 29$)	20.8% [14.5%–27.8%] $I^2 = 85.4\%$ [80.7%–88.9%] ($n = 36$)	46.9% [36.9%–57.1%] $I^2 = 93.7\%$ [92.2%–94.8%] ($n = 41$)	33.2% [25.8%–41.1%] $I^2 = 92.5\%$ [91%–93.7%] ($n = 57$)	79.2% [72.4%–85.2%] $I^2 = 70.2\%$ [59.7%–78%] ($n = 45$)	69.9% [61.2%–77.9%] $I^2 = 79.9\%$ [73.3%–84.9%] ($n = 41$)

Group	Estimated Median Survival (m_p)		Estimated Survival Probability (Resected)	
	Resected (Range)	Not Resected (Range)	1 Year (Range)	2 Year (Range)
All patients	22.4 (9–62) ($n = 70$)	9.5 (6–21) ($n = 51$)	78.9% (0%–100%) $I^2 = 48.1\%$ [28.7%–62.3%] ($n = 54$)	49.2% (0%–82%) $I^2 = 85.2\%$ [80.5%–88.7%] ($n = 37$)
Tumor resectable before treatment (group 1)	23.3 (12–54) ($n = 27$)	8.4 (6–14) ($n = 19$)	77.9% (48%–100%) $I^2 = 70.7\%$ [52.6%–81.8%] ($n = 18$)	47.4% (25%–70%) $I^2 = 69.1\%$ [42.2%–83.4%] ($n = 11$)
Tumor non-resectable before treatment (group 2)	20.5 (9–62) ($n = 29$)	10.2 (6–21) ($n = 25$)	79.8% (0%–100%) $I^2 = 92.1\%$ [89.8%–93.9%] ($n = 29$)	50.1% (0%–82%) $I^2 = 88.6\%$ [84%–91.9%] ($n = 21$)

N 111 studies

Gillen S, et al. PLoS Med 2010

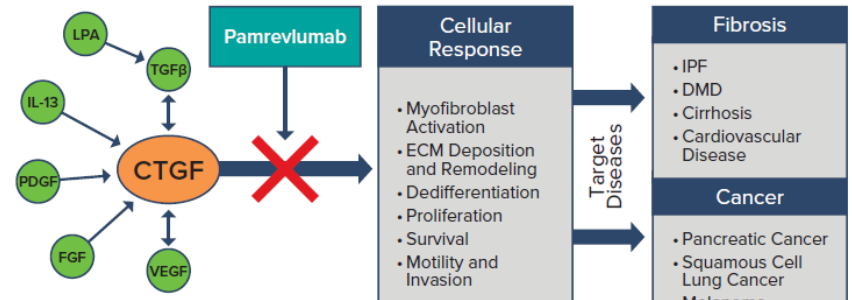
EXTENDED SURGERY: VASCULAR RESECTION

- **Venous resection**[1]
  - 28 studies (retrospective), 1458 patients
    - Median mortality rate: 4%
    - Median average length of stay: 17 days
    - Median R0: 75%
    - In high volume centers, the median survival was 15 months
- **Arterial resection (AR)**[2]
  - 26 studies (retrospective)
    - No AR: 2243 patients
    - AR: 336 patients
  - Increase in perioperative mortality OR: 5.04 (95% CI: 2.69-9.45)
  - Poor survival
    - 1 year OS: 49.1%
    - 3 year OS: 8.3% (5 year OS: 0%)
    - Pancreatectomy with AR was associated with more favourable OS compared with no IQ (OS 1 year OR: 4.28).

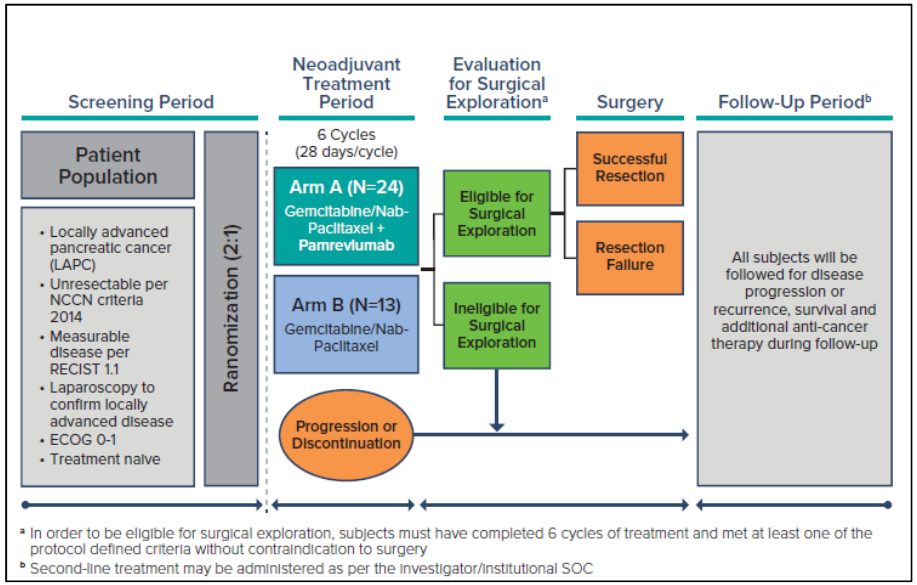
1. Chua TC, et al. J Gastrointest Surg 2010 2. Mollberg N, et al. Ann Surg 2011

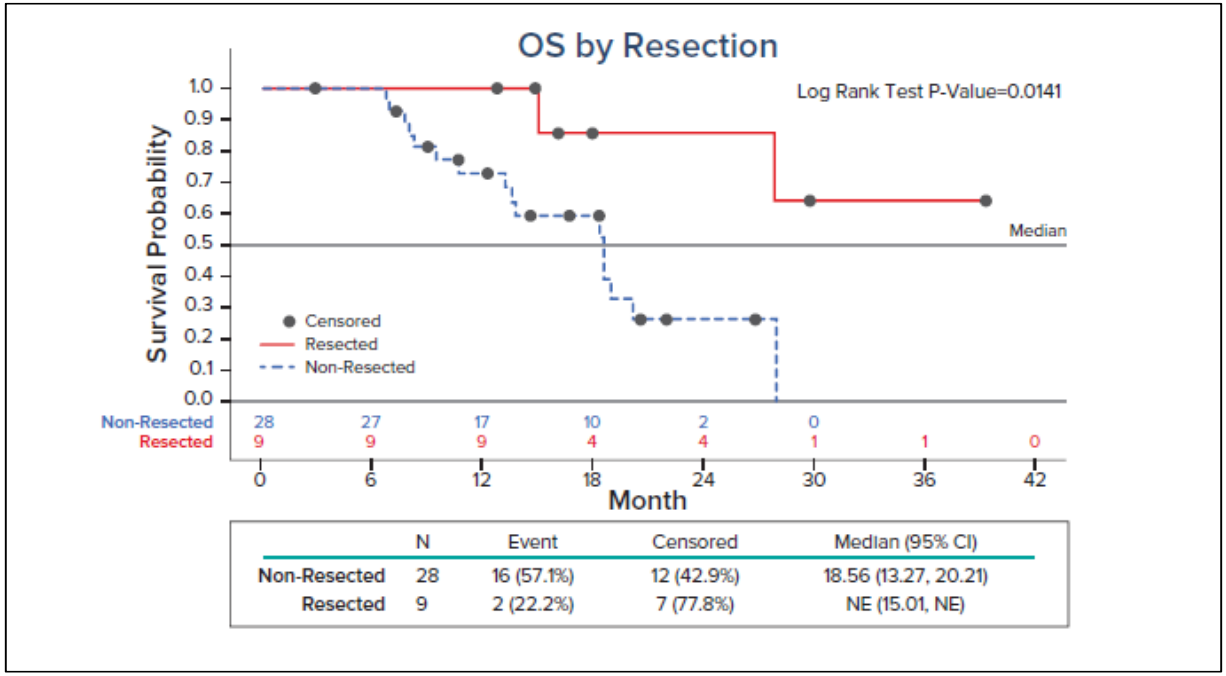
New drugs under investigator in LAPC

ANTI-CTGF HUMAN RECOMBINANT MONOCLONAL ANTIBODY PAMREVLUMAB



Connective tissue growth factor (CTGF)

