LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
CAMPUS GROSSHADERN
MEDIZINISCHE KLINIK UND POLIKLINIK III UND COMPREHENSIVE CANCER CENTER (CCC[LMU])

ADJUVANT TREATMENT CONCEPTS IN PANCREATIC CANCER

Prof. Dr. Stefan Böck

CCC MÜNCHEN COMPREHENSIVE CANCER CENTER



Content

I am a medical oncologist (from the group of Volker Heinemann) … so I will (of course) talk about **adjuvant chemotherapy** for pancreatic ductal adenocarcinoma (PDAC)

- I will not talk about adjuvant ***radiotherapy***, as there is – at least in my opinion – still no evidence-based role for RT after resection of PDAC
- I will also not talk about ***biomarkers*** (e.g. hENT1, HR-DDR genes) in the adjuvant setting, as profound evidence supporting their use in routine clinical practice is still lacking

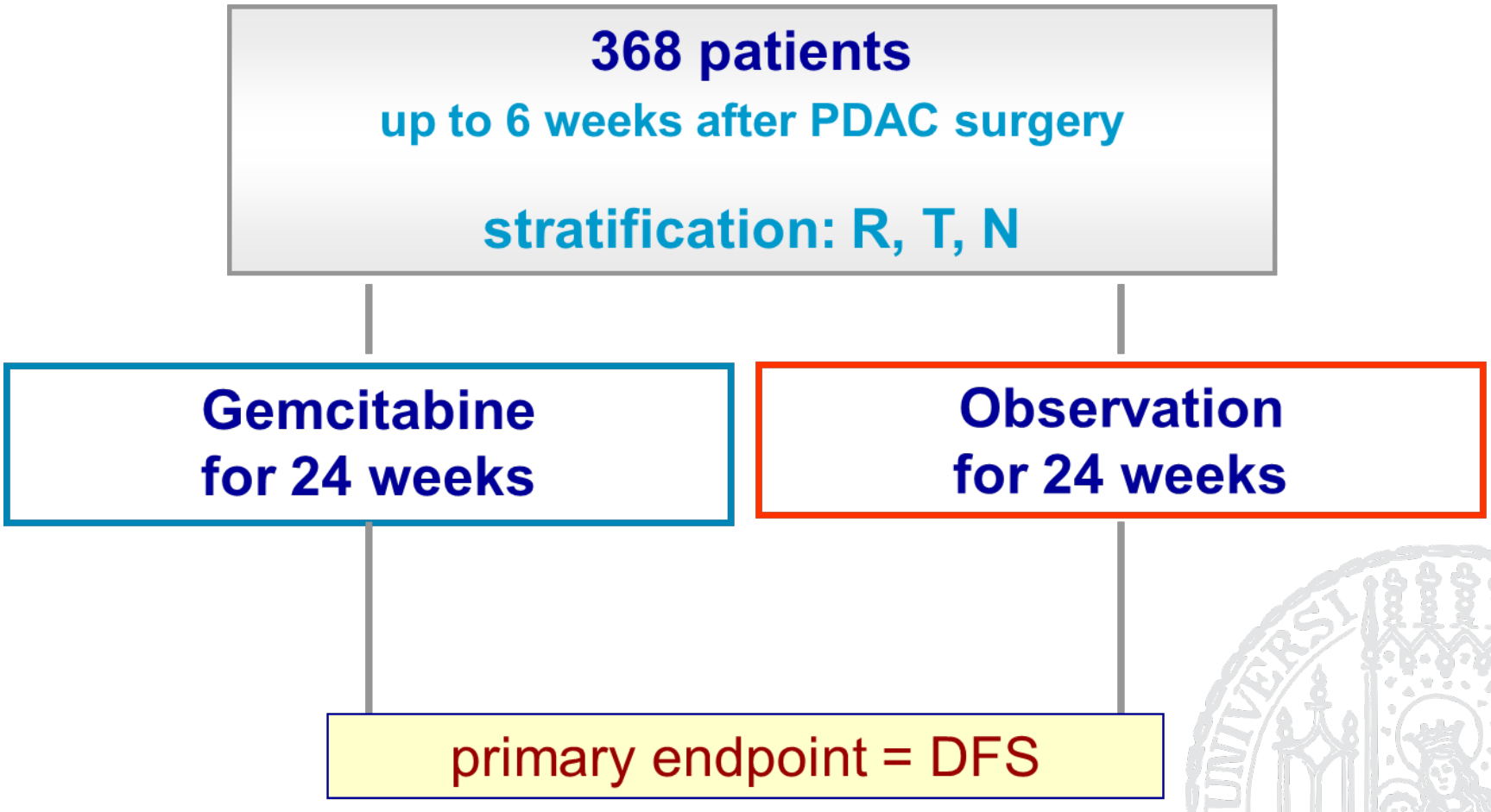
Important randomized phase III trials

CONKO-001 (2007/2013)	**Gem vs Observation**
JASP-02 (2009)	**Gem vs Observation**
ESPAC-3 (2010)	**Gem vs 5-FU/FA**
JASPAC-01 (2016)	**Gem vs S-1**
ESPAC-4 (2017)	**Gem vs Gem + Cap**
CONKO-005 (2017)	**Gem vs Gem + Erlotinib (R0)**
PRODIGE-24 (2018)	**Gem vs mFOLFIRINOX**
APACT (2019)*	**Gem vs Gem + nab-Paclitaxel**

* Abstract publication only

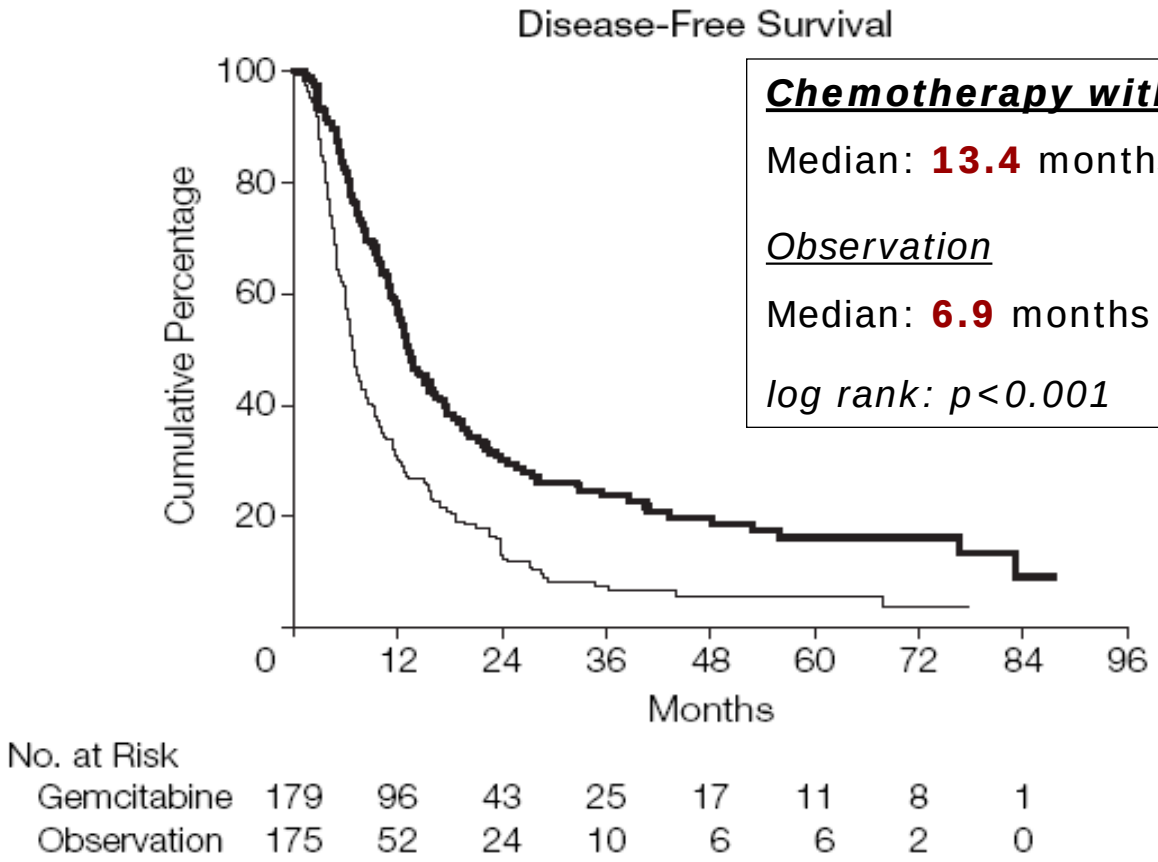
Gem: Gemcitabine; 5-FU: 5-Fluorouracil; FA: Folinic acid; Cap: Capecitabine

CONKO-001: Gemcitabine vs. Observation



Oettle H et al, JAMA 2007; 297: 267

CONKO-001: Gemcitabine vs. Observation



Chemotherapy with Gemcitabine

Median: **13.4** months (95% CI, 11.4; 15.3)

