膽胰癌化學治療

2015.06.27

臺大醫院腫瘤醫學部

楊士弘醫師

胰臟癌藥物治療的困難點

- 高抗藥性
- 藥物副作用
- 易轉移
- 身體(營養)狀況不佳
- 癌症相關併發症

Topic

- Chemotx for adjuvant tx
- Chemotx in advanced disease
  - 1st line
    - Gemcitabine-based regimens
    - Non-gemcitabine regimens
  - 2nd line

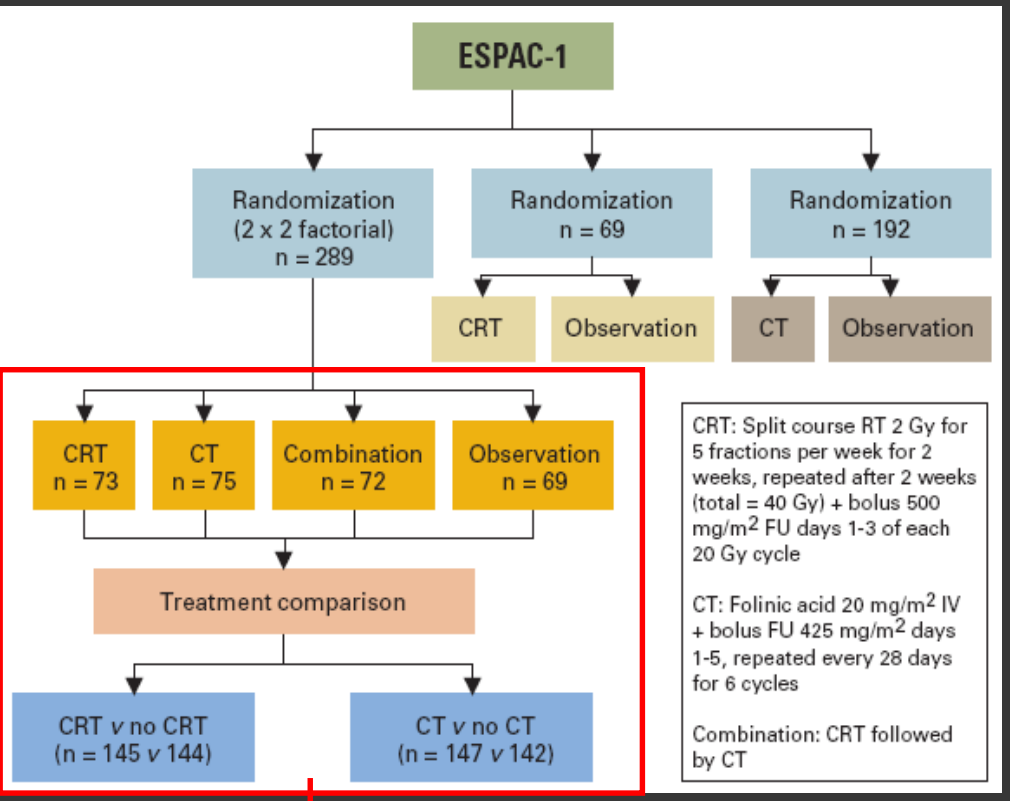
ESPAC-1

NEJM 2004;350:1200-10

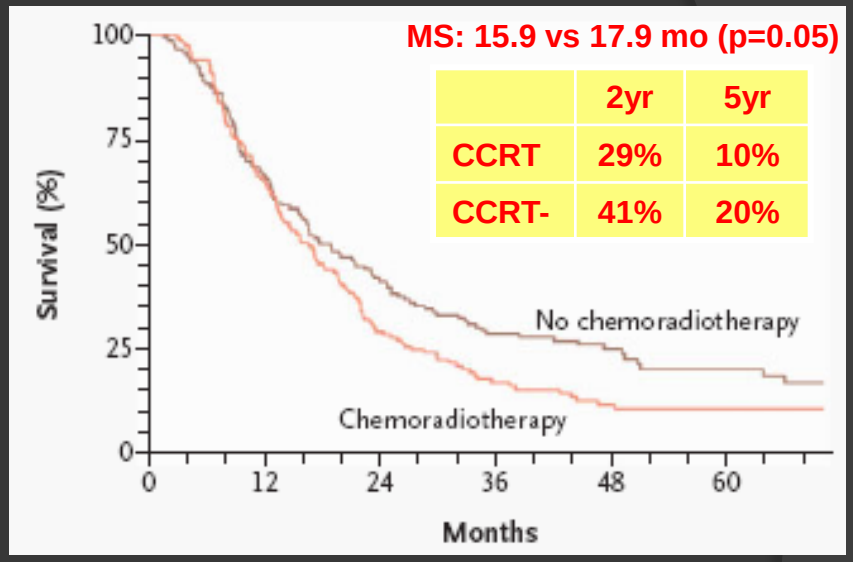
Poor RT quality control
Significant protocol violation

1° endpoint: 2-yr survival

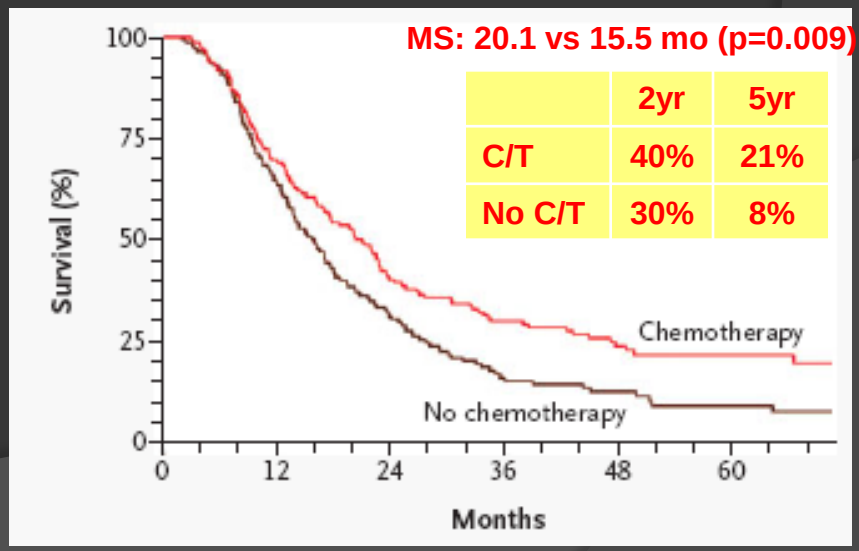
HR=1.28



Arm	Median Survival (months)	5-Year Survival (%)
Observation	16.9	11
Chemoradiotherapy	13.9	7
Chemotherapy	21.6	29
Chemoradiotherapy followed by chemotherapy	19.9	13



	2yr	5yr
CCRT	29%	10%
CCRT-	41%	20%



	2yr	5yr
C/T	40%	21%
No C/T	30%	8%

JAMA. 2007;297:267-277

CONKO-001

N=354

Resected Adenoca.
T1-4, N0-1
KPS ≥ 50
Ctx (-)
RT (-)

RANDOMIZE

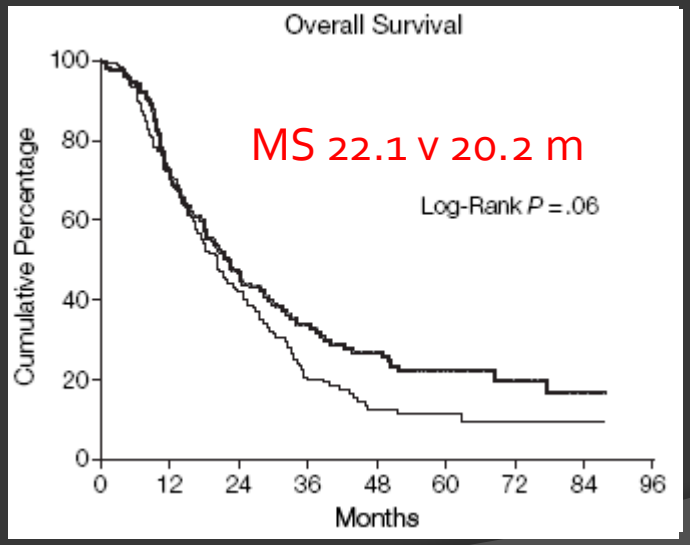
Ctx

- Control
- G 1000 mg/m^2 D1,8,15; 6 cycles

	G	C
T1	7	7
T2	18	17
T3	146	146
T4	8	5
N0	52	48
N1	127	127
R0	145	148
R1	34	27

Survival

1° endpoint: DFS



62% completed 6 cycles

≥ Gr 3 toxicity (cycles)

	G	C
Hema		
-Hb	0.6%	0.1%
-WBC	2.4%	0.1%
-PLT	0.8%	0
Non-hema		
-N/V	1.3%	0.2%
-Diarrhea	0.9%	0.4%
-Edema	0.5%	0.1%
-Infection	0.4%	0.3%

Relapse pattern

	G	C
Local	34%	41%
Distant	56%	49%

JAMA. 2010;304(10):1073-1081

ESPAC-3

N=1088

Resected
Adenoca.
Non-mets
ECOG ≤2
Ctx (-)
RT (-)

RANDOMIZE

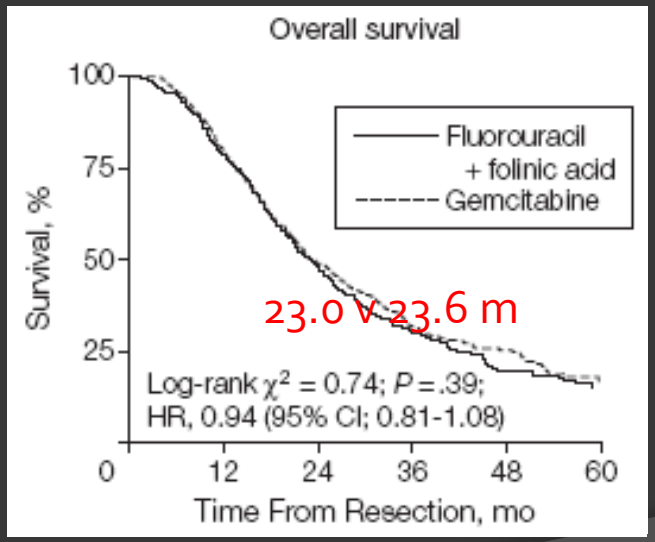
Ctx

5-FU 425 mg/m^2
LV 20 mg/m^2
D1-5; 6 cycles

G 1000 mg/m^2
D1,8,15; 6 cycles

	F	G
I	58	46
II	154	144
III	303	319
IVa	26	16
N0	162	145
N1	387	391
R0	365	348
R1	195	189

1° endpoint: OS



≥ Gr 3 toxicity

	F	G
Hema		
-WBC	6%	10%
-ANC	22%	22%
-PLT	0%	1.5%
Non-hema		
-N/V	6.5%	4.5%
-Diarrhea	13%	2%
-Stomatitis	10%	0%

Quality of Life

No significant difference

IUAC 1997 staging

JASPAC-01

Tegafur: 轉換成5-FU而發揮抗癌作用
Gimeracil: 抑制5-FU的分解，使藥效持續更久
Oteracil potassium: 減輕腹瀉等胃腸道的副作用