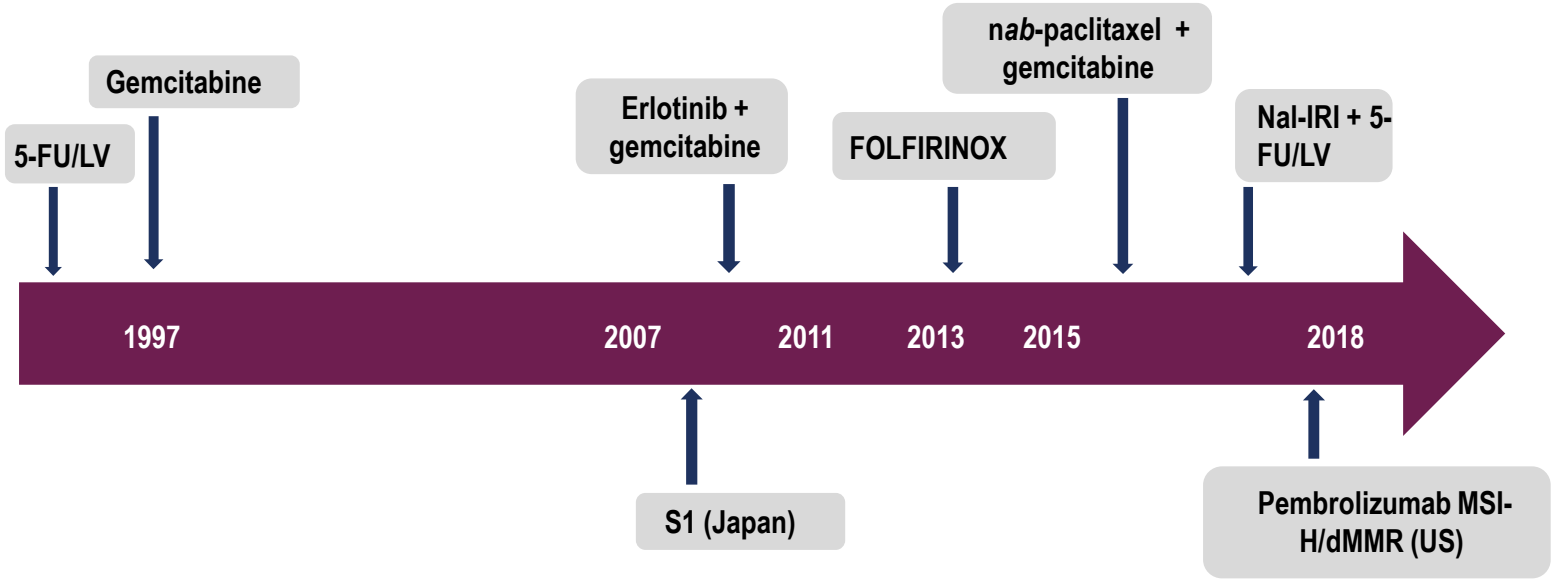




Picozzi et al, ASCO 2018

METASTATIC PDAC

EVOLUTION OF TREATMENT OF METASTATIC PANCREATIC CANCER: THE STORY SO FAR

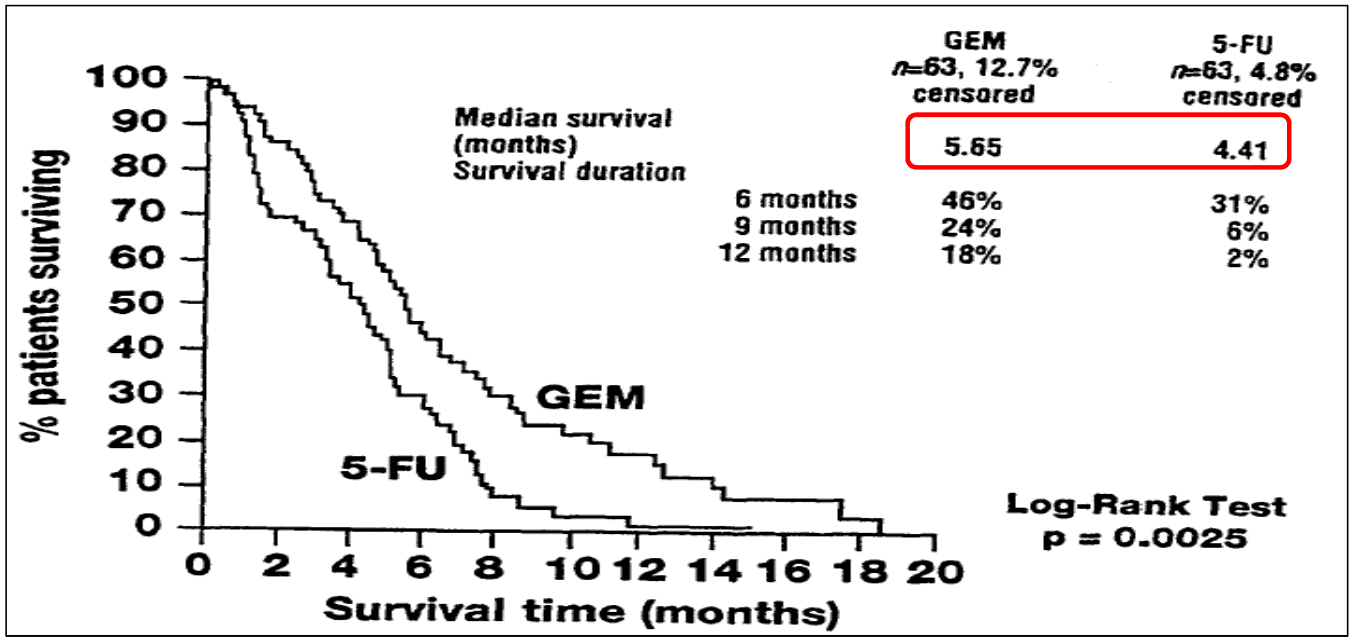


5-FU, 5-fluorouracil; dMMR, mismatch repair deficient; LV, leucovorin; mPCA, metastatic pancreatic adenocarcinoma; MSI-H, microsatellite instability-high; Nal-IRI, nanoliposomal irinotecan

Glimelius B, et al. Ann Oncol 1996. Burris HA 3rd, et al. J Clin Oncol 1997. Ueno H, et al. J Clin Oncol 2013. Moore MJ, et al. J Clin Oncol 2007. Conroy T, et al. N Engl J Med 2011. Von Hoff DD, et al. N Engl J Med 2013. Wang-Gillam A, et al. Lancet 2016. Le DT, et al. N Engl J Med 2015.