Observation

Median: **6.9** months (95% CI, 6.1; 7.8)

log rank: p<0.001

Oettle H et al, JAMA 2007; 297: 267

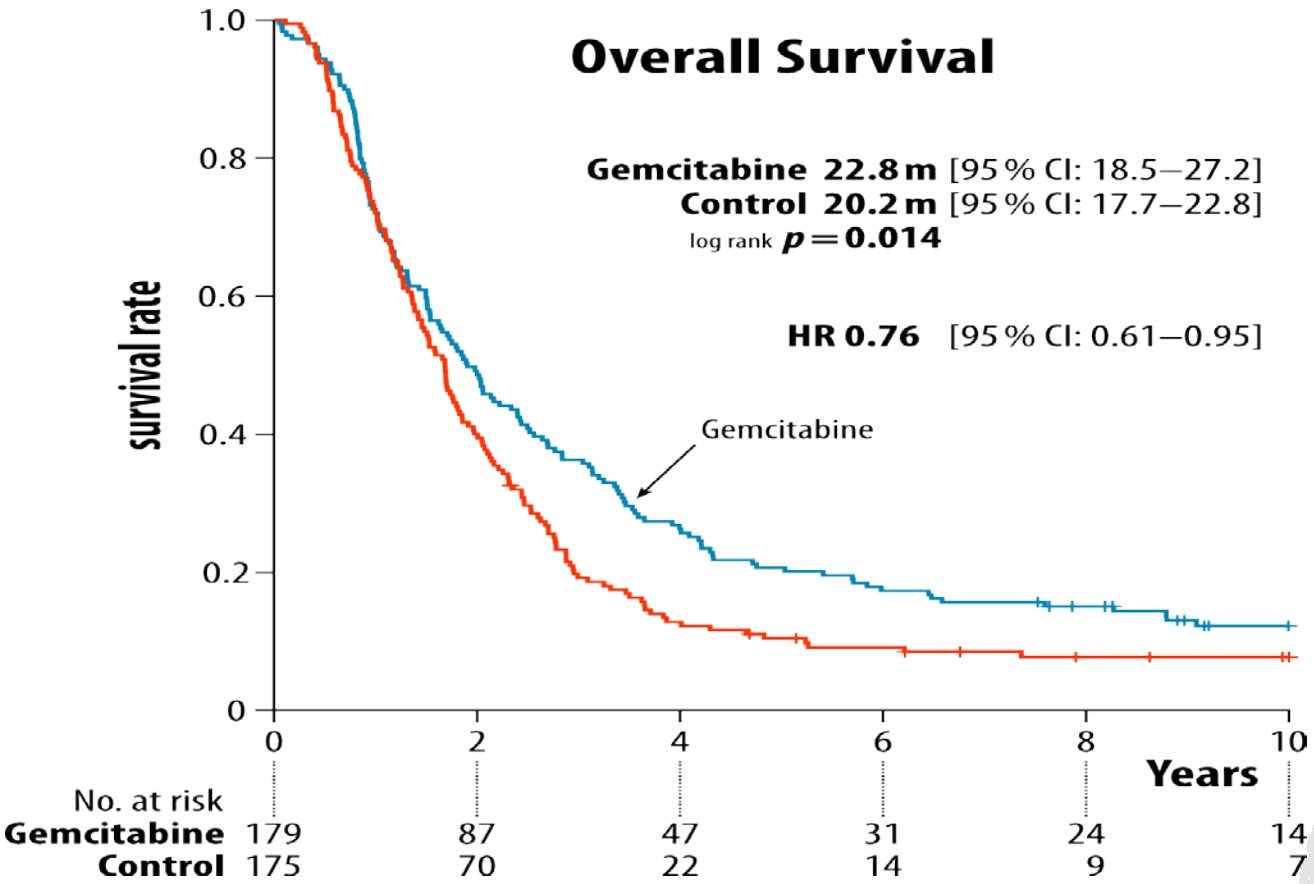
CONKO-001: Gemcitabine vs. Observation

	No. of Patients		Disease-Free Survival, Median (95% CI), mo		
	Gemcitabine	Observation	Gemcitabine	Observation	*P* Value*
All patients	179	175	13.4 (11.4-15.3)	6.9 (6.1-7.8)	<.001
R0	145	148	13.1 (11.6-14.6)	7.3 (5.9-8.7)	<.001
R1	34	27	15.8 (7.5-24.1)	5.5 (4.1-6.9)	<.001
N^-	52	48	24.8 (6.8-42.7)	10.4 (6.4-14.3)	.003
N^+	127	127	12.1 (10.7-13.4)	6.4 (5.7-7.2)	<.001
T1-2	25	24	48.2 (0-96.8)	10.0 (4.4-15.5)	.02
T3-4	154	151	12.9 (11.5-14.3)	6.7 (5.9-7.5)	<.001

Abbreviation: CI, confidence interval.
*Log-rank test.

Oettle H et al, JAMA 2007; 297: 267

CONKO-001: Gemcitabine vs. Observation



5-year OS:

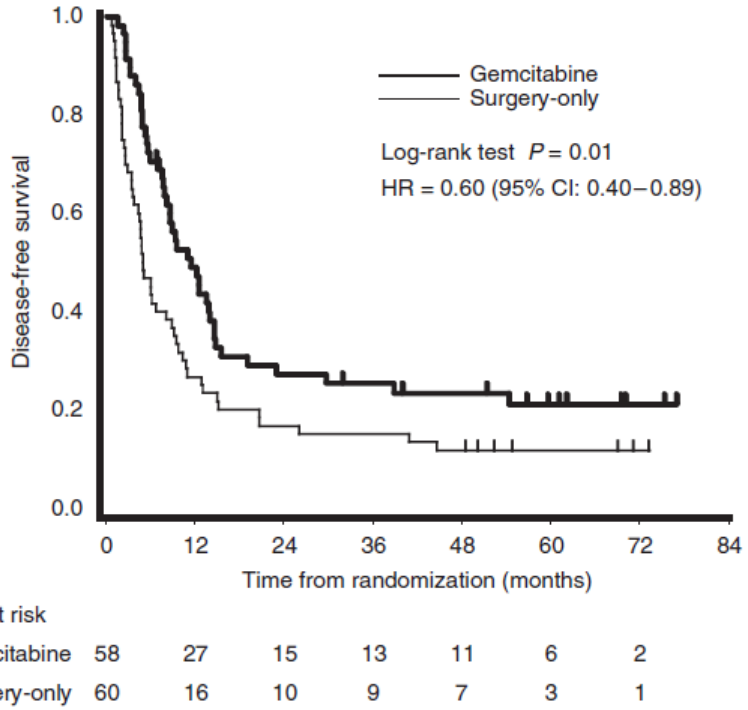
21 % vs. 10 %

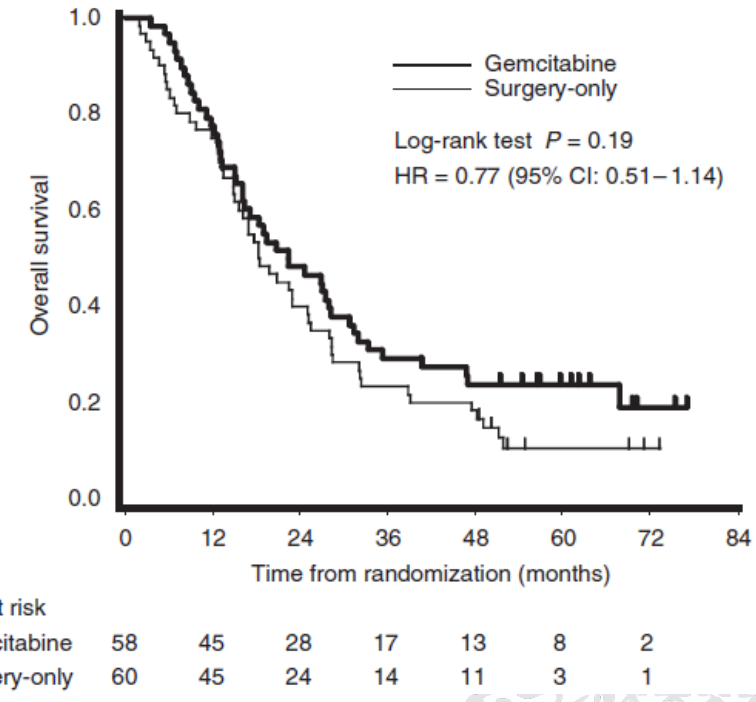
10-year OS:

12 % vs. 8 %

Oettle H et al, JAMA 2013; 310: 1473

JSAP-02: Gemcitabine vs. Observation





Gemcitabine 11.4 months

Observation 5.0 months

Gemcitabine 22.3 months

Observation 18.4 months

Ueno H et al, Br J Cancer 2009; 101: 908

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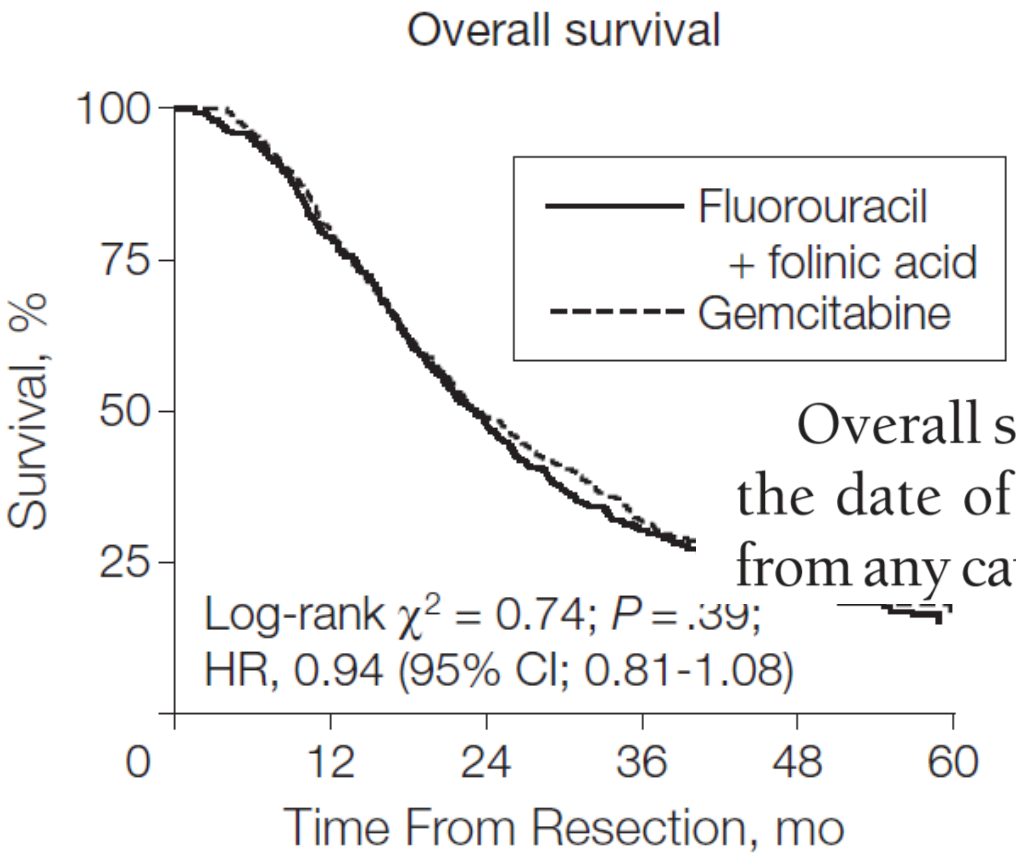
ESPAC-3v2: Gemcitabine vs. 5-FU/FA