N=385

Resected
Adenoca.
T1-4, N0-1 (UICC)
ECOG 0-1
Ctx (-)
RT (-)

RANDOMIZE

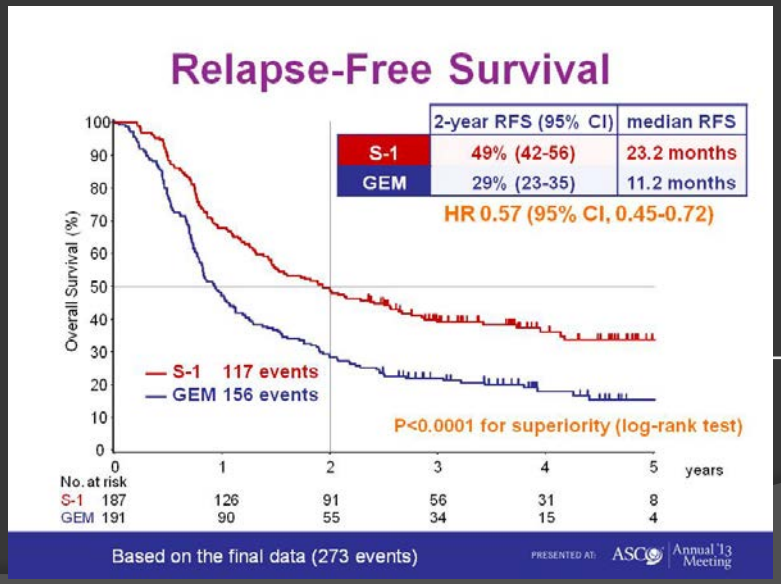
Ctx

S-1 80-120 mg/m^2
D1-28/6w; 6 cycles

G 1000 mg/m^2
D1,8,15; 6 cycles

	S	G
T1	12	11
T2	14	11
T3	165	163
T4	0	2
N0	73	67
N1	118	120
R0	165	164
R1	26	23

Survival



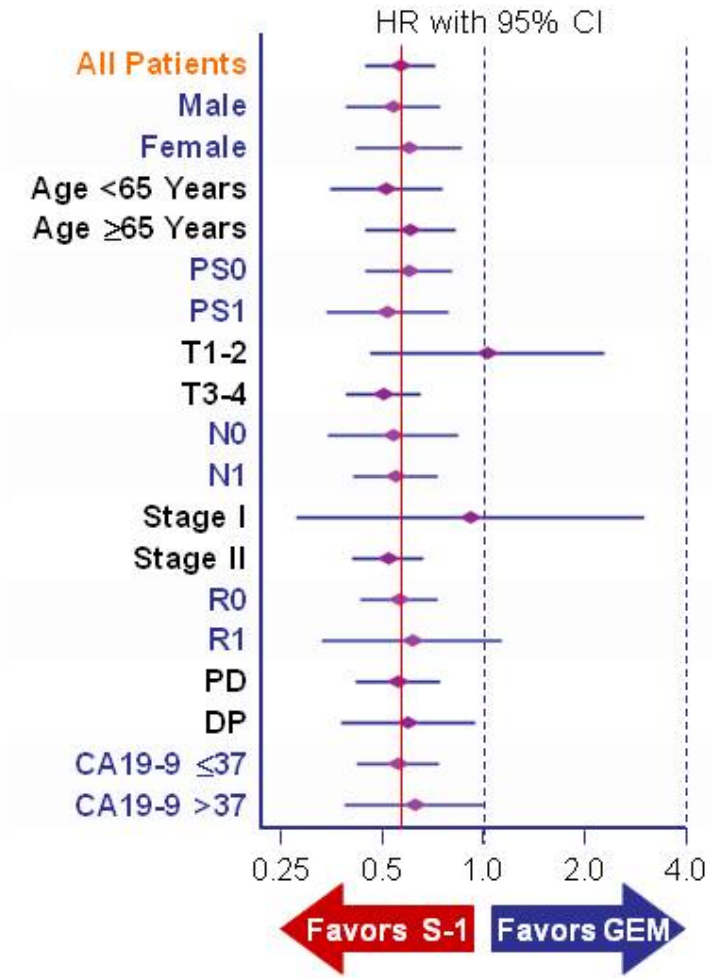
≥ Gr 3 toxicity

	S	G
Hema		
-Hb	13.4%	17.4%
-WBC	8.5%	38.7%
-PLT	4.3%	9.4%
Non-hema		
-N/V	5.3%	3.6%
-Diarrhea	4.8%	0
-Fatigue	5.4%	4.7%
-Stomatitis	2.7%	0

Relapse pattern

	S	G
Local	29%	33%
Liver	29%	39%
Peritoneum	21%	20%

RFS: Subset analysis

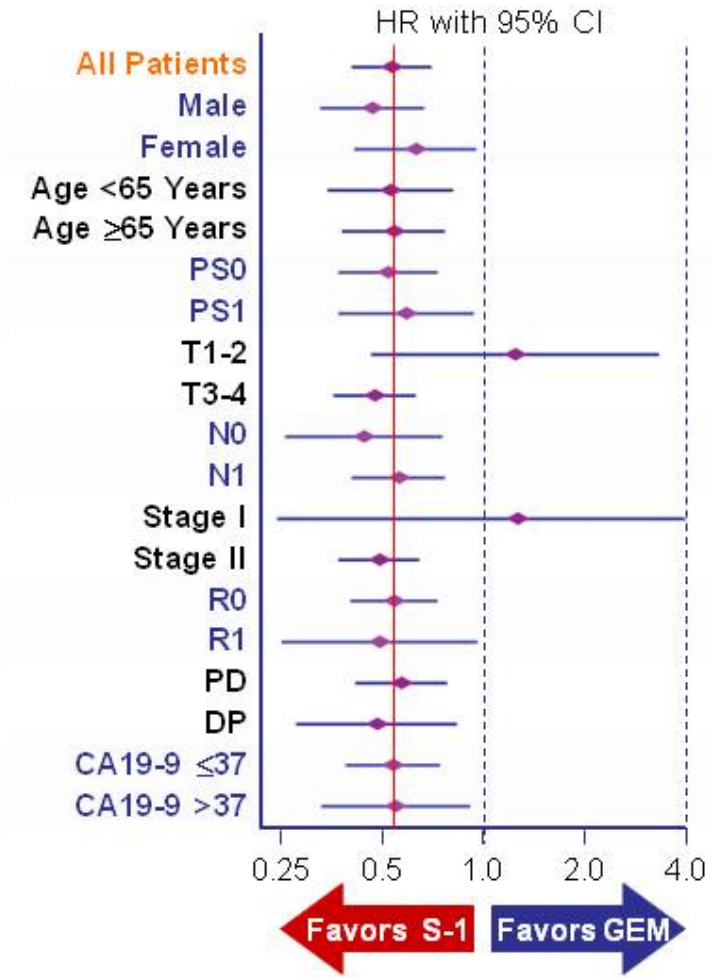


	GEM Events/N	S-1 Events/N	HR	P Value for Interaction
All Patients	156 / 191	117 / 187	0.57	
Male	85 / 104	67 / 106	0.54	0.617
Female	71 / 87	50 / 81	0.60	
Age <65 Years	62 / 75	46 / 76	0.52	0.472
Age ≥65 Years	94 / 116	71 / 111	0.61	
PS0	99 / 128	80 / 131	0.60	0.556
PS1	57 / 63	37 / 56	0.52	
T1-2	13 / 26	11 / 22	1.03	0.095
T3-4	143 / 165	106 / 165	0.51	
N0	50 / 73	32 / 67	0.54	0.986
N1	106 / 118	85 / 120	0.55	
Stage I	6 / 18	5 / 15	0.92	0.337
Stage II	150 / 173	110 / 170	0.52	
R0	132 / 165	99 / 164	0.56	0.837
R1	24 / 26	18 / 23	0.62	
PD	115 / 136	80 / 121	0.56	0.695
DP	37 / 50	37 / 66	0.60	
CA19-9 ≤37	114 / 146	86 / 151	0.56	0.692
CA19-9 >37	42 / 45	30 / 35	0.63	

Based on the final data (273 events)

PRESENTED AT: ASCO Annual '13 Meeting

OS: Subset analysis



	GEM Events/N	S-1 Events/N	HR	P Value for Interaction
All Patients	132 / 191	87 / 187	0.54	
Male	76 / 104	50 / 106	0.47	0.258
Female	56 / 87	37 / 81	0.64	
Age <65 Years	51 / 75	36 / 76	0.54	0.983
Age ≥65 Years	81 / 116	51 / 111	0.55	
PS0	86 / 128	57 / 131	0.53	0.733
PS1	46 / 63	30 / 56	0.60	
T1-2	8 / 26	8 / 22	1.26	0.066
T3-4	124 / 165	79 / 165	0.48	
N0	41 / 73	20 / 67	0.45	0.409
N1	91 / 118	67 / 120	0.57	
Stage I	2 / 18	2 / 15	1.27	0.357
Stage II	130 / 173	83 / 170	0.50	
R0	108 / 165	73 / 164	0.55	0.733
R1	24 / 26	14 / 23	0.50	
PD	101 / 136	64 / 121	0.58	0.682
DP	29 / 50	23 / 66	0.49	
CA19-9 ≤37	92 / 146	62 / 151	0.55	0.933
CA19-9 >37	40 / 45	24 / 35	0.56	

Based on the final data (219 events)

PRESENTED AT: ASCO Annual '13 Meeting

Compliance

	GEM (n=191)	S-1 (n=187)
Completed	110 (58%)	135 (72%)
Discontinued	81 (42%)	52 (28%)
Reasons for discontinuation		
Toxicity	48 (25%)	40 (21%)
Recurrence	26 (14%)	9 (5%)
Pt's refusal	5 (3%)	3 (2%)
Others	2 (1%)	0 (0%)
Relative dose intensity		
Median	84%	98%
Mean(±SD)	79 (±18)%	89 (±18)%

N Engl J Med 2014;371:1039-49

Summary - Adjuvant therapy

Table 2. Adjuvant Therapy for Pancreatic Cancer.*

Study	No. of Patients	Treatment	Survival	P Value
GITSG[58]	43	Observation Fluorouracil plus radiotherapy	10% at 2 yr 20% at 2 yr	0.007
EORTC[59]	218	Observation Fluorouracil plus radiotherapy	26% at 2 yr 34% at 2 yr	0.10
ESPAC-1[60]	289	Observation Chemoradiotherapy	16.9 mo (median)† 13.9 mo	
		Fluorouracil Chemoradiotherapy plus fluorouracil	21.6 mo 19.9 mo	
CONKO-01[61]	368	Observation Gemcitabine	10.4% at 5 yr 20.7% at 5 yr	0.01
ESPAC 3[62]	1088	Fluorouracil Gemcitabine	23.0 mo (median) 23.6 mo	0.39
RTOG 9704[63]	451	Fluorouracil plus radiotherapy Gemcitabine plus radiotherapy	22% at 5 yr 18% at 5 yr	0.12
JASPAC-01[64]	378	S-1 (oral fluoropyrimidine) Gemcitabine	70% at 2 yr 53% at 2 yr	<0.001

Topic

- Chemotx for adjuvant tx
- Chemotx in advanced disease
  - 1st line
    - Gemcitabine-based regimens
    - Non-gemcitabine regimens
  - 2nd line

Pre-gemcitabine era

MS: 3-6 months

TABLE 1. Therapeutic Activity of Single Agents in Pancreatic Cancer

Drug	No. of responses	Response rate (%)
5-fluorouracil •	60/212*	28
Mitomycin-C •	12/44*	27
BCNU	0/13	0
CCNU	2/4	—
MeCCNU	3/34	9
Streptozotocin •	8/22*	36
Chloroambucil	4/6	—
Cyclophosphamide	1/2	—
Mechlorethamine	1/1	—
Adriamycin •	2/15	13
Actinomycin-D	1/28	—
Methotrexate	1/25	—
ICRF-159	1/18	—
Galactitol	1/20	—
β-2TGdR	1/26	—

* Represents collective series.