EVOLUTION OF TREATMENT OF METASTATIC PANCREATIC CANCER: THE STORY SO FAR

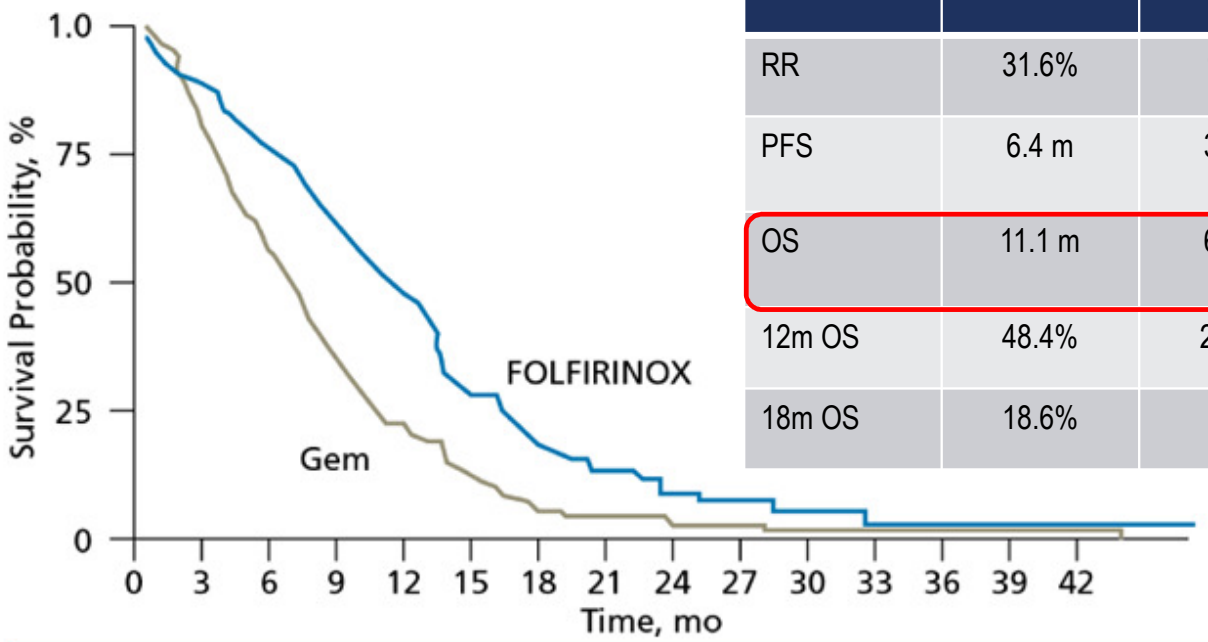
Improvements in Survival and Clinical Benefit With Gemcitabine as First-Line Therapy for Patients With Advanced Pancreas Cancer: A Randomized Trial



Treatment	n	Clinical Benefit	Median survival
5-FU	63	5 %	4.4 m
Gemcitabine	63	24 %	5.65 m

Burris H et al. J Clin Oncol 1997

FOLFIRINOX: PHASE II/III STUDY (PRODIGE 4 - ACCORD 11)



Outomes	FOLFIRINOX	Gemcitabine	HR p
RR	31.6%	9.4%	<0.001
PFS	6.4 m	3.3 m	0.47 <0.001
OS	11.1 m	6.8 m	0.57 <0.001
12m OS	48.4%	20.5%	
18m OS	18.6%	6%	

- Median follow-up 26.6 mo (95% CI, 20.5-44.9)
- OS analysis based on 273 deaths among 342 patients (79.8%)

[a] Investigator assessment.

Conroy T et al. NEJM. 2011

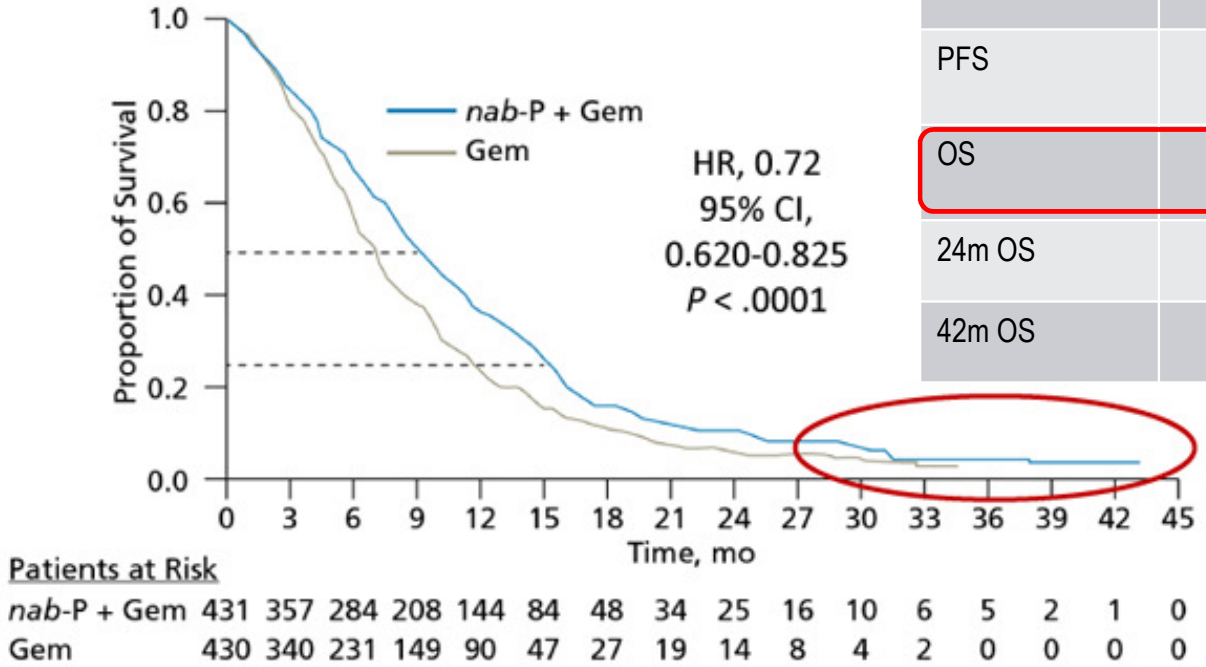
FOLFIRINOX: PHASE II/III STUDY (PRODIGE 4 - ACCORD 11)

Safety: Grade 3-4 TRAEs

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

Conroy T et al. NEJM. 2011

NAB-PACLITAXEL + GEMCITABINE: PHASE III STUDY (MPACT): SURVIVAL



Outomes	Gemcitabine – nab-Paclitaxel	Gemcitabine	HR, p
RR	23%	7%	<0.001
PFS	5.5 m	3.7 m	0.69 <0.001
OS	8.5	6.7	0.72 <0.001
24m OS	10%	5%	
42m OS	3%	0%	

Von Hoff D et al. NEJM. 2013

NAB-PACLITAXEL + GEMCITABINE: PHASE III STUDY (MPACT): GRADE 3-4 TRAES

Preferred Term	*nab*-P + Gem n = 421	Gem n = 402
AE leading to death, n (%)	18 (4)	18 (4)
Grade ≥ 3 hematologic AEs,[a] n/n (%)		
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)
Pts who received growth factors, n/n (%)	110/431 (**26**)	63/431 (15)
Febrile neutropenia,[b] n (%)	14 (**3**)	6 (1)
Grade ≥ 3 nonhematologic AEs[b] in > 5% of pts, n (%)		
Fatigue	70 (**17**)	27 (7)
Peripheral neuropathy[c]	70 (**17**)	3 (1)
Diarrhea	24 (6)	3 (1)
Grade ≥ 3 neuropathy		
Time to onset in days, median	140	113
Time to improvement by ≥ 1 grade in days, median	21	29
Time to improvement to grade ≤ 1 in days, median	**29**	NR
Use of *nab*-P resumed, n/n (%)	31/70 (44)	NA

[a] Based on lab values. [b] Based on investigator assessment of treatment-related AEs. [C] Groupings of preferred MedDRA terms.
AE, adverse event; Gem, gemcitabine; MedDRA, Medical Dictionary of Regulatory Activities; NA, not applicable; NR, not reported; *nab*-P, *nab*-paclitaxel; Pts, patients.