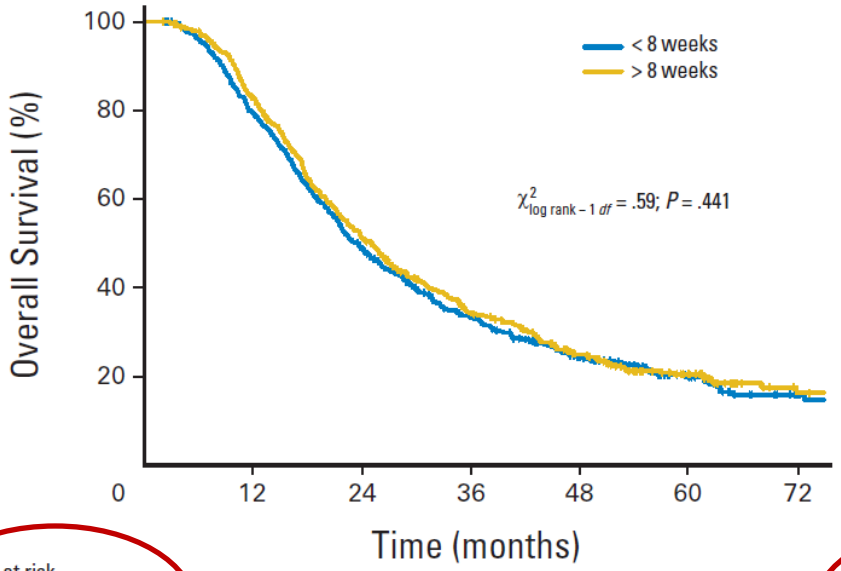


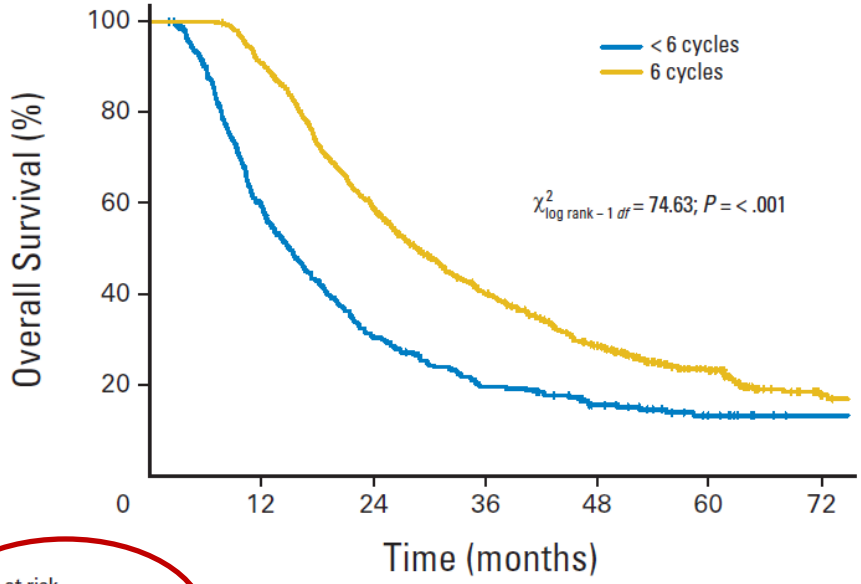
Overall survival was measured from the date of resection to date of death from any cause.

⇒ **Higher rates of non-hematological toxicity with 5-FU/FA (mainly stomatitis and diarrhea)**

Neoptolemos JP et al, JAMA 2010; 304: 1073

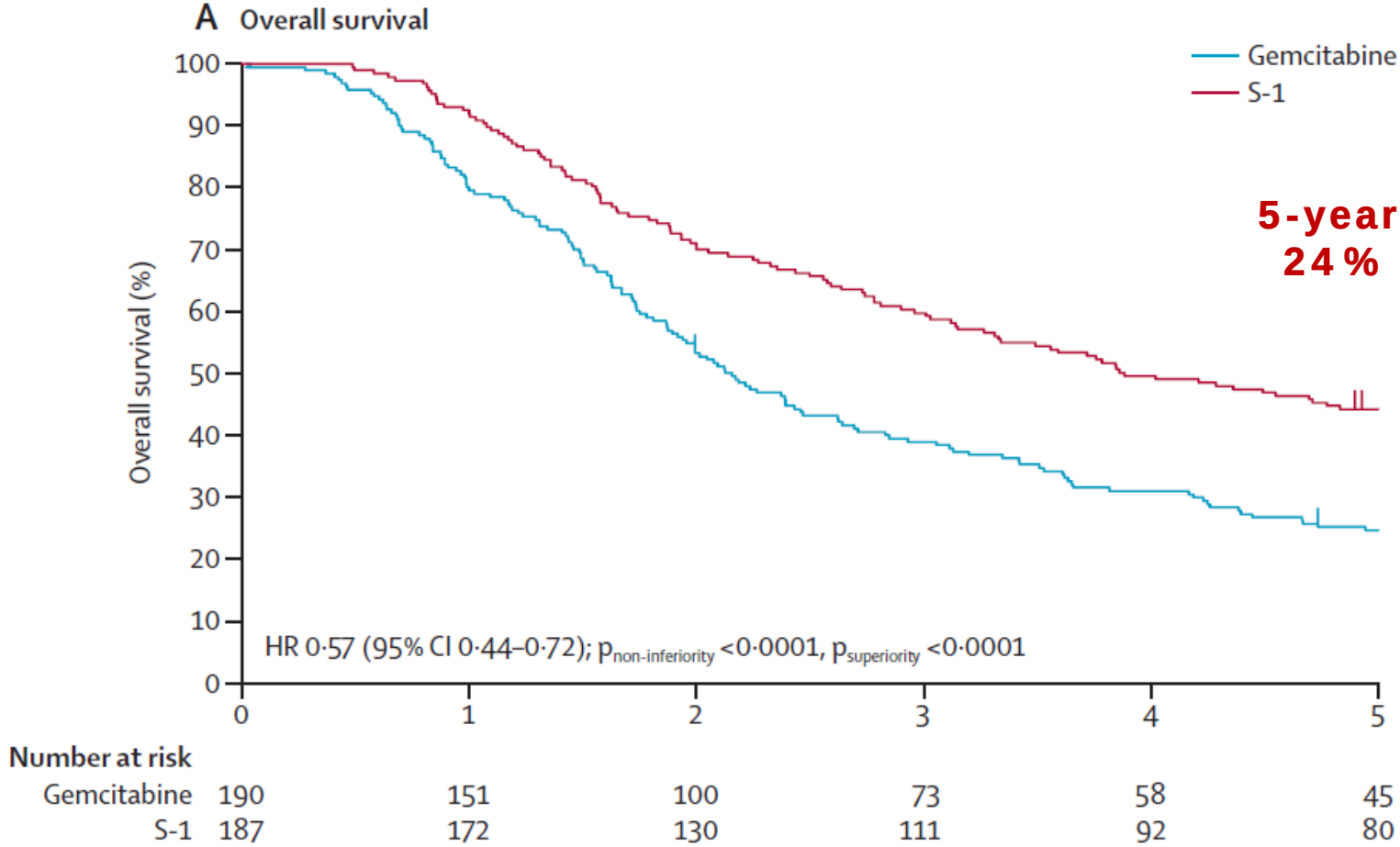
Optimal Duration and Timing of Adjuvant Chemotherapy After Definitive Surgery for Ductal Adenocarcinoma of the Pancreas: Ongoing Lessons From the ESPAC-3 Study





Valle JW et al, J Clin Oncol 2014; 32: 504

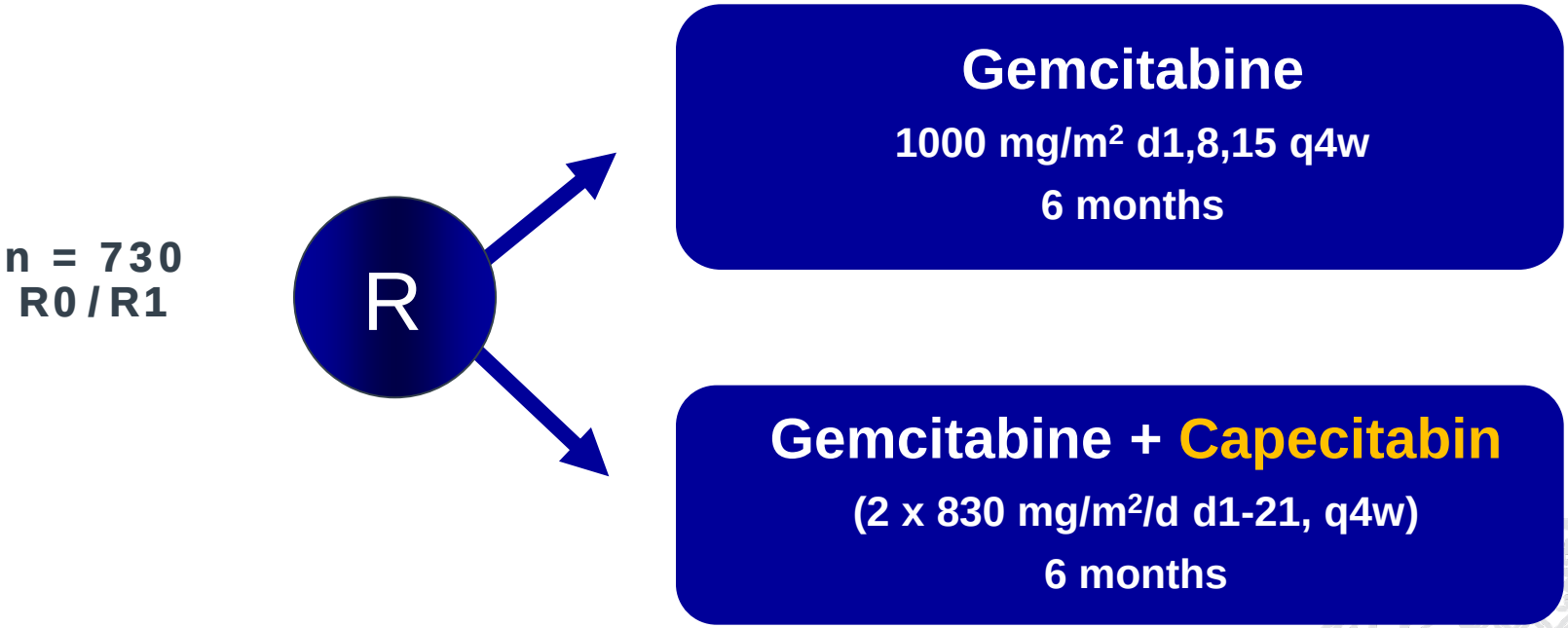
JASPAC-01: Gemcitabine vs. S-1 (Asia)