TABLE 2. Combination Chemotherapy in Pancreatic Cancer

Combination	No. of responses	Response rate (%)
5-FU + BCNU	10/30	33
5-FU + BCNU	4/15	27
5-FU + Testolactone	10/13	77
5-FU + MeCCNU	—	17
5-FU + mitomycin-C	—	30
Streptozotocin + mitomycin-C + 5-FU	10/23	43
5-FU + Streptozotocin + mitomycin-C	5/16	31
5-FU + Adriamycin + mitomycin-C	10/25	40

舊藥有比較差?

Zimmerman SE et al, Cancer. 1981 Mar 15;47(6 Suppl):1724-8

New drugs 差強人意

新藥有更好?

Drug	Response rate
5-FU	0-20%
Capecitabine	7.3%
S-1	22.6%
UFT	0%
Pemetrexed	5.7%
Raltitrexed	0-5%
Paclitaxel	5.5%
Docetaxel	0-15%
Nab-paclitaxel	5%
Irinotecan	9%
Oxaliplatin	0%
Cisplatin	24%

Burris HA 3rd et al, J Clin Oncol. 1997 Jun;15(6):2403-13

Gemcitabine vs 5-FU

- Chemonaive
- Unresectable (75% stage IV)
- KPS ≥50 but **<80**
- Adequate organ function
- Morphine equiv ≥ 10 mg/d
- MPAC pain score ≥ 20

Lead-in

Pain stabilized for 2-7d

RANDOMIZATION

Gemcitabine (N=63)

1000 mg/m^2 weekly x 7, off x 1, then weekly x 3 of 4 weeks

5-FU (N = 63)

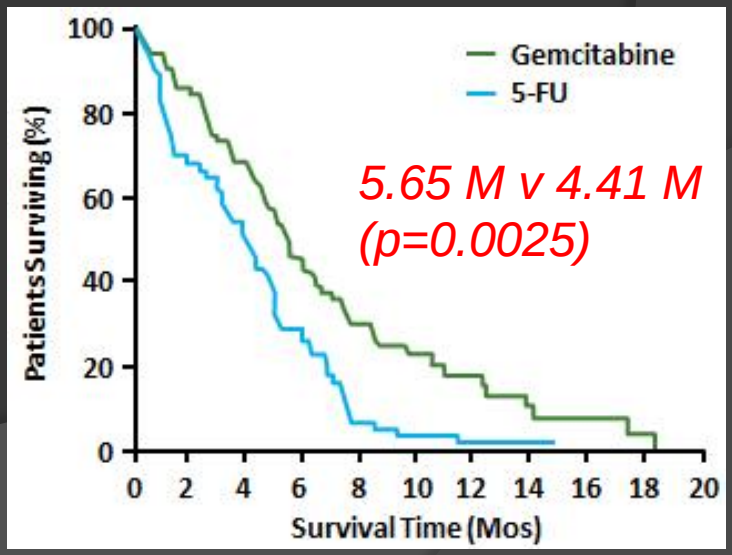
600 mg/m^2 weekly

1˚ endpoint: clinical benefit

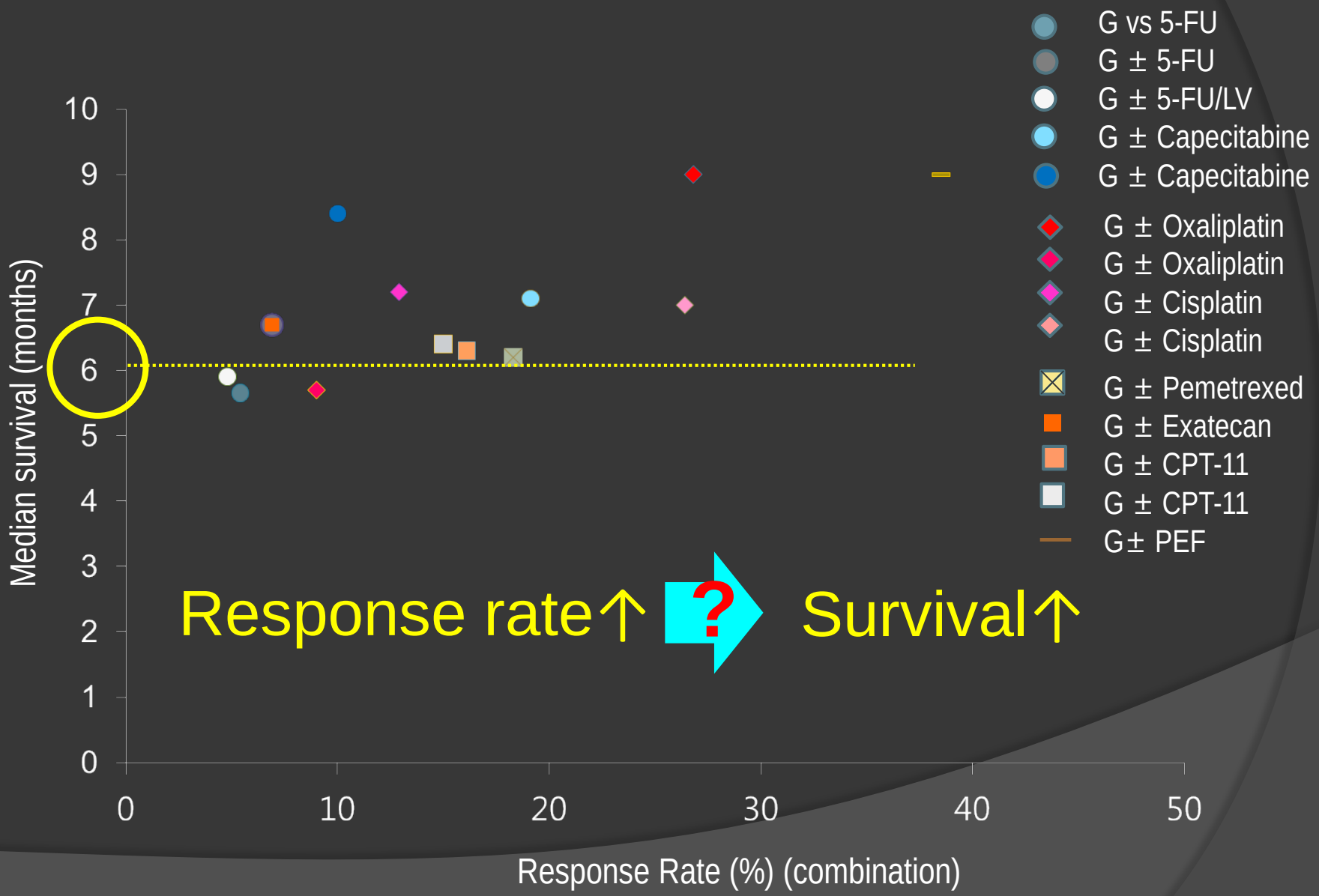
- Pain
- Function
- Weight

=> sustained (≥ 4 wks) improvement in ≥1 parameter without worsening in any others

	G	F
CBR (%)	**23.8**	**4.8**
RR (%)	5.4	0

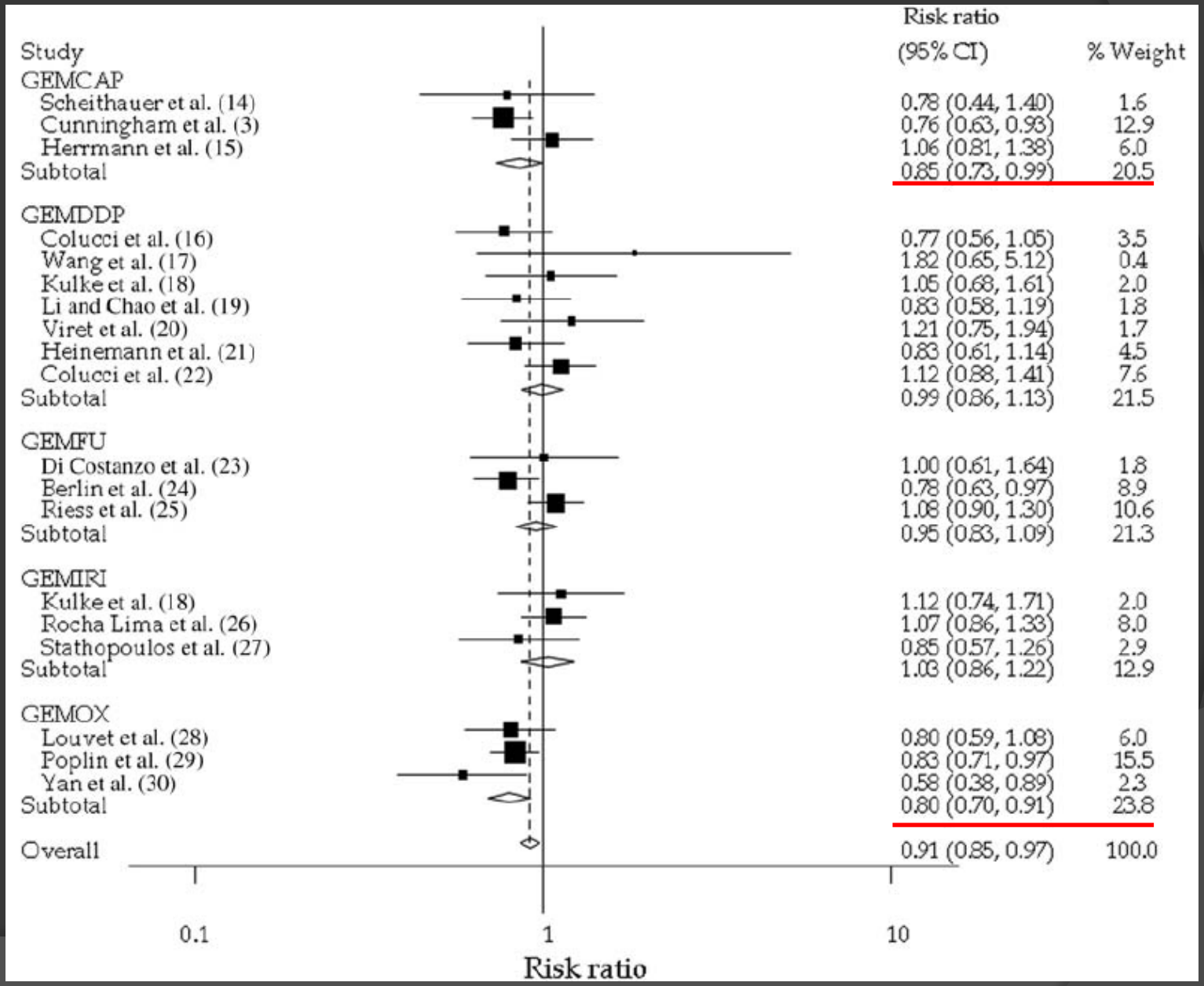


Gemcitabine-based phase III trails



Meta-analysis

Xie DR et al, Jpn J Clin Oncol. 2010 May;40(5):432-41

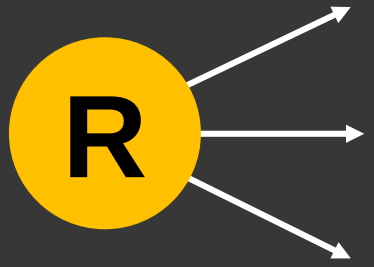


Ueno H et al, J Clin Oncol. 2013 May 1;31(13):1640-8

GEST study

- Untreated
- Unresectable (75% stage IV)
- Adeno/Adenosq ca
- ECOG 0-1
- Adequate organ function
- 20-80 y/o