Von Hoff D et al. NEJM. 2013

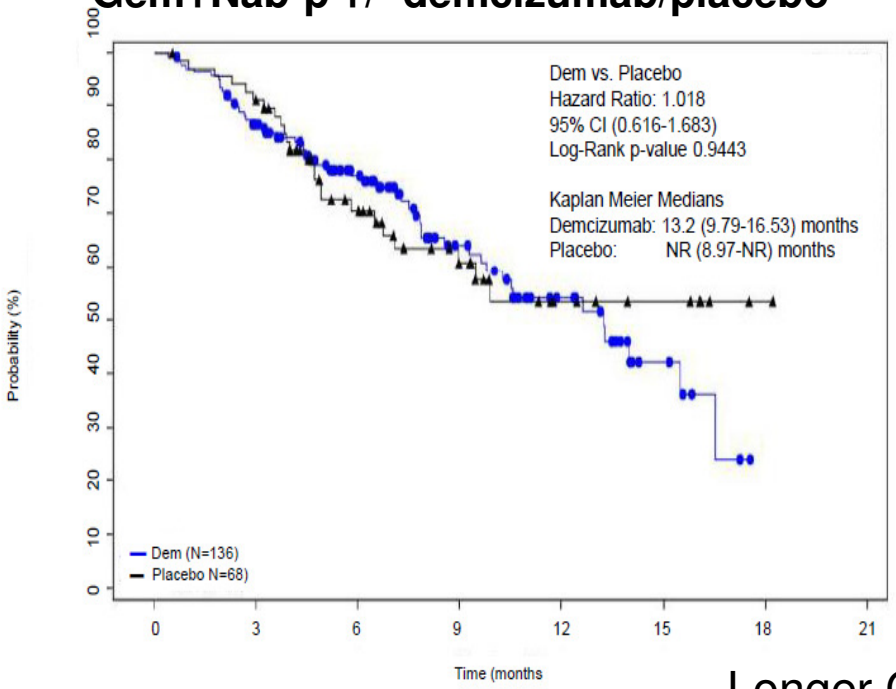
FIRST-LINE TREATMENT OF MPC: NAB-PACLITAXEL + GEMCITABINE OR FOLFIRINOX?

	nab-P/Gem (n = 431)	FOLFIRINOX (n = 171)
Sites	Global	France
Age >75?	Yes	?
PS	0-2	0-1
Efficacy		
RR,%	29	31.6
PFS, months	5.5	6.4
OS (updated), months	8.7	11.1
1 year, %	35	48
Safety, G≥3 events, %		
Febrile neutropenia	3	5
Growth factors	26	43
Fatigue	17	24
Vomiting	3	15
Diarrhoea	6	13
Neuropathy	17	9

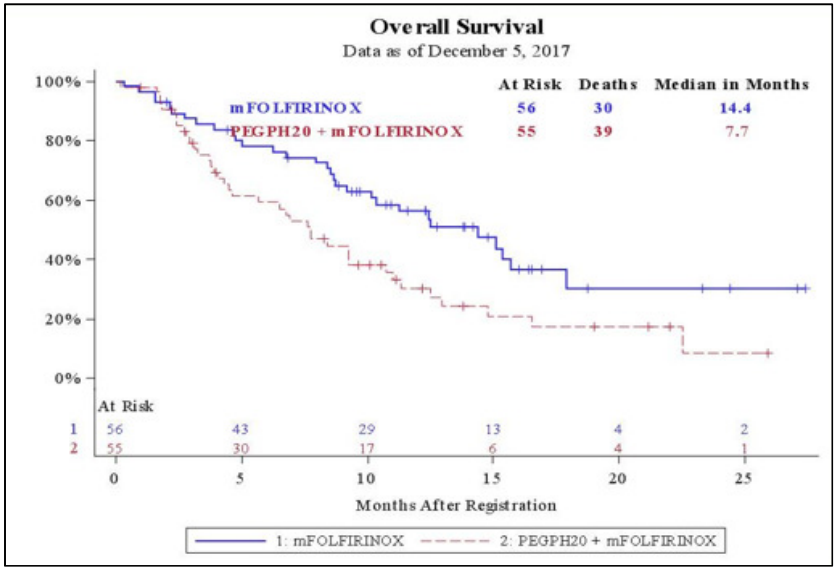
Von Hoff DD, et al. N Engl J Med 2013; Goldstein D, et al. J Natl Cancer Inst 2015; Conroy T, et al. N Engl J Med 2011

LONGER OS WITH FOLFIRINOX AND NAB-P + GEMCITABINE THAN IN PIVOTAL TRIALS

mOS in the YOSEMITE trial: Gem+Nab-p +/- demcizumab/placebo[1]



mOS in the SWOG S1313 trial: mFOLFIRINOX +/- PEGPH20[2]

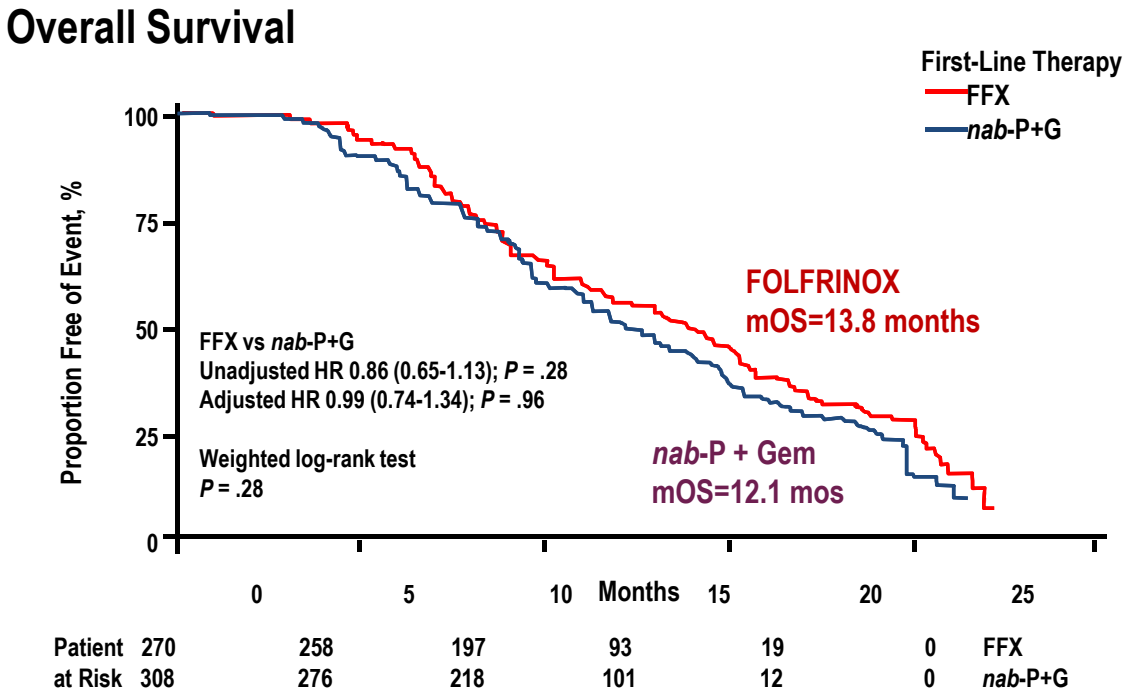


Longer OS than in pivotal trials:
Better management of the combined therapy?
Better options in 2L?