5-year OS rate:
24 % *vs* 44 %

Uesaka K et al, Lancet 2016; 388: 248

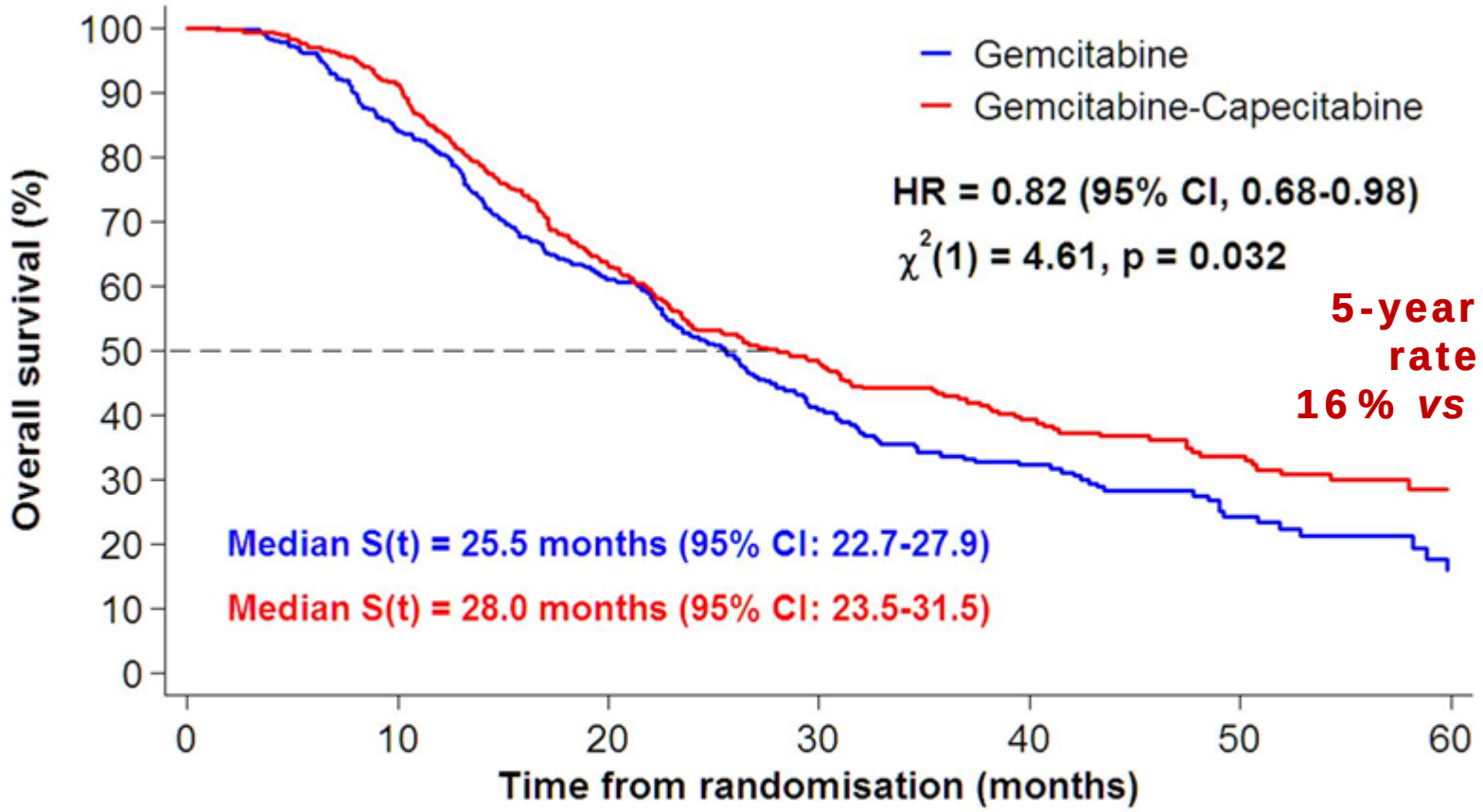
ESPAC-4: Gem vs. Gem + Capecitabine



Primary endpoint: OS (from randomization to death from any cause)