Stratification factors:
- Metastatic vs. Locally advanced
- Institution



S-1
80, 100, 120 mg
4 wks/6 wks

Gemcitabine
1000 mg/m^2 weekly
3 of 4 weeks

S-1
60, 80, 100 mg
2 wks/3 wks

Gemcitabine
1000 mg/m^2 weekly
2 of 3 weeks

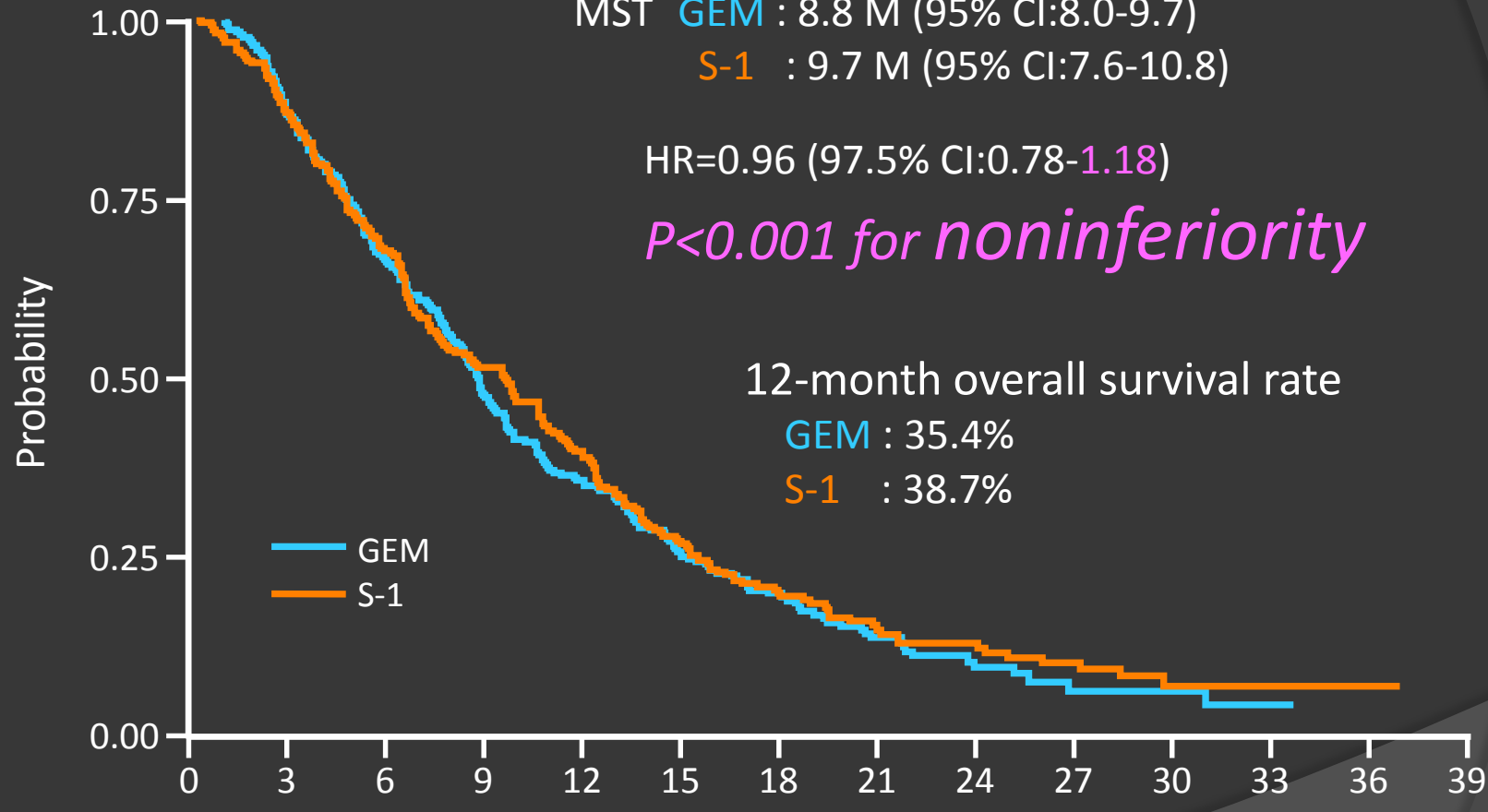
1˚ endpoint: overall survival

- ***Non-inferiority: S-1 vs. Gemcitabine***
  - Assume 8.0 vs. 7.5 M
  - margin 1.33 (2 M shorter)
- **Superiority: Gemcitabine+S-1 vs. Gemcitabine**
  - Assume 10.5 vs. 7.5 M

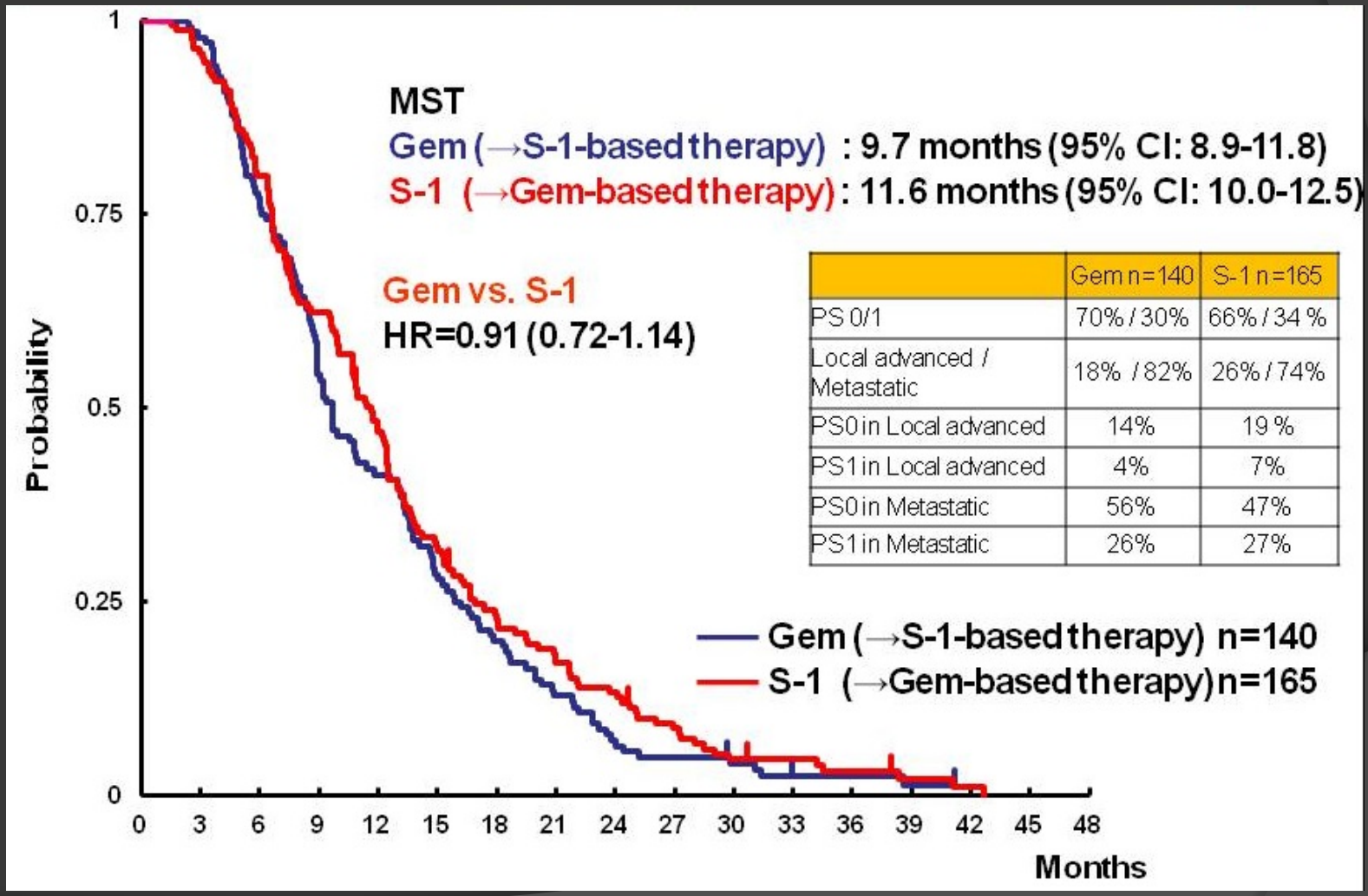
1-side $\alpha = 0.025$
$\beta = 0.1$

Ueno H et al, J Clin Oncol. 2013 May 1;31(13):1640-8

Overall Survival (S-1 vs. Gemcitabine)



OS from 1st Line Chemotherapy in Cross-over Cases (F/U Results)



	Gem n=140	S-1 n=165
PS 0/1	70% / 30%	66% / 34 %
Local advanced / Metastatic	18% / 82%	26% / 74%
PS0 in Local advanced	14%	19 %
PS1 in Local advanced	4%	7%
PS0 in Metastatic	56%	47%
PS1 in Metastatic	26%	27%