1.Cubillo A et al. Ann Oncol 2017; 2. Ramanathan RK et al. J Clin Oncol 2018

‘’REAL WORLD’’ DATA ANALYSIS: SIMILAR OS WITH 1L FOLFIRINOX AND *NAB*-PACLITAXEL/GEM IN MPC

- A retrospective study, 654 patients
- Data were colected from medical records by oncologists in the US to represent clinical practice



Kim SS, et al. J Clin Oncol 2018

IS SECOND LINE TREATMENT IN MPC A REALITY?

Treatment in 1L	% 2L	Rand trials	Options
FOLFIRINOX[1]	**46% mOS 4.4 m**	**No**	**Gem, Nab-p + Gem**
Nab-p + Gem[2]	**38% mOS 5.3 m**	**Napoli trial[3] mOS 6.1 m**	**Nal-IRI + 5-FU, FOLFOX, 5-FU**

- ✓ Close monitoring 1L, CT scan every 8-12 weeks
- ✓ We have available active 2L treatment regimens recommended by ESMO[4] and ASCO[5] guidelines

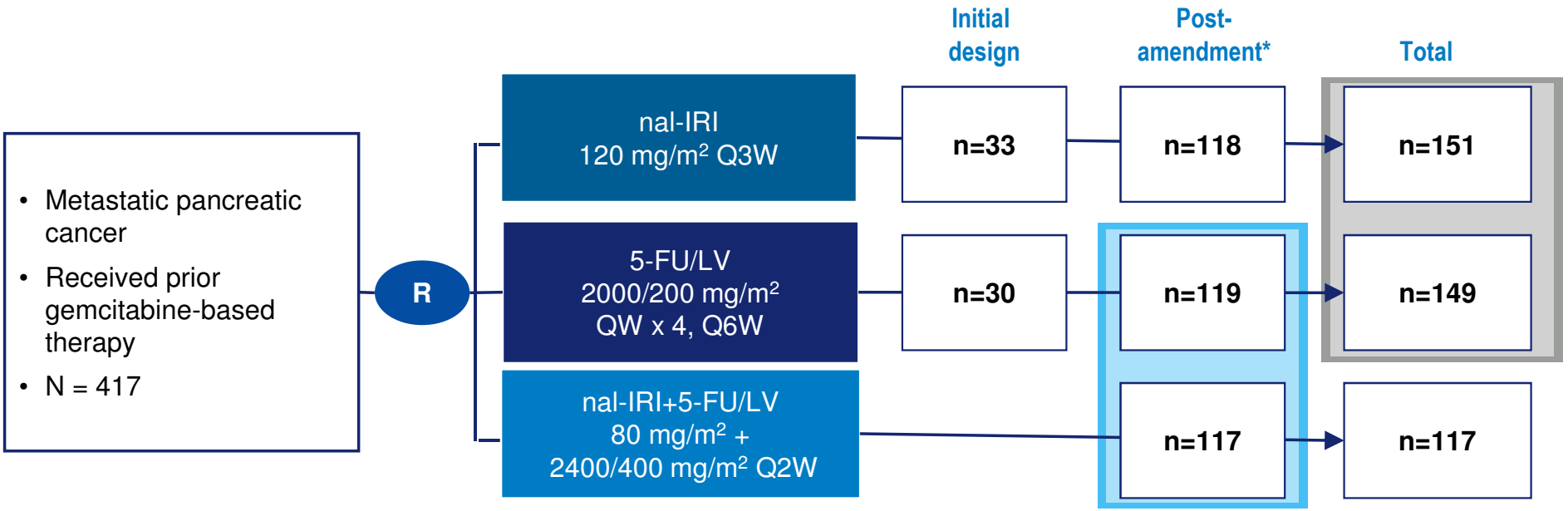
1.Conroy T, et al. N Engl J Med 2011. 2.Von Hoff DD et al. N Engl J Med 2013; 3.Wang-Gillam A, et al. Lancet 2016;
4. ESMO Guidelines Committee. Ann Oncol 2017; 5. Sohal D, et al. J Clin Oncol 2018.

SECOND-LINE OXALIPLATIN-BASED REGIMENS CONFLICTING RESULTS FROM PHASE III TRIALS

Pts [N = 268]	CONKO-003[1] PD on Gem Therapy [n = 160]		PANCREOX[2] Previous Gem Therapy [n = 108]	
Treatment	**OFF** (n = 76)	**5FU/LV** (n = 84)	**mFOLFOX6** (n = 54)	**5FU/LV** (n = 54)
OS, median	**5.9 months**	**3.3 months**	**6.1 months**	**9.9 months**
	HR 0.66 (95% CI, 0.48-0.91) *P* = .01		HR 1.78 (95% CI, 1.08-2.93) *P* = .02	
PFS, median	**2.9 months**	**2.0 months**	**3.1 months**	**2.9 months**
	HR 0.68 (95% CI, 0.50-0.94) *P* = .02		HR 1.00 (95% CI, 0.66-1.53) *P* = .99	

1. Oettle H et al. J Clin Oncol 2014; 2. Gill S et al. J Clin Oncol 2016.

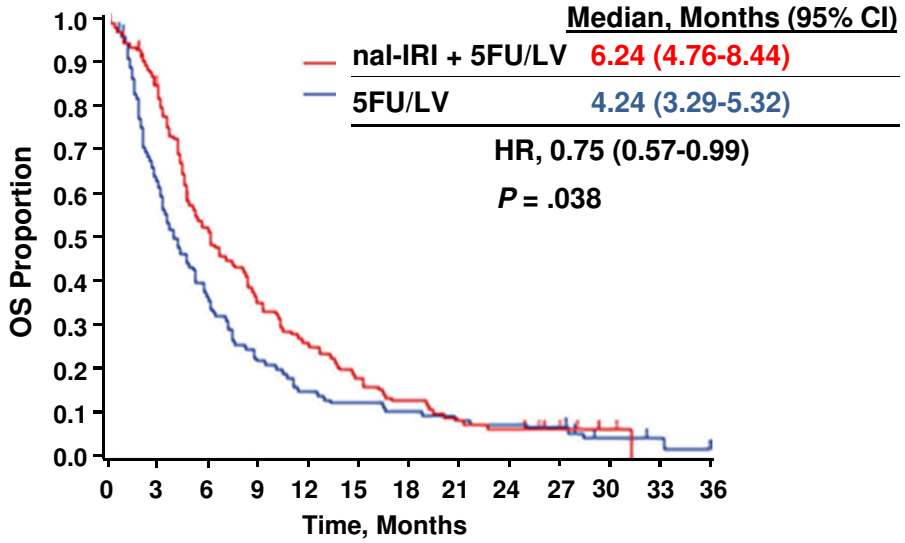
SECOND LINE LIPOSOMAL IRINOTECAN (NAL-IRI) + 5FU IN PATIENTS WHO PROGRESS ON GEMCITABINE-BASED THERAPY: PHASE III NAPOLI-1 TRIAL