Neoptolemos JP et al, Lancet 2017; 389: 1011

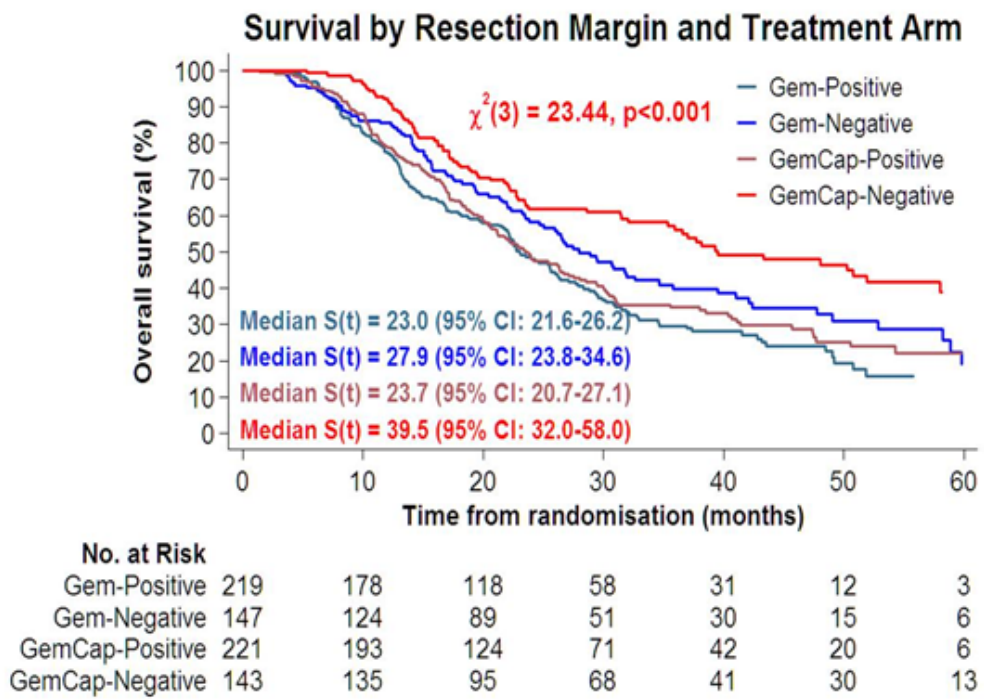
ESPAC-4: Gem vs. Gem + Capecitabine

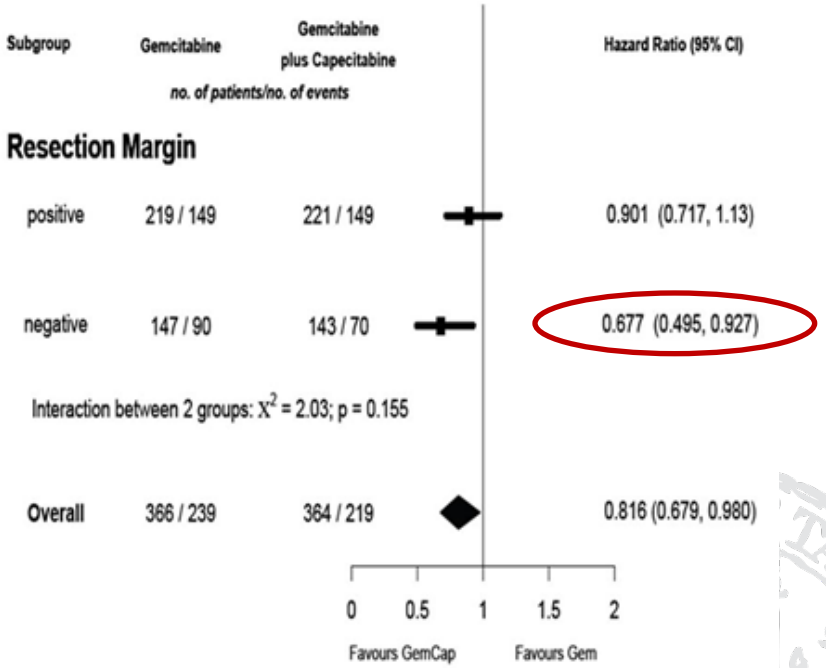


No. at Risk							
Gem	366	302	207	109	61	27	9
GemCap	364	328	219	139	83	50	19

ESPAC-4: Gem vs. Gem + Capecitabine

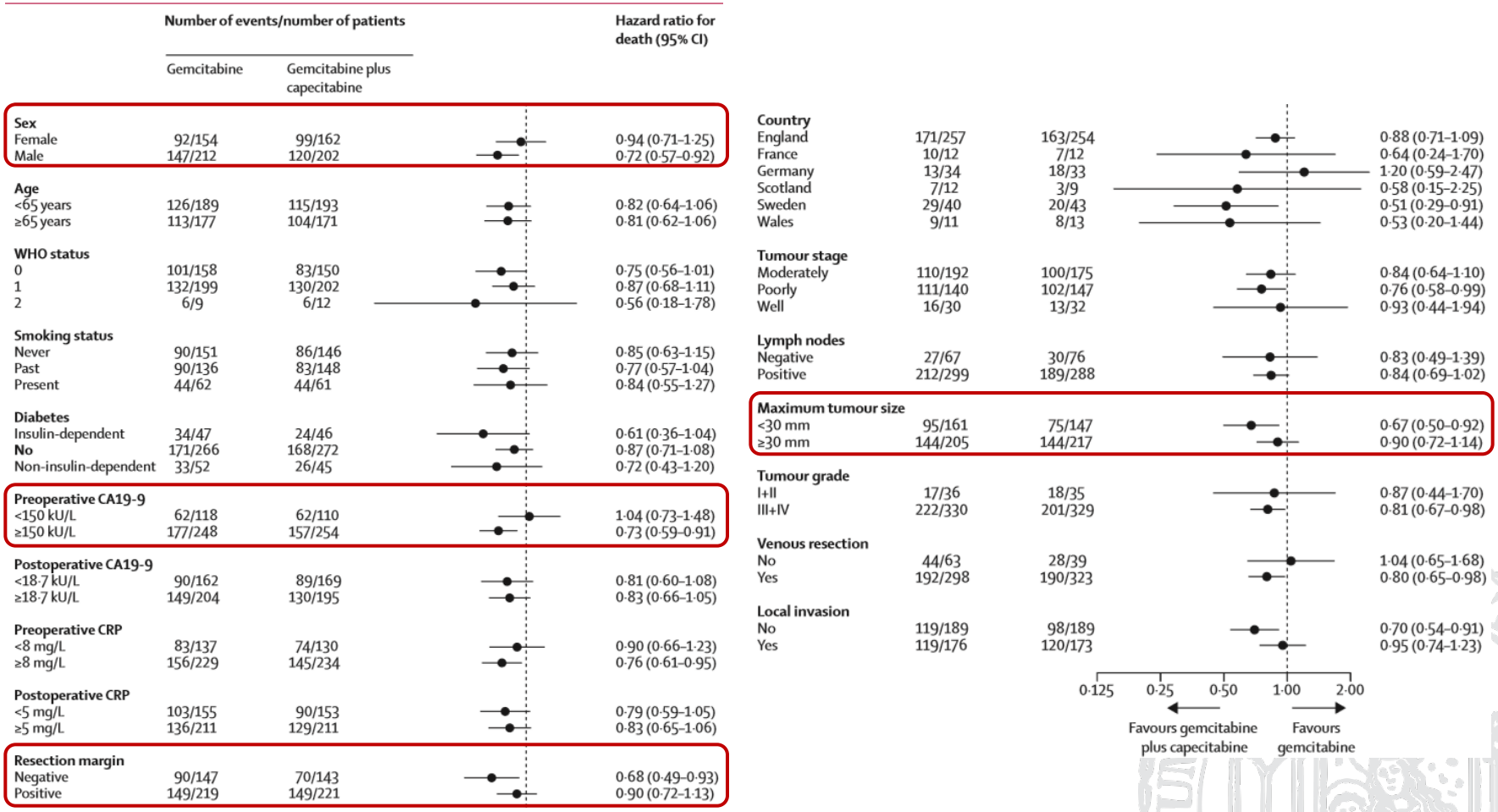
Treatment Effect by R-Status





Neoptolemos JP et al, Lancet 2017; 389: 1011

ESPAC-4: Gem vs. Gem + Capecitabine



	Number of events/number of patients		Hazard ratio for death (95% CI)
	Gemcitabine	Gemcitabine plus capecitabine	
Sex			
Female	92/154	99/162	0·94 (0·71–1·25)
Male	147/212	120/202	0·72 (0·57–0·92)
Age			
<65 years	126/189	115/193	0·82 (0·64–1·06)
≥65 years	113/177	104/171	0·81 (0·62–1·06)
WHO status			
0	101/158	83/150	0·75 (0·56–1·01)
1	132/199	130/202	0·87 (0·68–1·11)
2	6/9	6/12	0·56 (0·18–1·78)
Smoking status			
Never	90/151	86/146	0·85 (0·63–1·15)
Past	90/136	83/148	0·77 (0·57–1·04)
Present	44/62	44/61	0·84 (0·55–1·27)
Diabetes			
Insulin-dependent	34/47	24/46	0·61 (0·36–1·04)
No	171/266	168/272	0·87 (0·71–1·08)
Non-insulin-dependent	33/52	26/45	0·72 (0·43–1·20)
Preoperative CA19-9			
<150 kU/L	62/118	62/110	1·04 (0·73–1·48)
≥150 kU/L	177/248	157/254	0·73 (0·59–0·91)
Postoperative CA19-9			
<18·7 kU/L	90/162	89/169	0·81 (0·60–1·08)
≥18·7 kU/L	149/204	130/195	0·83 (0·66–1·05)
Preoperative CRP			
<8 mg/L	83/137	74/130	0·90 (0·66–1·23)
≥8 mg/L	156/229	145/234	0·76 (0·61–0·95)
Postoperative CRP			
<5 mg/L	103/155	90/153	0·79 (0·59–1·05)
≥5 mg/L	136/211	129/211	0·83 (0·65–1·06)
Resection margin			
Negative	90/147	70/143	0·68 (0·49–0·93)
Positive	149/219	149/221	0·90 (0·72–1·13)
Country			
England	171/257	163/254	0·88 (0·71–1·09)
France	10/12	7/12	0·64 (0·24–1·70)
Germany	13/34	18/33	1·20 (0·59–2·47)
Scotland	7/12	3/9	0·58 (0·15–2·25)
Sweden	29/40	20/43	0·51 (0·29–0·91)
Wales	9/11	8/13	0·53 (0·20–1·44)
Tumour stage			
Moderately	110/192	100/175	0·84 (0·64–1·10)
Poorly	111/140	102/147	0·76 (0·58–0·99)
Well	16/30	13/32	0·93 (0·44–1·94)
Lymph nodes			
Negative	27/67	30/76	0·83 (0·49–1·39)
Positive	212/299	189/288	0·84 (0·69–1·02)
Maximum tumour size			
<30 mm	95/161	75/147	0·67 (0·50–0·92)
≥30 mm	144/205	144/217	0·90 (0·72–1·14)
Tumour grade			
I+II	17/36	18/35	0·87 (0·44–1·70)
III+IV	222/330	201/329	0·81 (0·67–0·98)
Venous resection			
No	44/63	28/39	1·04 (0·65–1·68)
Yes	192/298	190/323	0·80 (0·65–0·98)
Local invasion			
No	119/189	98/189	0·70 (0·54–0·91)
Yes	119/176	120/173	0·95 (0·74–1·23)

Neoptolemos JP et al, Lancet 2017; 389: 1011

Phase III study	Disease-free survival[#] [median; months]		Overall survival [median; months]	
	Reference arm	Experimental arm	Reference arm	Experimental arm
JSAP-02[3] (*N=119*)	**5.0*** (Observation)	**11.4*** (Gemcitabine)	**18.4** (Observation)	**22.3** (Gemcitabine)
CONKO-001[2] (*N=368*)	**6.7*** (Observation)	**13.4*** (Gemcitabine)	**20.2*** (Observation)	**22.8*** (Gemcitabine)
JASPAC 01[4] (*N=385*)	**11.3*** (Gemcitabine)	**22.9*** (S-1)	**25.5*** (Gemcitabine)	**46.5*** (S-1)

"Eight patients who had stage IV pancreatic tumours but had complete surgical clearance and were anxious to join the trial were enrolled in the study." (ESPAC-4)

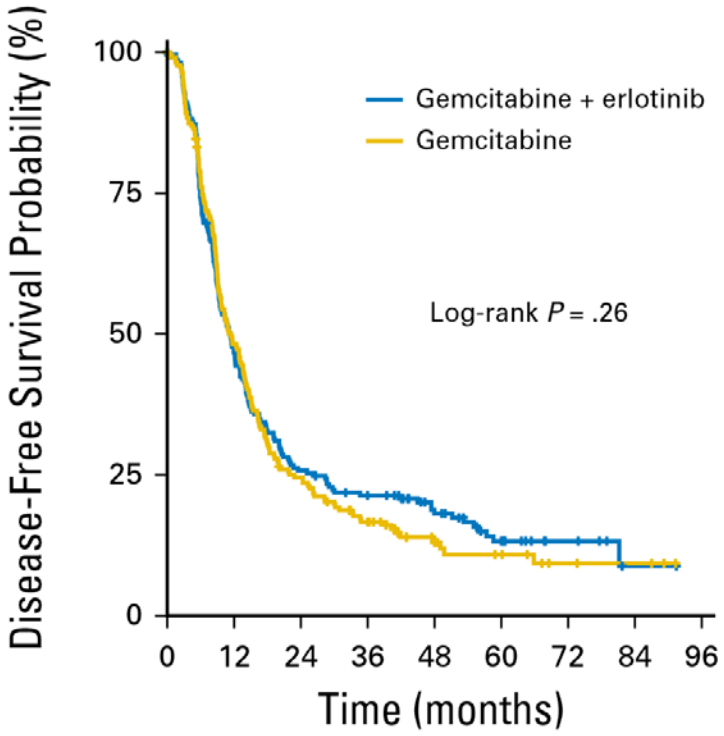
[#] JASPAC 01 and ESPAC-4 reported relapse-free survival

* p<0.05

To discuss ESPAC-4:
- Follow-up schedule
- Unexpected low rate of salvage treatments upon relapse (39% / 33%); recruitment period: *2008-2014*

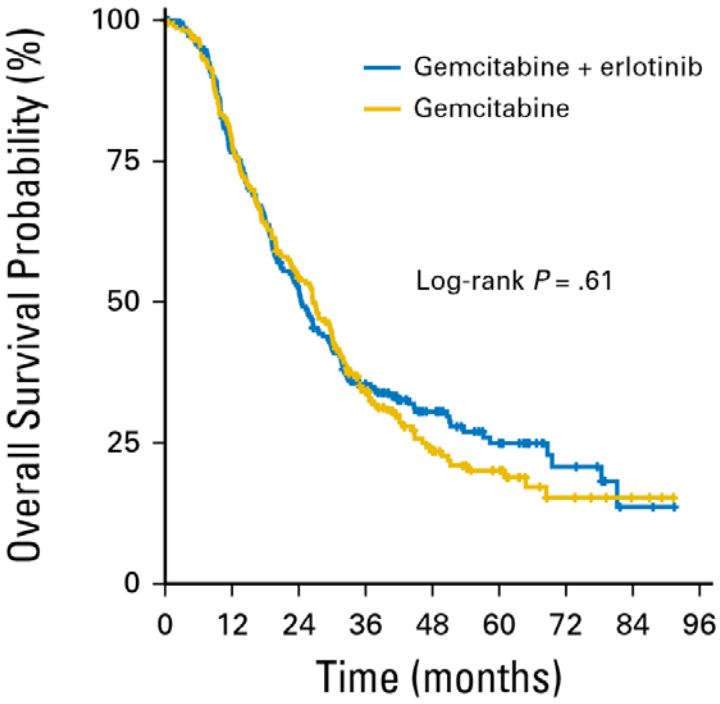
Boeck S & Heinemann V, Lancet 2017; 390: 847