A. Fukutomi et al, ASCO 2012

Ueno H et al, J Clin Oncol. 2013 May 1;31(13):1640-8

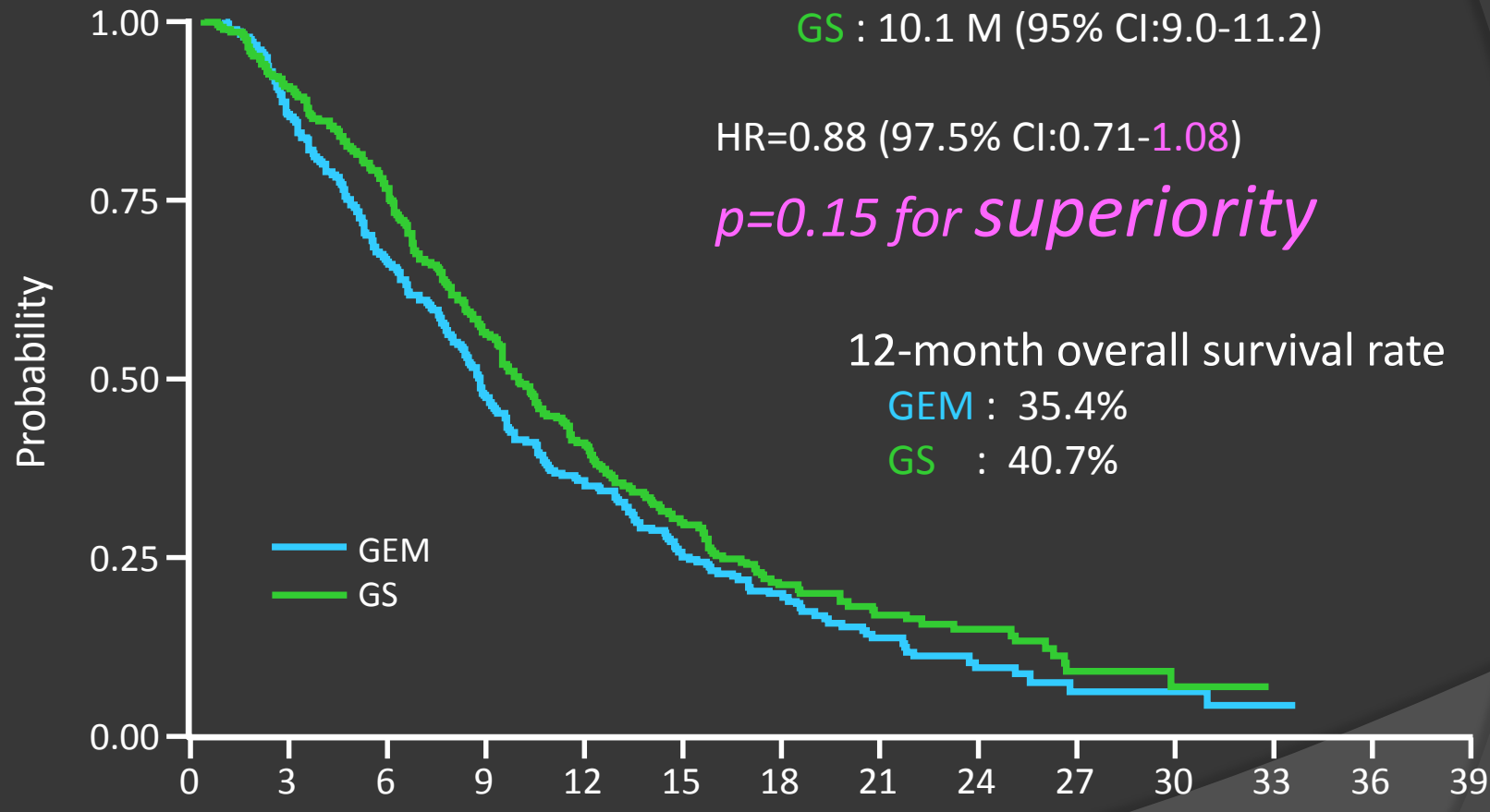
Overall Survival (Gemcitabine/S-1 vs. Gemcitabine)

MST GEM : 8.8 M (95% CI:8.0-9.7)
GS : 10.1 M (95% CI:9.0-11.2)

HR=0.88 (97.5% CI:0.71-1.08)

p=0.15 for superiority

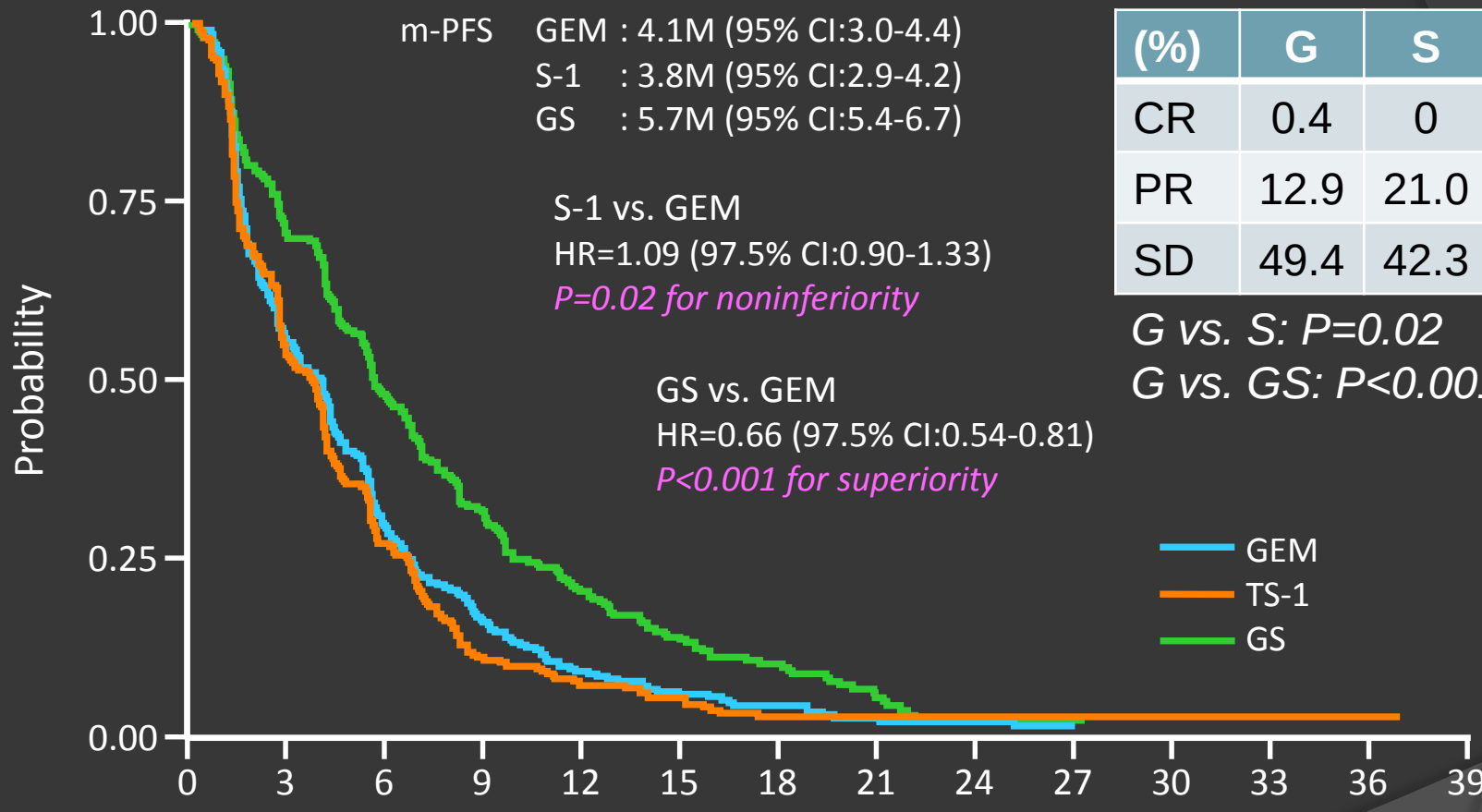
12-month overall survival rate
GEM : 35.4%
GS : 40.7%