Wang-Gillam A et al. Lancet 2016

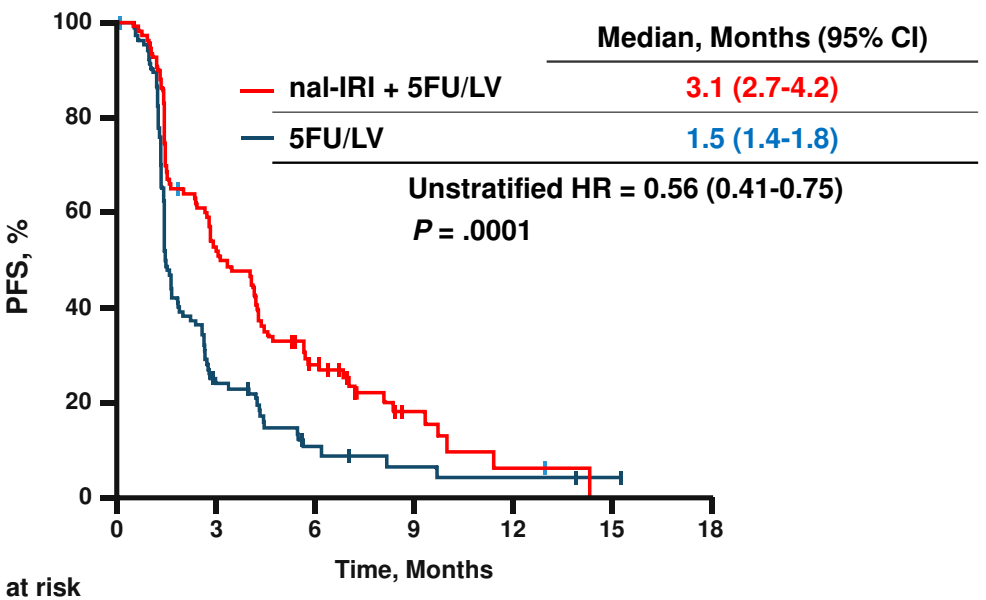
NAPOLI 1: OVERALL AND PROGRESSION FREE SURVIVAL

Updated Overall Survival[1]



Number at risk												
nal-IRI + 5FU/LV	117	97	59	40	29	21	15	10	8	5	2	0
5FU/LV	119	68	40	24	17	14	12	10	9	8	3	2

Progression Free Survival[2]



Number at risk							
nal-IRI + 5FU/LV	117	50	22	7	2	0	0
5FU/LV	119	23	8	3	2	1	0

23 (9.8%) patients surviving beyond 20 months

1. Chen L-T et al. Ann Oncol 2016; 2. Wang-Gillam A et al. Lancet 2016

NAPOLI 1: SAFET PROFILE

- Reported for ≥5% of patients, safety population

Grade ≥3 TEAE, %	nal-IRI + 5FU/LV (n = 117)	nal-IRI Monotherapy (n = 147)	5FU/LV (n = 134)
Any TEAE	80	76	56
Neutropenia	28	15	1
Fatigue	14	6	4
Diarrhea	13	21	5
Vomiting	12	14	4
Anemia	9	11	7
Asthenia	8	7	7
Nausea	8	5	3
Abdominal pain	7	8	7
Decreased appetite	5	9	2
Hypokalemia	3	12	2
Hyponatremia	3	6	2
Hyperglycemia	2	5	2