CONKO-005: Gem vs. Gem + Erlotinib



No. at risk:

Gemcitabine + erlotinib	219	98	54	41	27	14	6	1	0
Gemcitabine	217	102	51	32	14	9	4	3	0



No. at risk:

Gemcitabine + erlotinib	219	160	109	67	39	23	10	2	0
Gemcitabine	217	167	113	63	31	19	7	3	0

Sinn M et al, J Clin Oncol 2017; 35: 3330

PRODIGE 24/CCTG PA.6 trial: study design

NCT01526135

- R0 or R1 resected pancreatic cancer
- postoperative CT-scan mandatory
- CA19-9 level < 180 U/mL within 12 weeks after surgery

Stratification:
- center
- resection margin (R0 vs R1)
- CA19-9 level (≤ 90 vs 91-179 U/mL)
- pN0 (< 12 vs ≥ 12 examined nodes) vs pN1

RANDOMIZE 1:1

mFolfirinox

Oxaliplatin 85 mg/m², Leucovorin 400 mg/m²,
Irinotecan 180 mg/m²*, all at D1
Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours
Every 2 weeks; 12 cycles
**Reduced to 150 mg/m² after patient 162*

Gemcitabine

1000 mg/m², qw 3/4 *weeks;*
6 cycles

for both arms:
- 6 months of chemotherapy
- CT scans: every 3 months

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Thierry Conroy

Conroy T et al, NEJM 2018; 379: 2395

Safety: main nonhematologic AEs

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

* 8.6% during cycle 1; 6.3% during cycle 2; 3% at cycles 3-5; 1% at cycles 6-12
Grade 3-4 diarrhea is significantly related to a higher number of lymph nodes examined, p = 0.02.

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Six-month treatment completion

	mFolfirinox No = 238	Gemcitabine No = 243	P
All cycles of chemotherapy	66.4%	79.0%	0.002
Planned administrations	12	18	—
Median No. administrations	12 [1-12]	18 [1-18]	
No. administrations delayed	14.4%	3.9%	< 0.001
Relative dose-intensity > 0.70	48.7%	91.4%	< 0.001
Early stop	80 (33.6%)	51 (21.0%)	0.002
due to :			
- relapse	15 (6.3%)	26 (10.7%)	
- toxicity	21 (8.8%)	11 (4.5%)	
- Principal Investigator's decision	7 (2.9%)	2 (0.8%)	
- patient decision	13 (5.4%)	2 (0.8%)	

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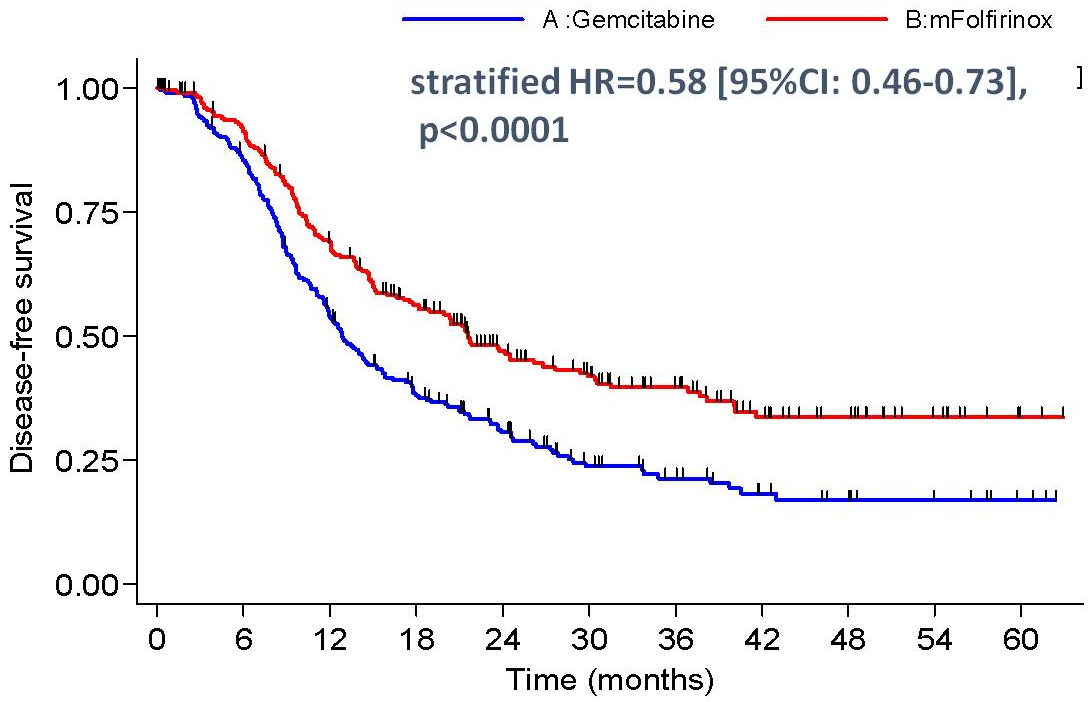
Disease-Free Survival



No DFS events: 314

Median DFS:

- **21.6 mths [95%CI: 17.7-27.6] with mFolfirinox**
- **12.8 mths [95%CI: 11.7-15.2] with Gemcitabine**

3-year DFS:

- **39.7% [95%CI: 32.8-46.6] with mFolfirinox**
- **21.4% [95%CI: 15.8-27.5] with Gemcitabine**

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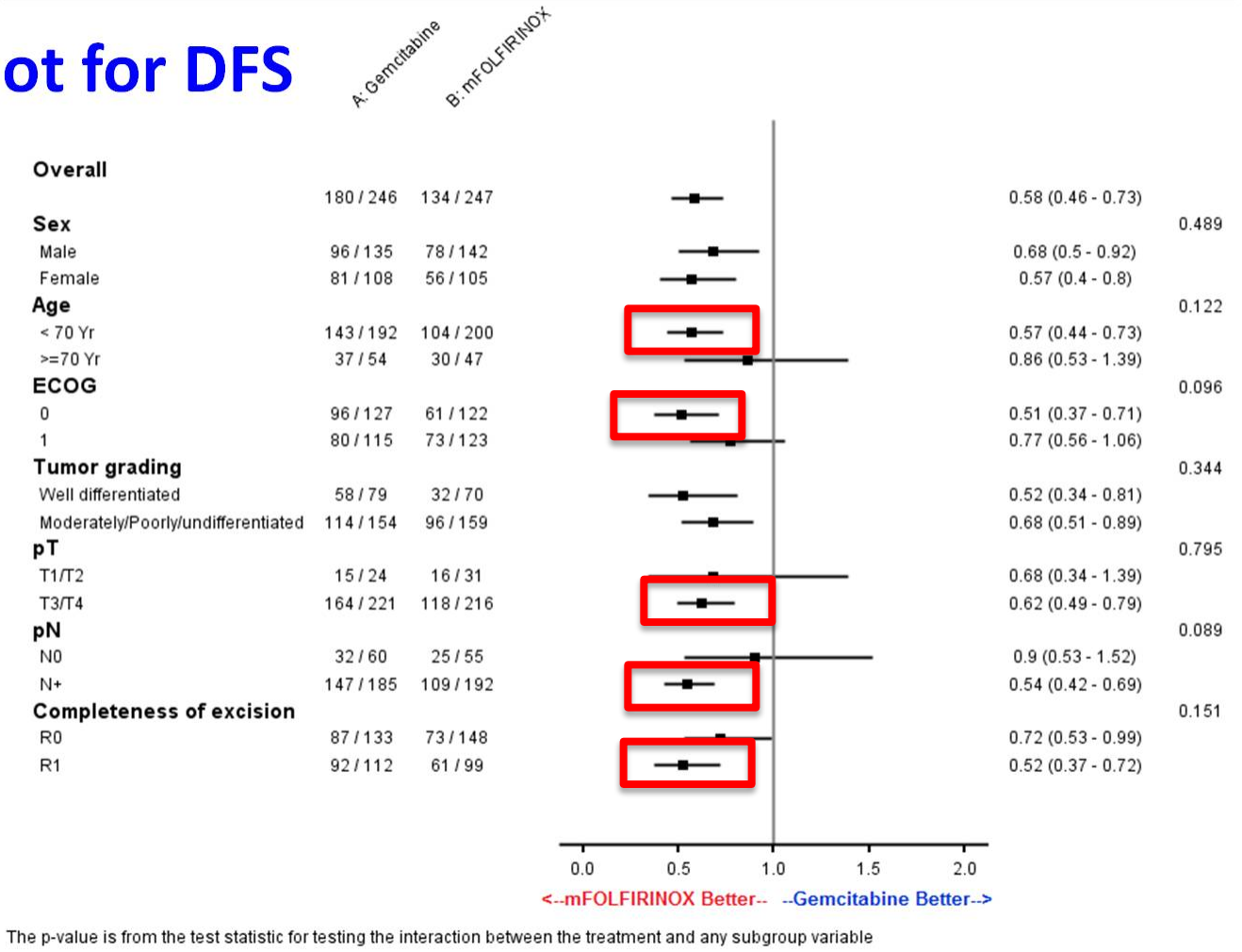
Conroy T et al, NEJM 2018; 379: 2395