At risk							
GEM	277	184	97	41	12	3	
GS	275	209	108	42	19	3	

Ueno H et al, J Clin Oncol. 2013 May 1;31(13):1640-8

Progression-free survival

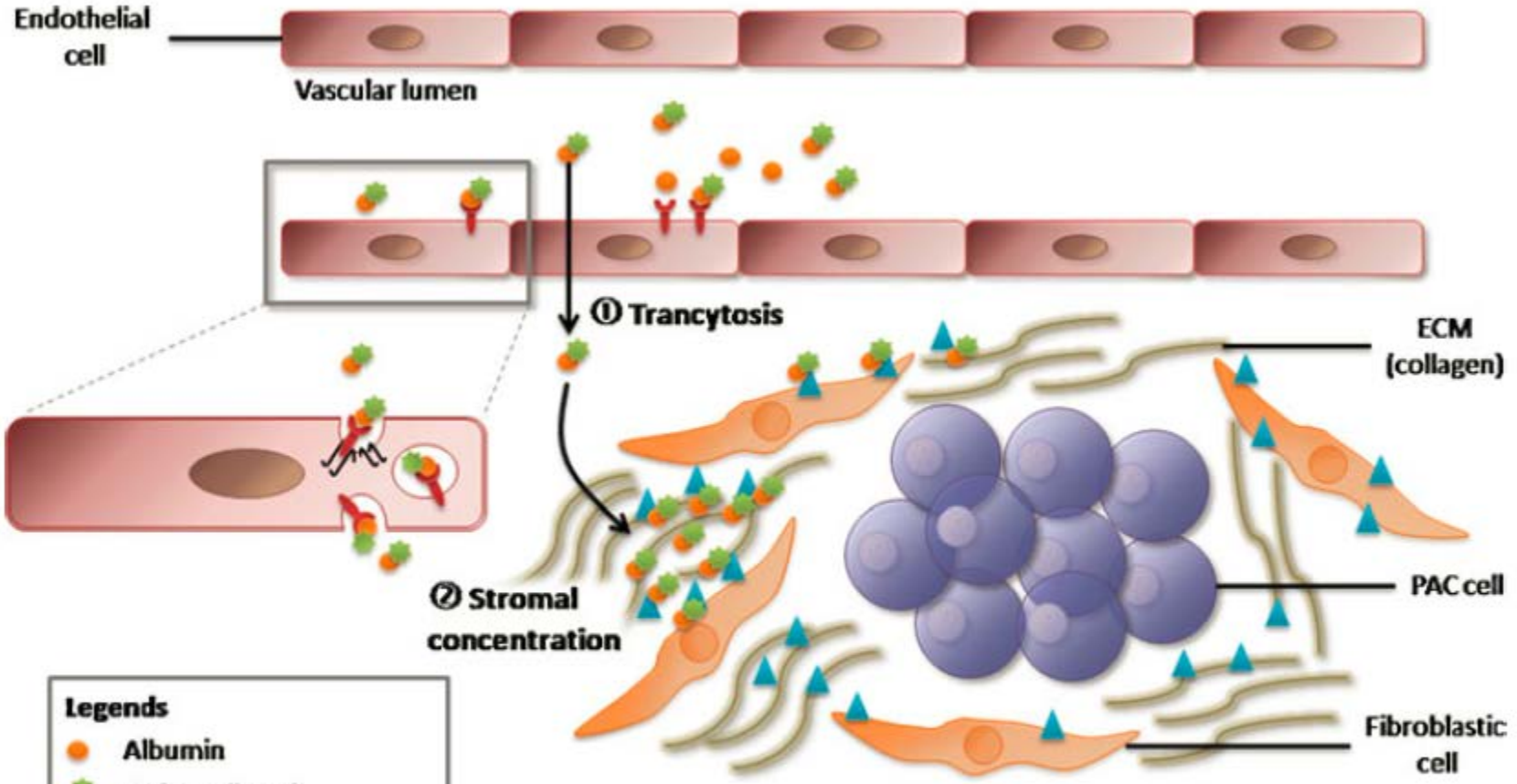


Response rate

(%)	G	S	GS
CR	0.4	0	0.8
PR	12.9	21.0	28.5
SD	49.4	42.3	42.1

G vs. S: P=0.02
G vs. GS: P<0.001

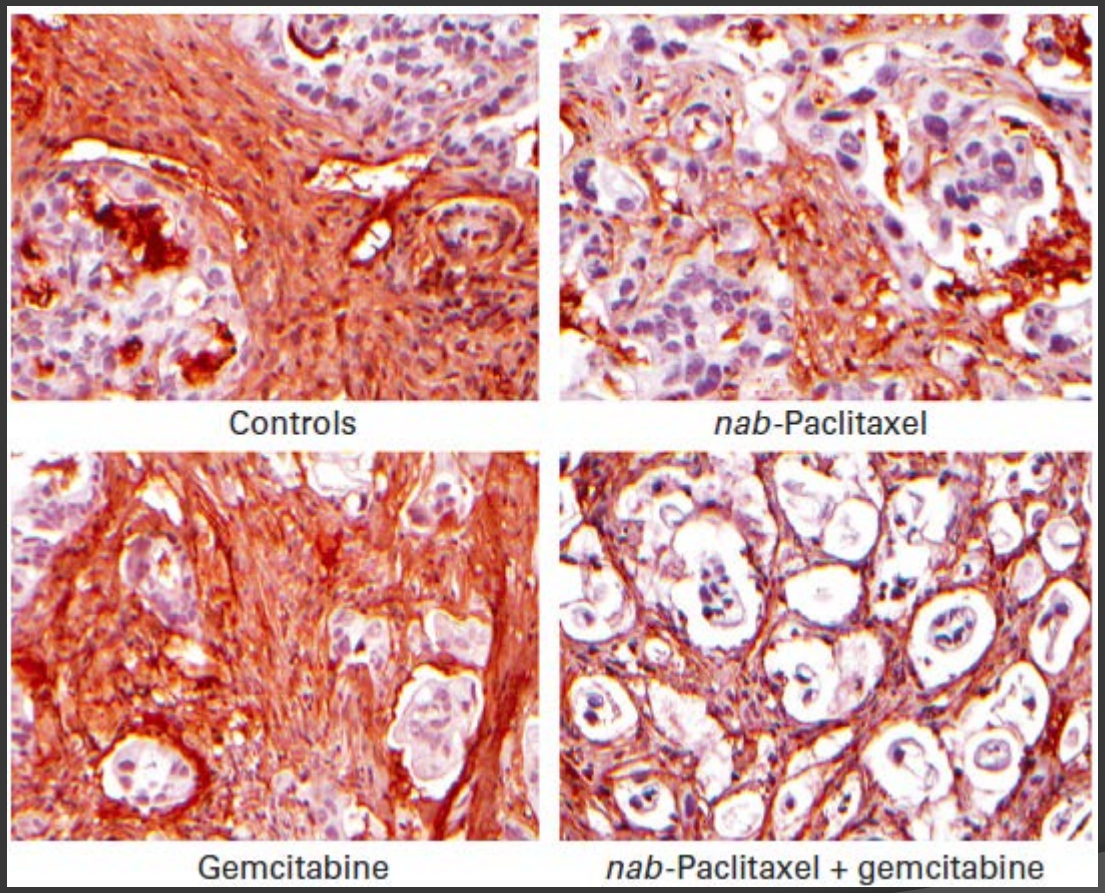
Mechanism – nab-paclitaxel

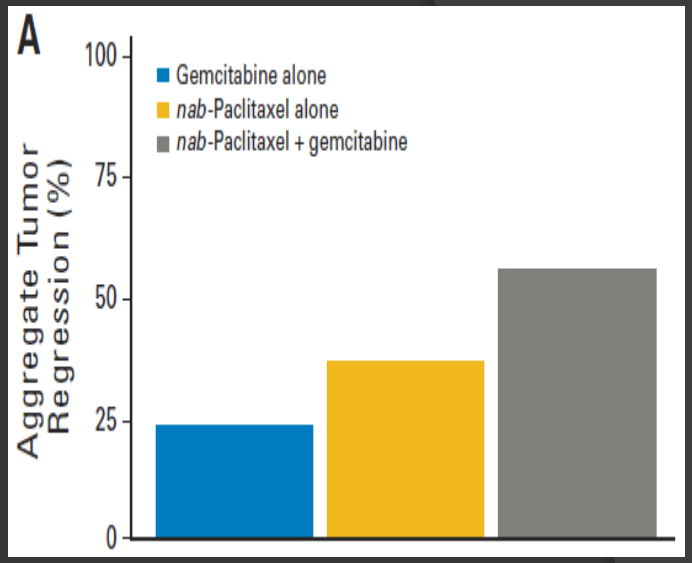


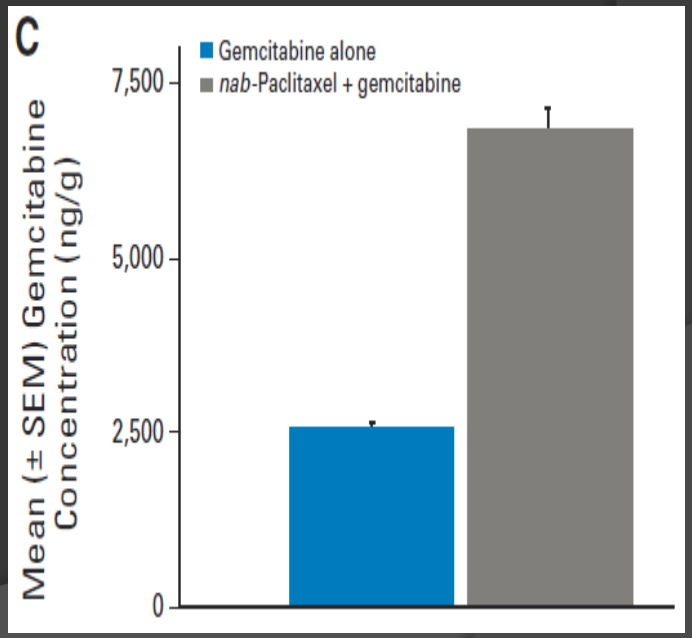
SPARC (secreted protein acidic and rich in cysteine)

Neuzillet C et al, Cancer Metastasis Rev. 2013 Dec;32(3-4):585-602

Animal study - G/nab-paclitaxel







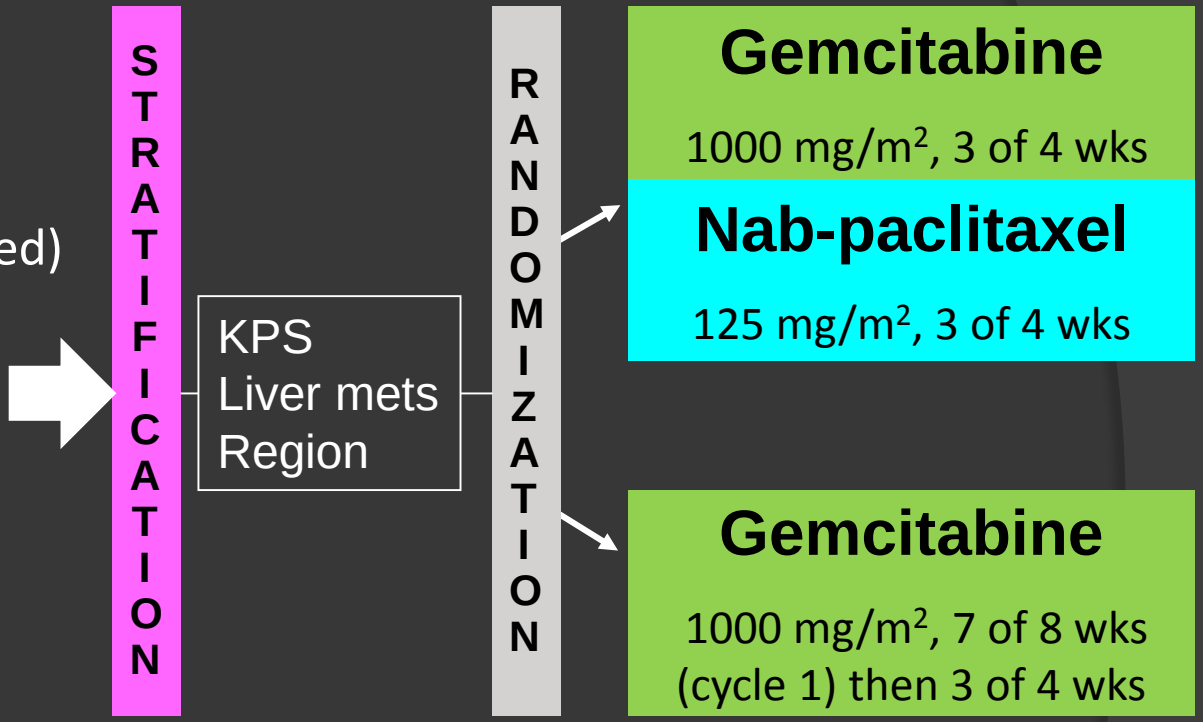
Von Hoff DD et al, J Clin Oncol. 2011 Dec 1;29(34):4548-54

Von Hoff DD et al, N Engl J Med. 2013 Oct 31;369(18):1691-703

MPACT Trial Gemcitabine ± nab-paclitaxel

Inclusion

- Untreated (Adj CCRT allowed)
- Stage IV
- Adenocarcinoma
- KPS ≥70
- Adequate organ function
- >18 y/o



- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, safety

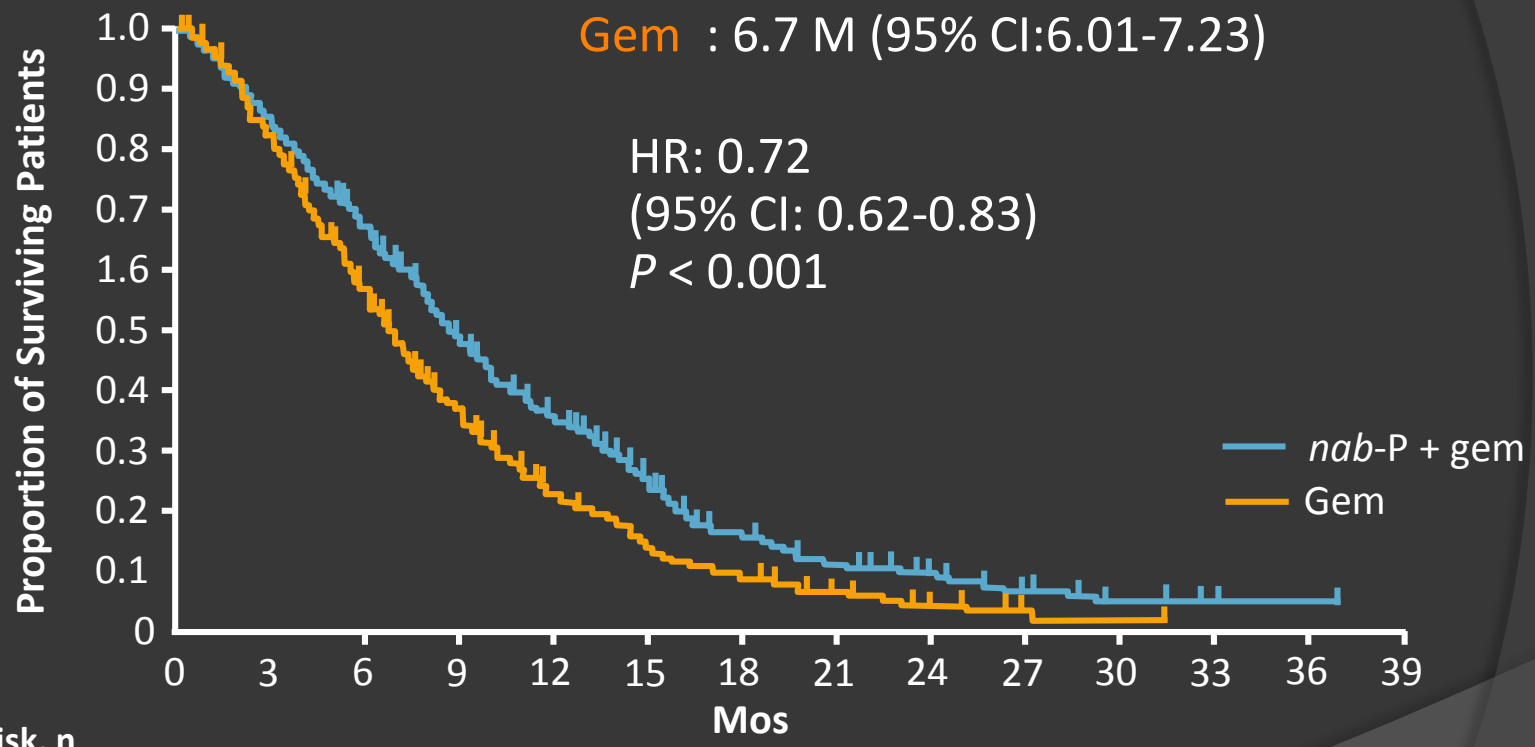
Von Hoff DD et al, N Engl J Med. 2013 Oct 31;369(18):1691-703

MPACT Trial Gemcitabine ± nab-paclitaxel

MST nab-P + Gem : 8.5 M (95% CI:7.89-9.53)

Gem : 6.7 M (95% CI:6.01-7.23)

HR: 0.72
(95% CI: 0.62-0.83)
P < 0.001



Pts at Risk, n													
nab-P + gem	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gem	430	340	220	124	69	40	26	15	7	3	1	0	0	0

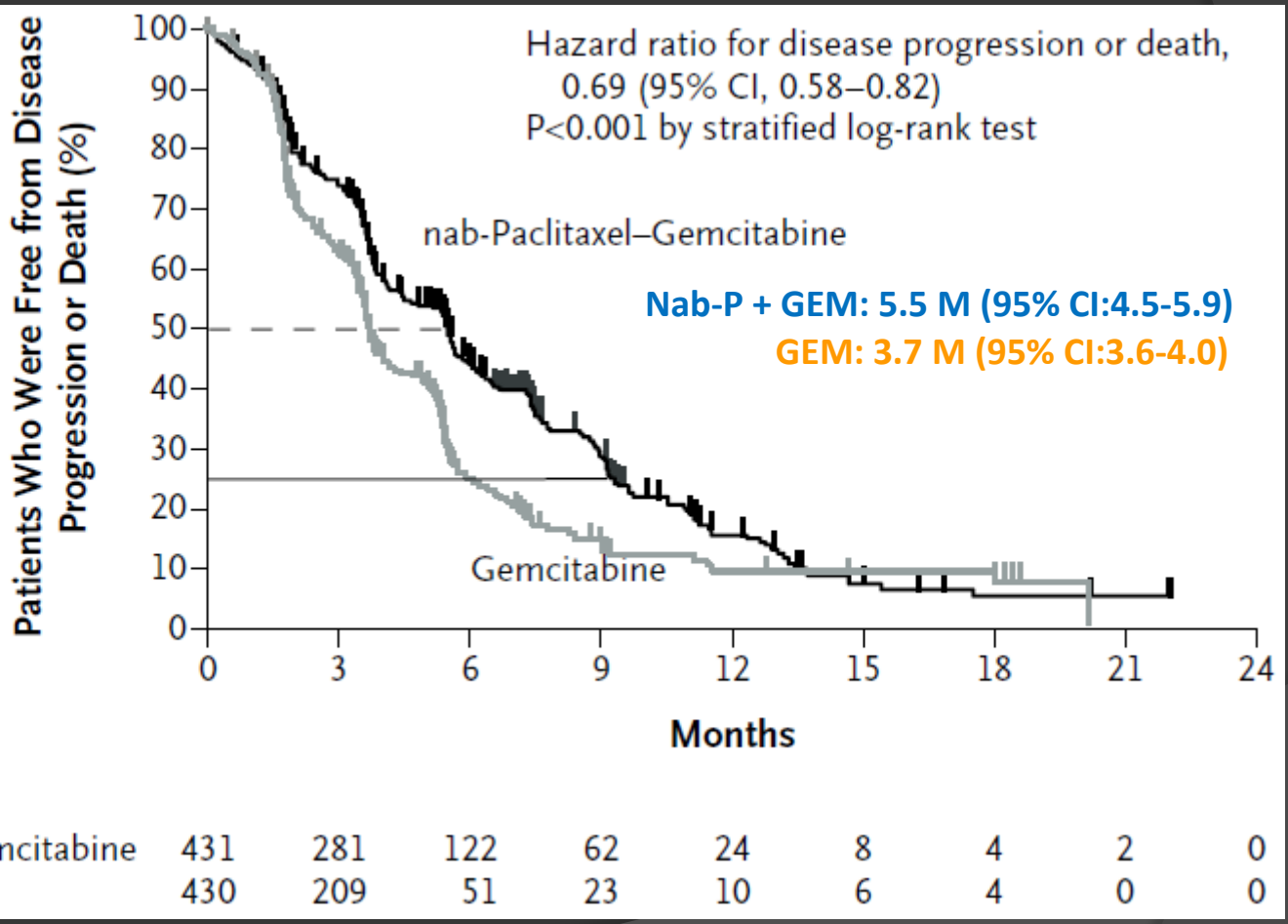
Von Hoff DD et al, N Engl J Med. 2013 Oct 31;369(18):1691-703

MPACT Trial Gemcitabine ± nab-paclitaxel

Response

(%)	G nab-P	G
CR	<1	0
PR	23	7
SD	27	28

P <0.001



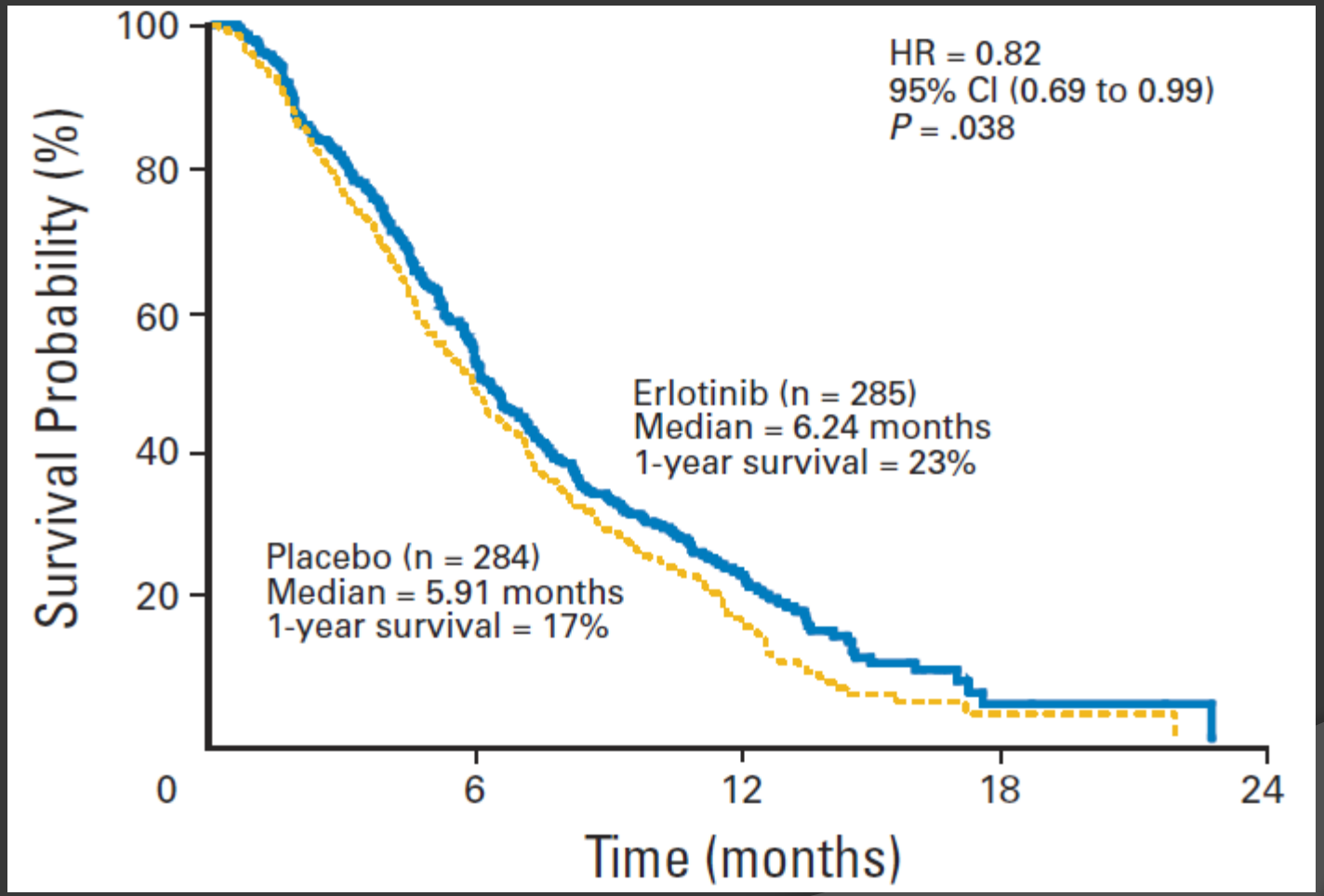
Erlotinib

- 作用機轉: 表皮生長因子受體抑制劑
- 適應症: 肺癌、(胰臟癌)
- 副作用:
  - 50%左右患者可發生丘疹、斑疹、膿皰樣皮炎，多在服藥第一周出現，4周後可逐漸減輕。少數可能非常嚴重需停藥或減少藥量
  - 皮膚乾燥、瘙癢
  - 噁心、嘔吐、腹瀉
  - 肝功能異常
  - 間質性肺炎

Erlotinib

Variable	%			
	Erlotinib and Gemcitabine (n = 282)		Placebo and Gemcitabine (n = 280)	
	All	Grade 3/4	All	Grade 3/4
Any toxicity				
All patients	100	62	99	57
100 mg/d erlotinib and placebo	100	61		
150 mg/d erlotinib and placebo	100	78		
Specific toxicity				
Diarrhea	56	6	41	2
Fatigue	89	15	86	15
ILD-like syndrome*	2.1		0.4	
Infection (any)	43	17	34	16
Rash	72	6	29	1
Stomatitis	23	< 1	14	0