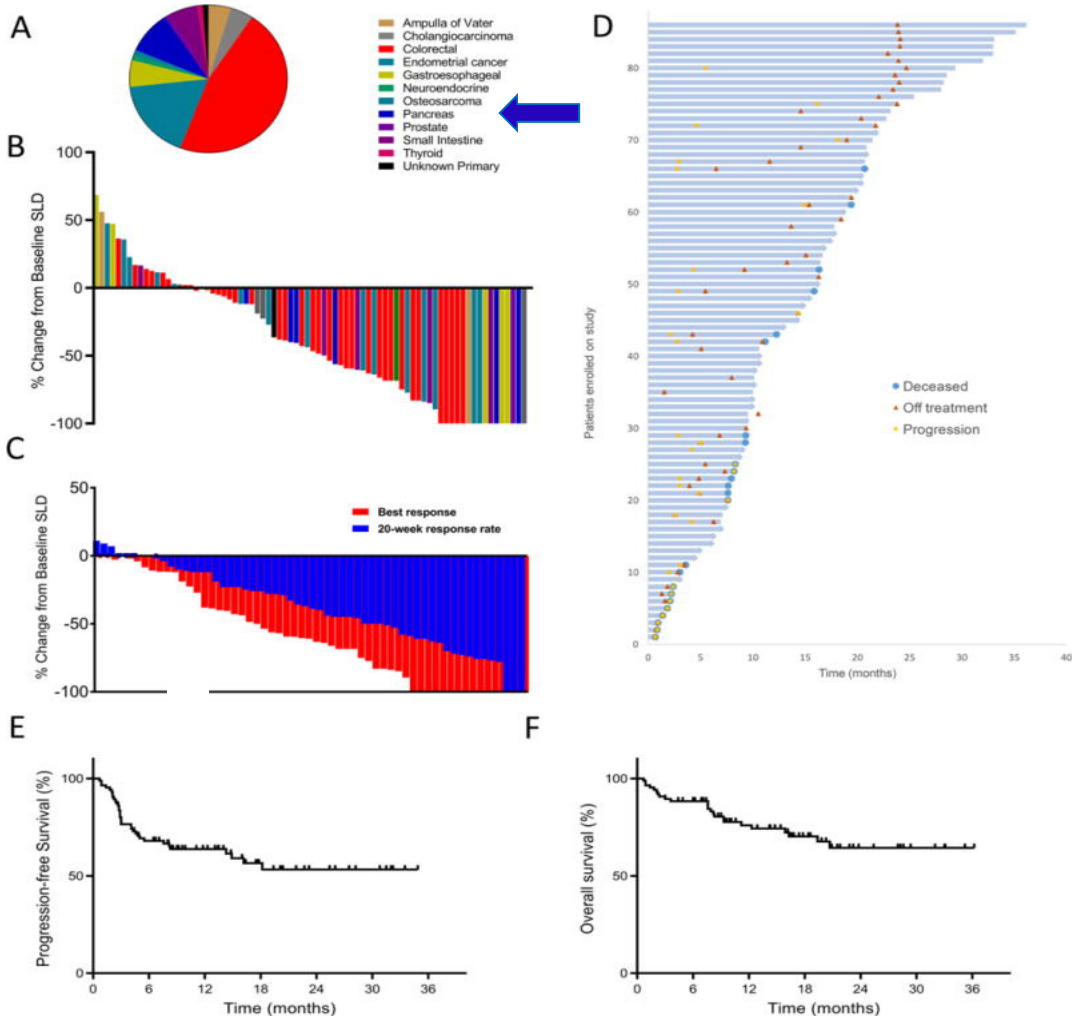
TEAE, treatment-emergent adverse event

Chen L-T et al. Ann Oncol 2016

PD-1 INHIBITION EFFECTIVE IN MSI-HIGH NON-CRC CANCERS

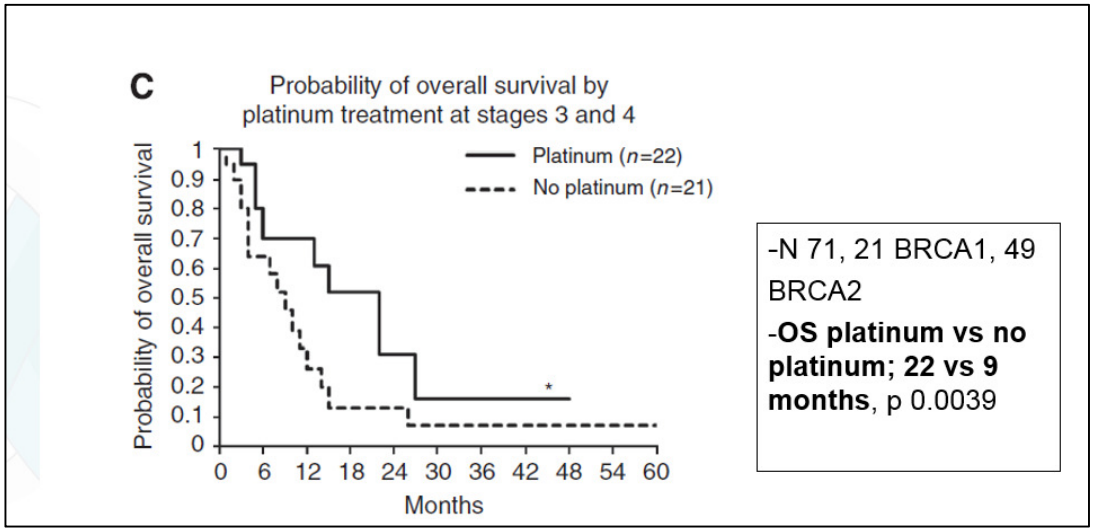
MSI-high/dMMR
Across 12 tumor types
N=86

- **Aprox. 1% mPC MSI-H/dMMR (IHC, PCR, NGS)**
- **Pembrolizumab FDA approved for MSI-H / dMMR**



Le D, et al. Science 2017

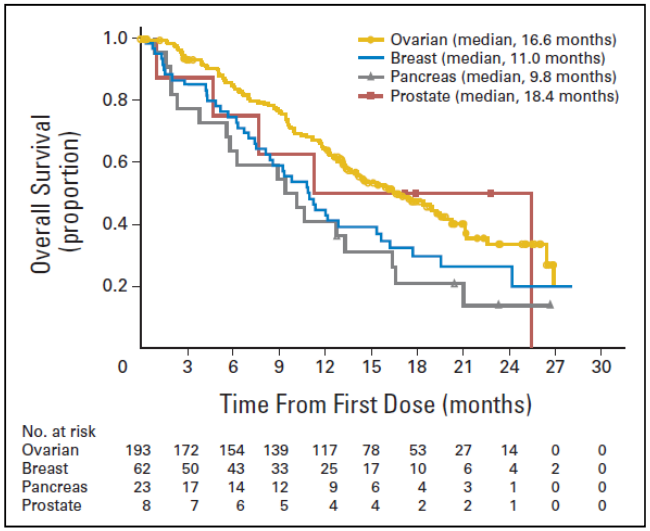
HOW DO WE HAVE TO TREAT PANCREATIC CANCER PATIENTS WITH BRCA 1 AND 2 MUTATED TUMORS?