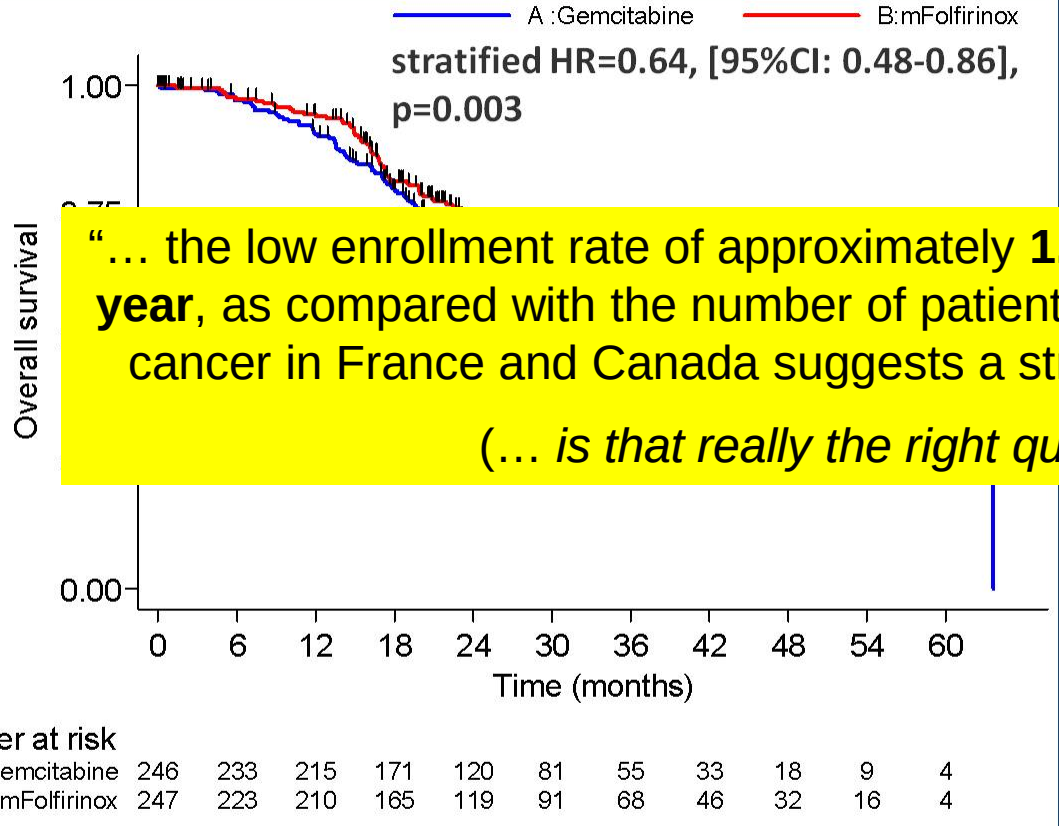
Forest plot for DFS



The p-value is from the test statistic for testing the interaction between the treatment and any subgroup variable

Conroy T et al, NEJM 2018; 379: 2395

Overall Survival



"… the low enrollment rate of approximately **1.5 patients per center per year**, as compared with the number of patients with resected pancreatic cancer in France and Canada suggests a strict selection of patients."

(… *is that really the right question*?)

Median overall survival:

- **54.4 months** [95%CI: 41.8-NR]

3.9]

3-year overall survival:

No OS events=192

- **63.4% (mFolfirinox) vs 48.6 % (Gem)**

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Conroy T et al, NEJM 2018; 379: 2395

PRODIGE-24: Treatment upon relapse

Table S6. Treatments after Relapse of Pancreatic Cancer.*

Treatment	No. patients (%)	
	mFOLFIRINOX (N = 127)	Gemcitabine (N = 169)
Chemotherapy†	80 (63.0)	128 (75.7)
FOLFIRINOX	9 (11.5)	97 (75.8)
Gemcitabine	38 (47.5)	2 (1.6)
Gemcitabine + nab-paclitaxel	23 (28.7)	7 (5.5)
Other gemcitabine-based	2 (2.5)	0
FOLFOX/XELOX	2 (2.5)	16 (12.5)
FOLFIRI	4 (5.0)	0
Capecitabine	1 (1.2)	2 (1.6)
LV5FU2	1 (1.2)	4 (3.1)
(Chemo)radiotherapy	16 (12.6)	10 (5.9)
Surgery	6 (4.7)	8 (4.7)
No treatment	13 (10.2)	10 (5.9)
Missing data	12 (9.5)	13 (7.7)

* Only the first treatment administered after relapse (excluding second cancers and deaths as first event) was taken into account.

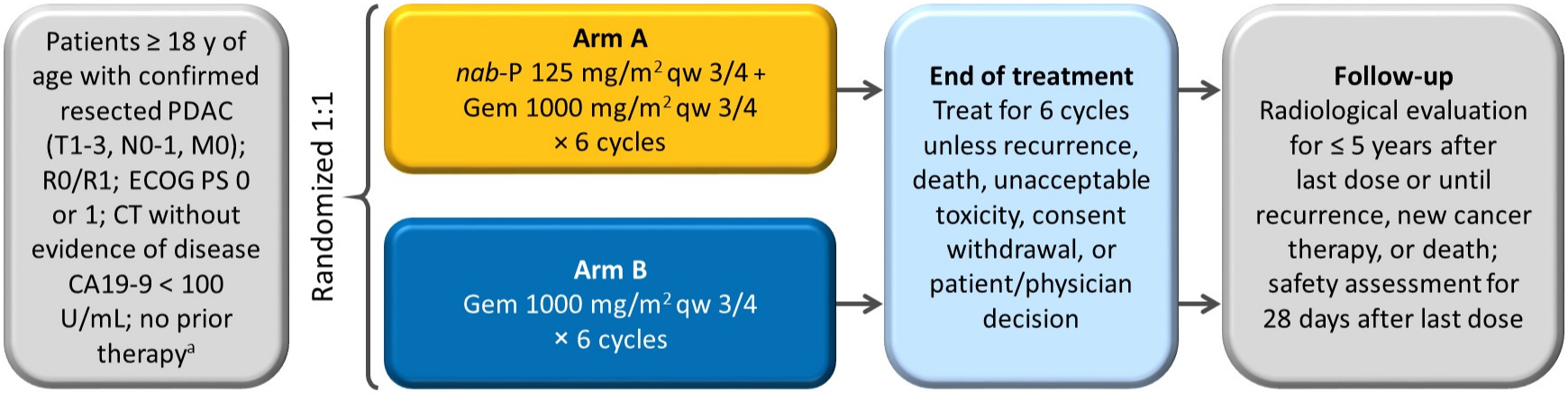
†P=0.16 between groups.

Recruitment period: **2012 -2016**

Conroy T et al, NEJM 2018; 379: 2395 (Supplement)

STUDY DESIGN

APACT: phase III, multicenter, international, open-label, randomized trial



- Patients were randomized as early as possible after adequate recovery from surgery but no later than 12 weeks after surgery
- Stratification factors: resection status (R0 vs R1); lymph node status (LN+ vs LN−); geographic region (North America, Europe and Australia vs Asia Pacific)

CA19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance status; LN, lymph node; PDAC, pancreatic ductal adenocarcinoma; qw 3/4, the first 3 of 4 weeks; R0/R1, macroscopic complete resection with tumor-free/microscopically positive margin.

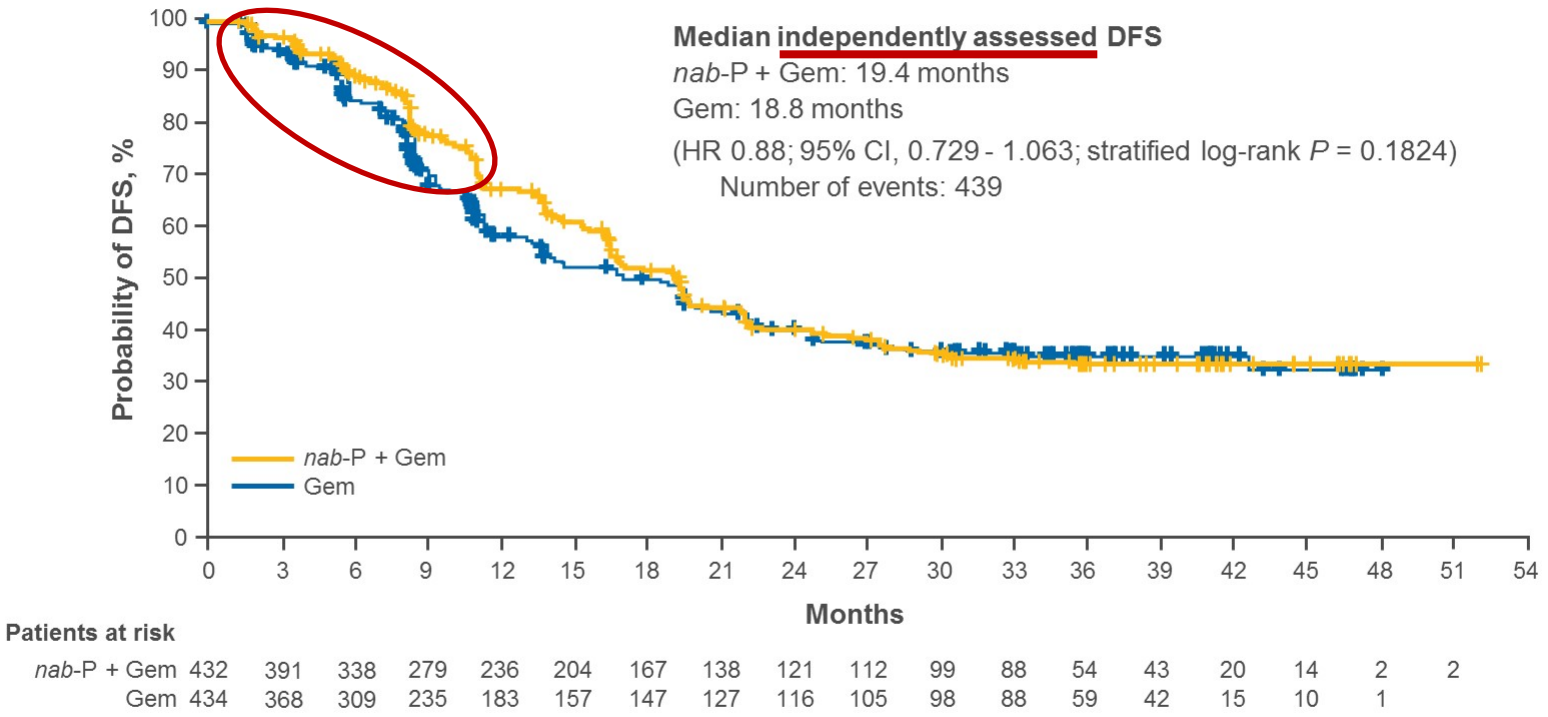
[a] Neoadjuvant, radiation, or systemic therapy.