-N 71, 21 BRCA1, 49 BRCA2

-**OS platinum vs no platinum; 22 vs 9 months**, p 0.0039

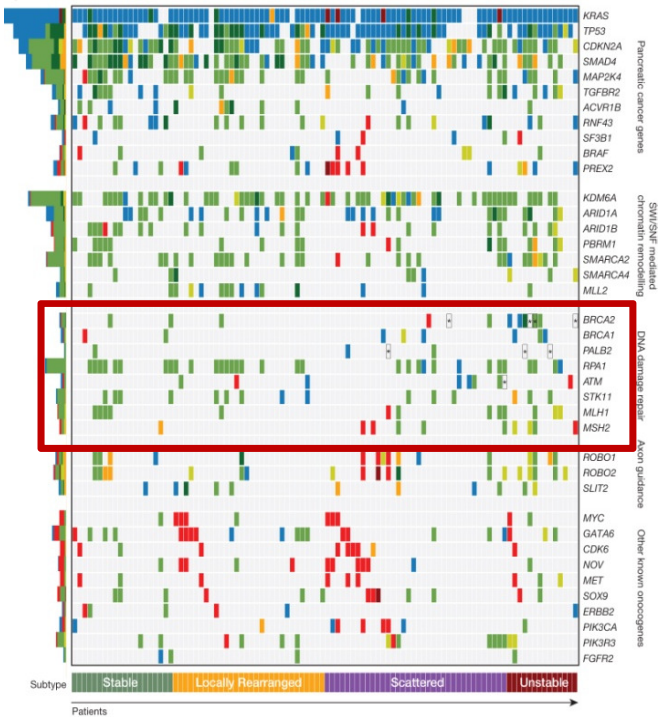
Platinum treatment

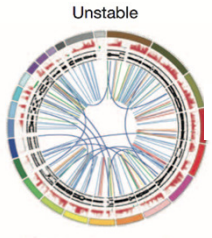


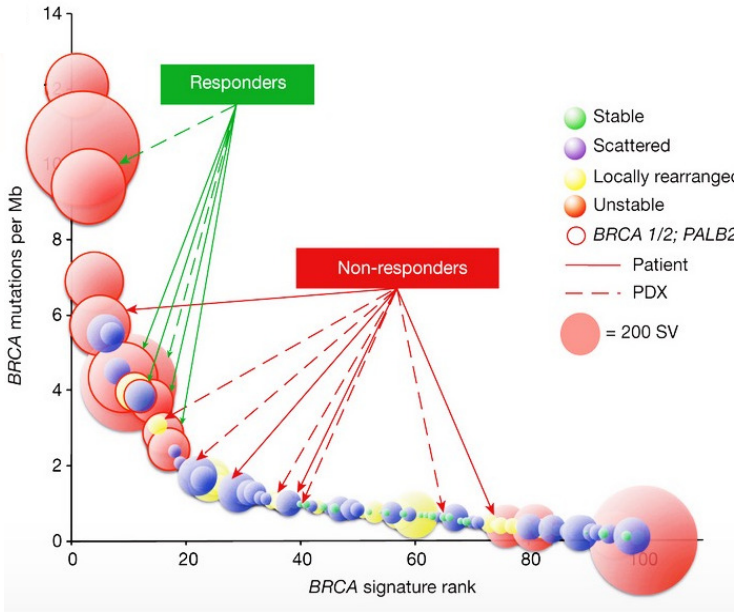
Olaparib treatment

1. Golan et al, Br J Cancer 2014; Kaufman et al, J Clin Oncol 2014

UNSTABLE GENOME AND BRCA SIGNATURE CORRELATE WITH RESPONSIVENESS TO PLATINUM-BASED THERAPY

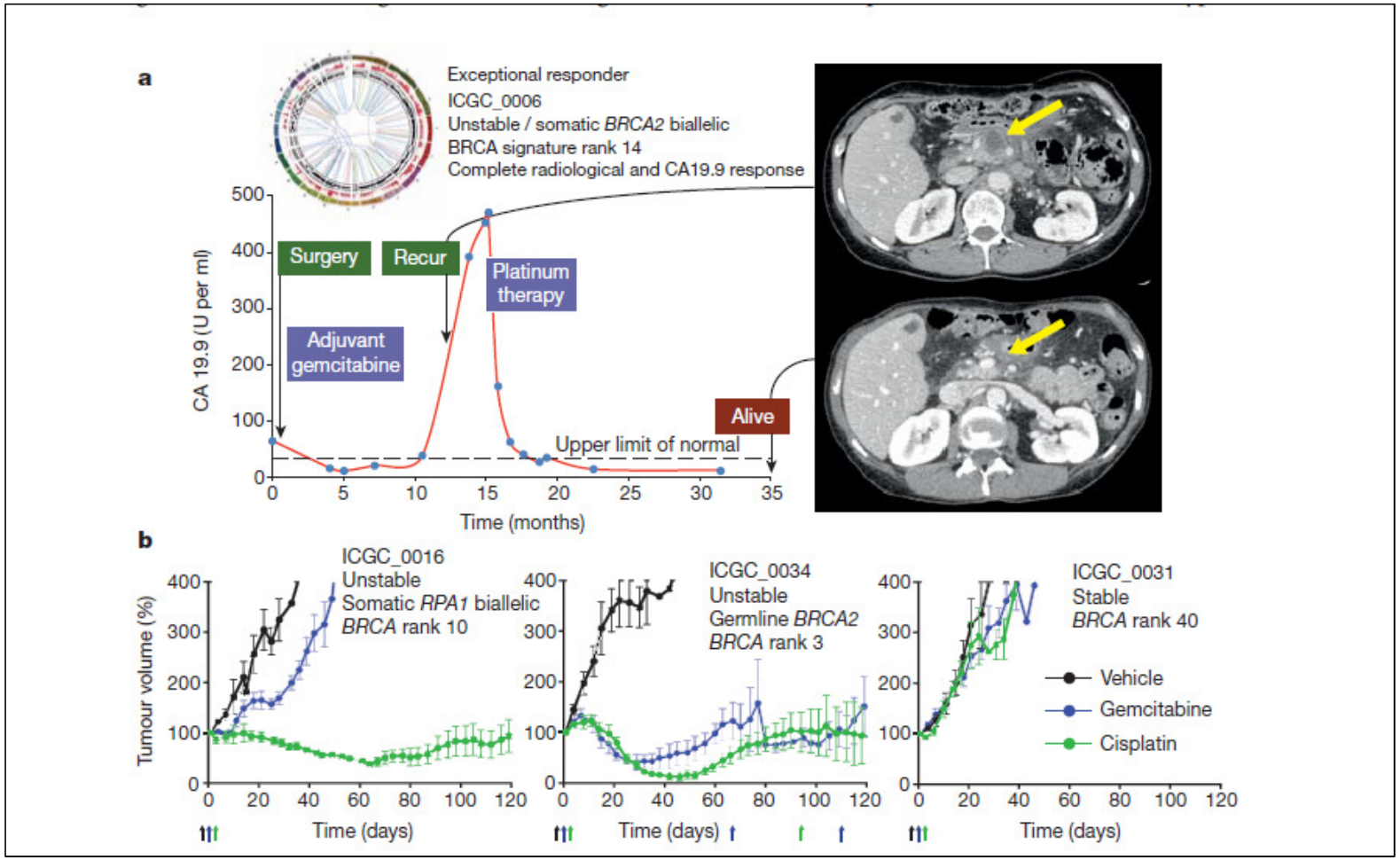






Waddell N et al. Nature 2015

RESPONSES TO PLATINUM THERAPY



Waddell N et al. Nature 2015

METASTATIC PDAC

Ongoing Phase III Studies in Metastatic PDAC

Therapeutic target	Treatment	Phase	Setting	NCT reference
Cancer cell stemness	Gem-nab +/- napabucasin	III	First line	02993731
Hialuronic acid	Gem-nab + PEGPH20/placebo	III	First line Hyaluronan-high tumours	02715804
Mitocondrial energy metabolism	mFOLFIRINOX + CPI613 or FOLFIRINOX	III	First line	0350442
Aminoacids metabolism	Chemo +/- eryspase	III	Second line	036645441

Clinicaltrials. gov

METASTATIC PDAC

Ongoing Studies in Metastatic PDAC with PARP inhibitors

Study	Setting	Phase	N	NCT reference
Olaparib vs placebo	Non progression on first-line platinum	III	145	02184195
GemCis+/- veliparib	First and subsequent lines	II	107	01585805
mFOLFOX6+ veliparib	First and subsequent lines	I/II	79	01489865
FOLFIRI vs mFOLFIRI + veliparib	Second line	II	143	02890355
Cediranib + olaparib	Multiples tumors	II	126	02498613

Clinicaltrials. gov

METASTATIC PDAC

Ongoing Studies in Metastatic PDAC with immunotherapy

Therapeutic target	Treatment	Phase	NCT reference
PD-1 + CTLA-4	Durvalumab + tremelimumab	II	02558894
CCR2	PF-04136309 + gemcitabine-nab-paclitaxel	II	02732937
CFS1R	Cabiralizumab + nivolumab vs chemotherapy	II	03336216
CFS1R	Pexidartinib + durvalumab	I	02777710
CD40	RO70097890 + gemcitabine-nab-paclitaxel	I	02588443

Clinicaltrials. gov

SUMMARY OF NON-METASTATIC PDAC

- Adjuvant FOLFIRINOX is a new standard of care for fit patients and very selected patients after resection in high-volume centers
- Many patients are still candidates for gemcitabine (+/- capecitabine)
- Data with gemcitabine /nab-paclitaxel are awaited
- In LA PDAC first approach is chemotherapy
- Which chemotherapy do we have to used in LA PDAC? Wait for randomized trials. It is understandable to use a combination—especially GEM/*nab*-paclitaxel (see LAPACT study, Philip P, et al)
- In LA PDAC we have to consider surgery in case of a response to systemic treatment, but be cautious with extended surgery

SUMMARY OF METASTATIC PDAC

- Treatment of advanced pancreatic cancer has incrementally improved in the past years
- FOLFIRINOX and nab-paclitaxel gemcitabine are two standard of care first-line therapeutic options with comparable benefit
- Performance status, comorbidities, age, and patient convenience should be considered in deciding the appropriate treatment
- The proportion of patients with mPC that are candidates to receive 2nd and even 3rd line therapy is increasing
- In Europe Nal-IRI+5FU is the only approved 2nd line treatment regimen based on level 1 evidence from a phase III trial
- Checkpoint inhibitors may induce a clinical response in MSI-H patients with mPC. PC with BRCA 1 and 2 gene mutations might be more sensitive to platinum or PARP inhibitors
- Moving treatment regimens from metastatic to earlier settings may impact the sequence of treatments
- Management of mPC should be considered as continuum approach

THANK YOU