3

Presented by Margaret Tempero, MD, at ASCO 2019; abstract 4000: Adjuvant *nab*-Paclitaxel Plus Gemcitabine vs Gemcitabine

Tempero MA et al, ASCO 2019; abstract #4000

PRIMARY ENDPOINT: INDEPENDENTLY ASSESSED DFS (ITT POPULATION)



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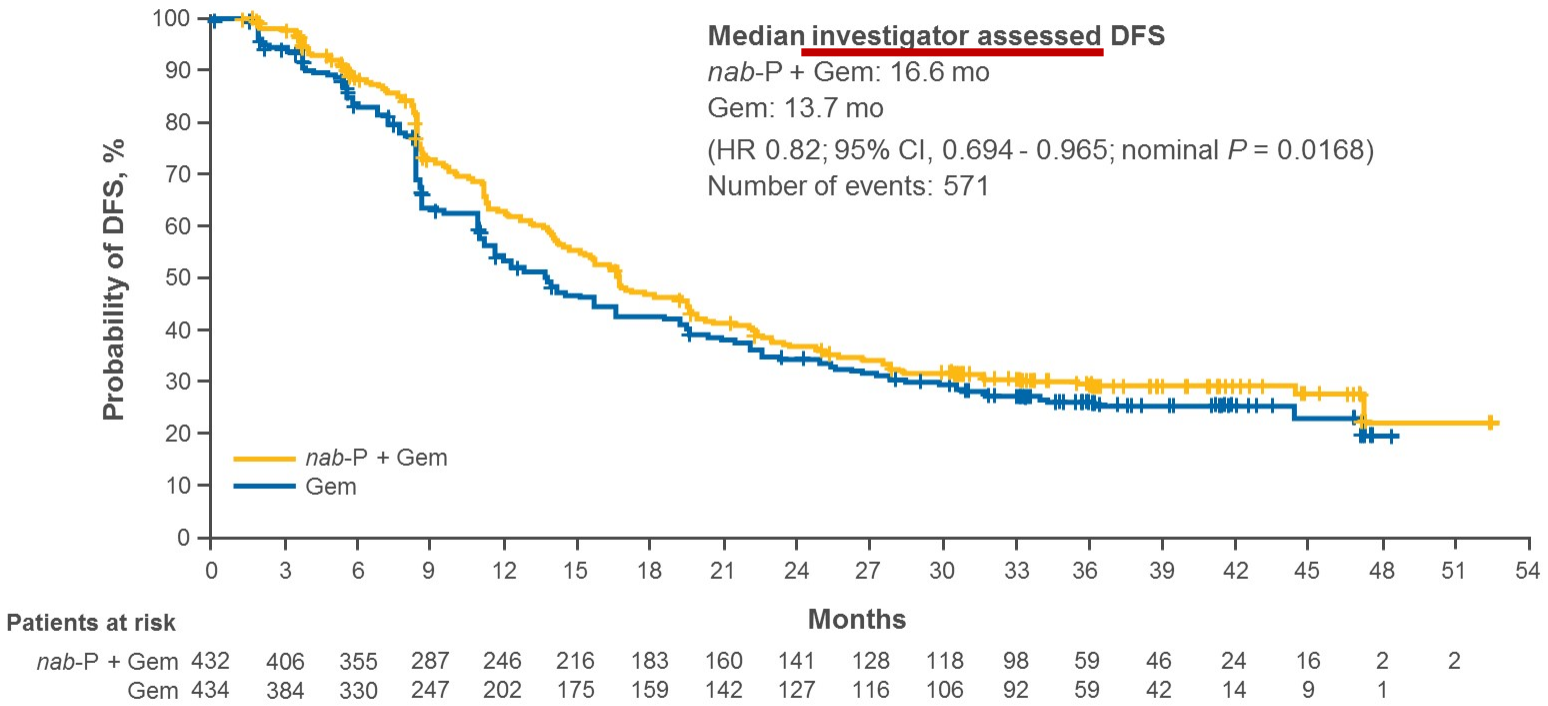
Presented by Margaret Tempero, MD, at ASCO 2019; abstract 4000: Adjuvant *nab*-Paclitaxel Plus Gemcitabine vs Gemcitabine

Tempero MA et al, ASCO 2019; abstract #4000

PRESPECIFIED SENSITIVITY ANALYSIS: INVESTIGATOR ASSESSED DFS (ITT POPULATION)



- The concordance rate between disease recurrence by independent radiological review and by investigator review was 77%

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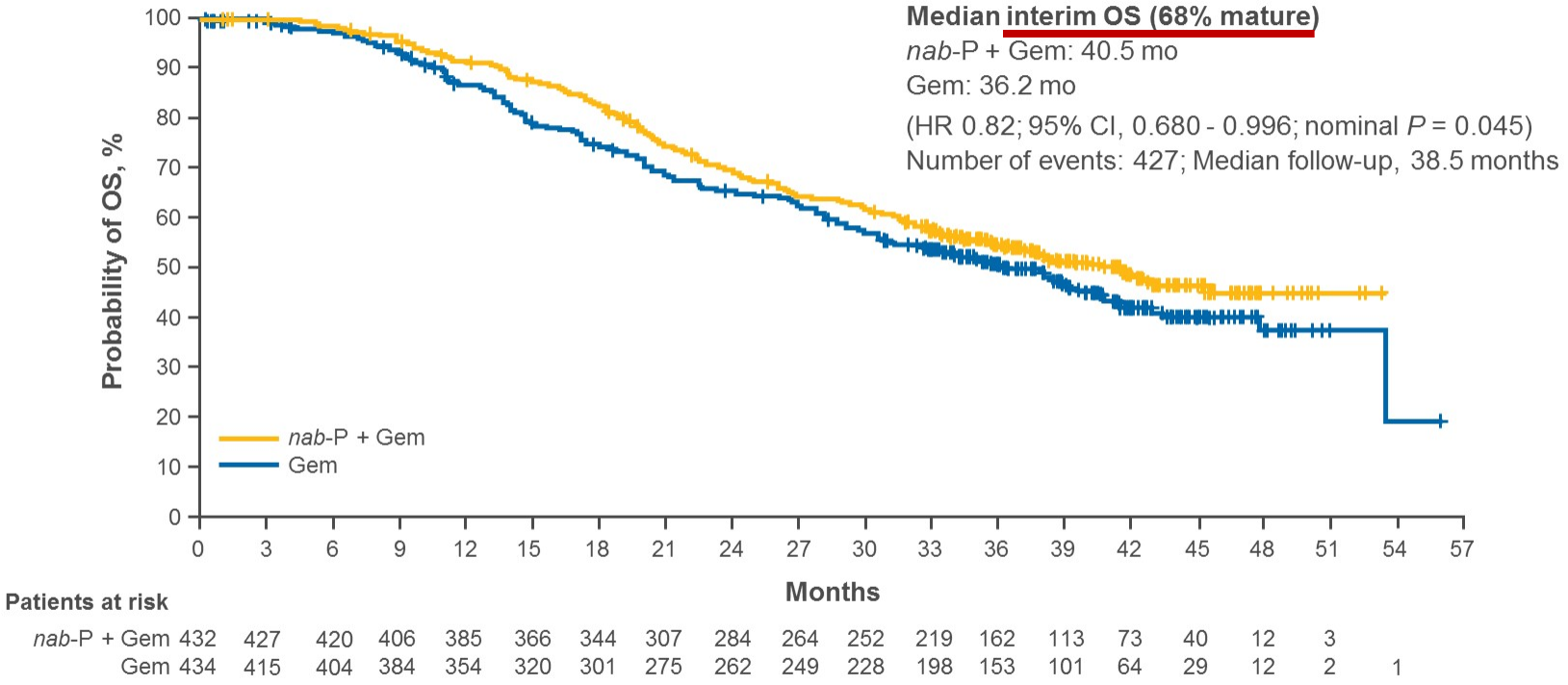
SECONDARY ENDPOINT: INTERIM OS (ITT POPULATION)



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TREATMENT EXPOSURE AND DOSE MODIFICATIONS (TREATED POPULATION)

Parameters	*nab*-P + Gem		Gem
Treatment exposure	**(n = 429)**		**(n = 423)**
Treatment duration, median (range), weeks	24.0 (0.7 - 33.0)		24.0 (1.3 - 31.9)
Treatment cycles, median (range), n	6.0 (1 - 6)		6.0 (1 - 6)
	***nab*-P**	**Gem**	
Relative dose intensity, median, %	75.1	80.0	91.2
Cumulative dose, median, mg/m^2	1500	13,200	15,000
Dose modifications			
Patients with ≥ 1 dose reduction, n (%)	273 (64)	266 (62)	213 (50)

- Overall, 69% of patients completed 6 treatment cycles (*nab*-P + Gem, 66%; Gem, 71%)
- 59% of patients on *nab-P* + Gem received dosing of *nab-P* in cycle 6

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SAFETY (TREATED POPULATION)

apact
Adjuvant Pancreatic Adenocarcinoma Clinical Trial
albumin-bound paclitaxel (ABI-007-PANC-003) + gemcitabine

Event, n (%)	*nab*-P + Gem	Gem
Safety summary	**(n = 429)**	**(n = 423)**
Patients with ≥ 1 grade ≥ 3 TEAE	371 (86)	286 (68)
Patients with ≥ 1 serious TEAE	176 (41)	96 (23)
Grade ≥ 3 hematologic TEAEs (occurring in ≥ 5% of patients in either treatment arm)		
Any hematologic TEAEs	250 (58)	204 (48)
Neutropenia	212 (49)	184 (43)
Anemia	63 (15)	33 (8)
Leukopenia	36 (8)	20 (5)
Febrile neutropenia	21 (5)	4 (1)
Grade ≥ 3 nonhematologic TEAEs (occurring in ≥ 5% of patients in either treatment arm)		
Peripheral neuropathy (SMQ)[a]	64 (15)	0
Fatigue	43 (10)	13 (3)
Diarrhea	22 (5)	4 (1)
Asthenia	21 (5)	8 (2)
Hypertension	17 (4)	27 (6)

- TEAEs led to death in 2 patients in each arm
- Ten patients (16%) with grade ≥ 3 peripheral neuropathy improved to grade ≤ 1
- The incidence of TEAEs of special interest—gastrointestinal events, hepatic toxicity, and sepsis—was generally low in both arms

MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.
[a] Reported as a group term.

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Summary

- **Adjuvant chemotherapy** improves both DFS and OS in R0/R1 resected PDAC
- **Treatment options in 2020 include** (all for 24 weeks)

  Single-agent gemcitabine

  Single-agent S-1 (in Asia only)

  Gemcitabine combined with capecitabine

  mFOLFIRINOX
- **Design of adjuvant trials** remains challenging (see APACT)

btw: what is the % of resected PDAC patients at your center that does receive adjuvant chemotherapy?

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