Erlotinib



J Clin Oncol 25:1960-1966. © 2007

Topic

- Chemotx for adjuvant tx
- Chemotx in advanced disease
  - 1st line
    - Gemcitabine-based regimens
    - Non-gemcitabine regimens
  - 2nd line

Dahan L et al, Gut. 2010 Nov;59(11):1527-34

Non-G first line therapy

FFCD 0301

1° endpoint: OS

N=202

Age >18
Stage IV
Adenoca
WHO PS 0-2
Ctx (-)
RT (-)

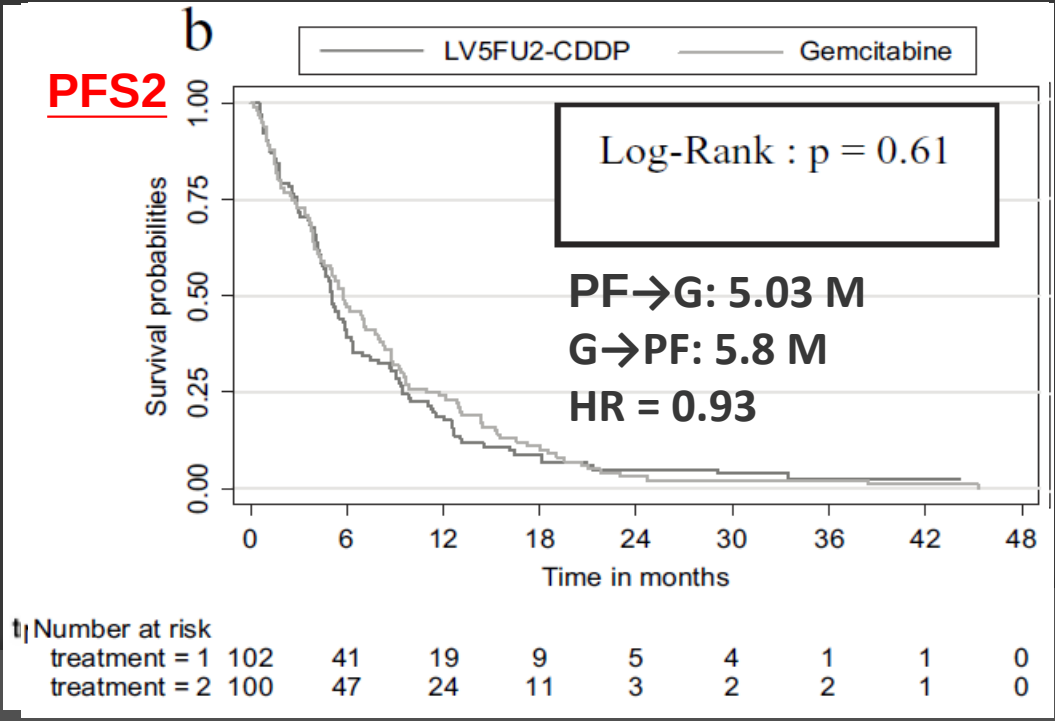
RANDOMIZE

CDDP 50 mg/m²
LV5FU2 200/400/2400 mg/m²
q2w

→ G 1000 mg/m²
7/8 then 3/4 wks

G 1000 mg/m²
7/8 then 3/4 wks

→ CDDP 50 mg/m²
LV5FU2 200/400/2400 mg/m²
q2w



1st line	PF	G
N	102	100
RR	15%	19%
SD	32%	29%
2nd line	**→G**	**→PF**
N	69	55
RR	10%	7%
SD	28%	38%

Non-G first line therapy

Heinemann V et al, Gut. 2013 May;62(5):751-9

AIO-PK0104

1° endpoint: TTF2

N=281

Age 18-75
Stage III/IV
Exocrine
KPS ≥ 60
Ctx (-)
RT (-)

RANDOMIZE

Cap 2000 mg/m²/d
14/7 on/off

+

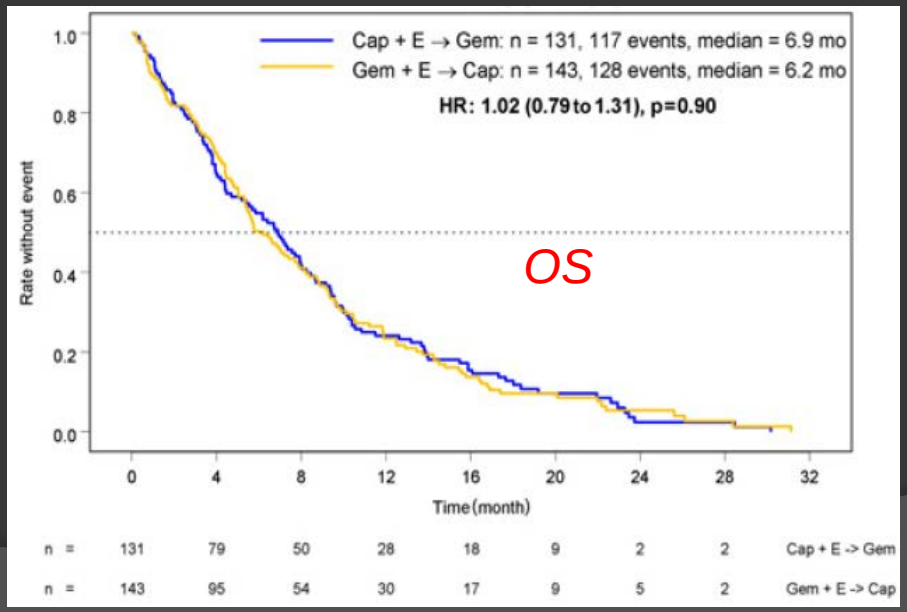
Erlotinib 150 mg/d

+

G 1000 mg/m²/wk
6/1 on /off; 1st cy
3/1 on/off, later

G 1000 mg/m²/wk
6/1 on /off; 1st cy
3/1 on/off, later

Cap 2000 mg/m²/d
14/7 on/off



Efficacy

	CE	GE
N	131	143
RR	5%	16%
SD	33%	36%
	→G	→C
N	77	63
RR	6%	3%
SD	30%	19%

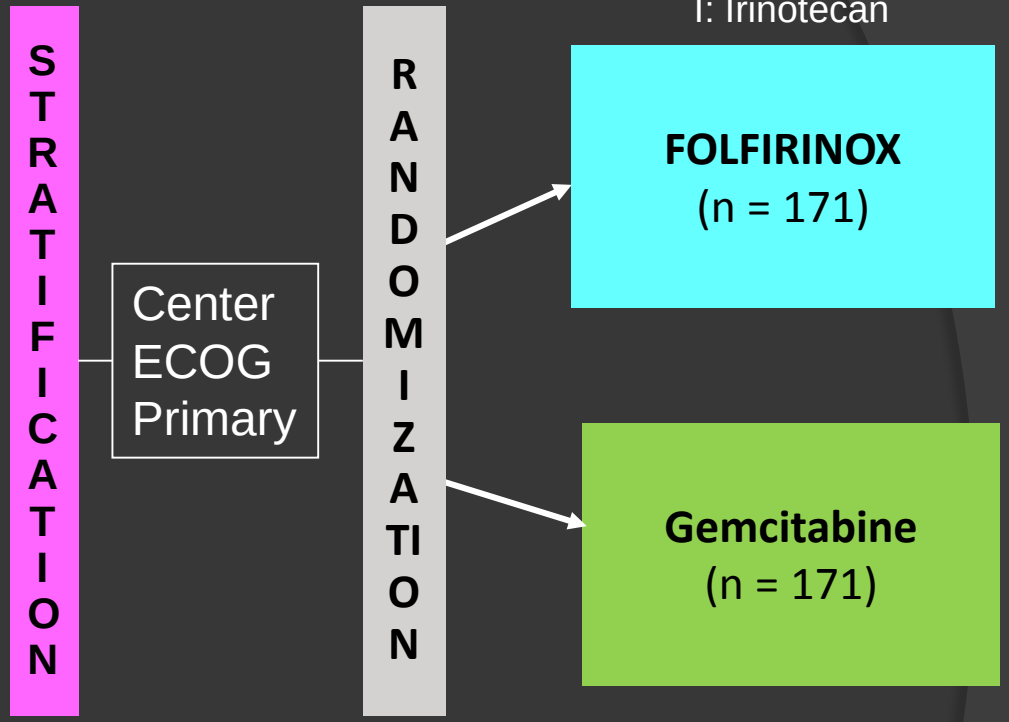
Conroy T et al, N Engl J Med. 2011 May 12;364(19):1817-25

PRODIGE 4/ACCORD 11

F: 5-FU
O: Oxaliplatin
I: Irinotecan

Inclusion

- Untreated
- Stage IV
- Adenocarcinoma
- ECOG 0-1
- Adequate organ function
- >18 y/o



- Primary endpoint: RR (phase 2); OS (phase 3)
  - 11/40 responders in phase 2 -> phase 3
- Secondary endpoints: safety (phase 2); PFS, RR, safety, QOL (phase 3)

Conroy T et al, N Engl J Med. 2011 May 12;364(19):1817-25

PRODIGE 4/ACCORD 11

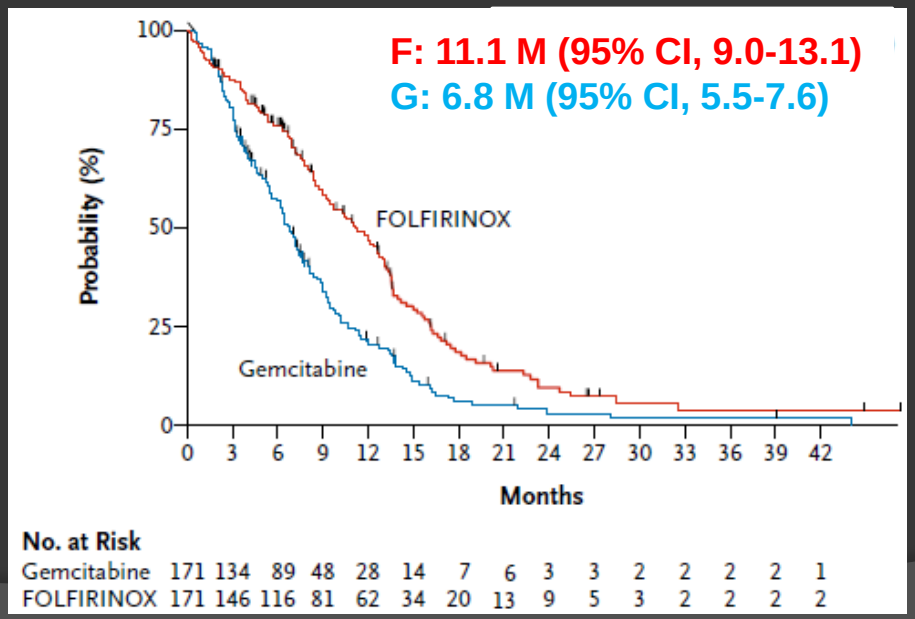
- ECOG: 0(40%), 1 (60%)
- Dose intensity: G (100%); F(82%), I (81%), O (78%)
- G-CSF:
  - FOLFIRINOX: 42.5%
  - Gemcitabine: 5.3%

Response

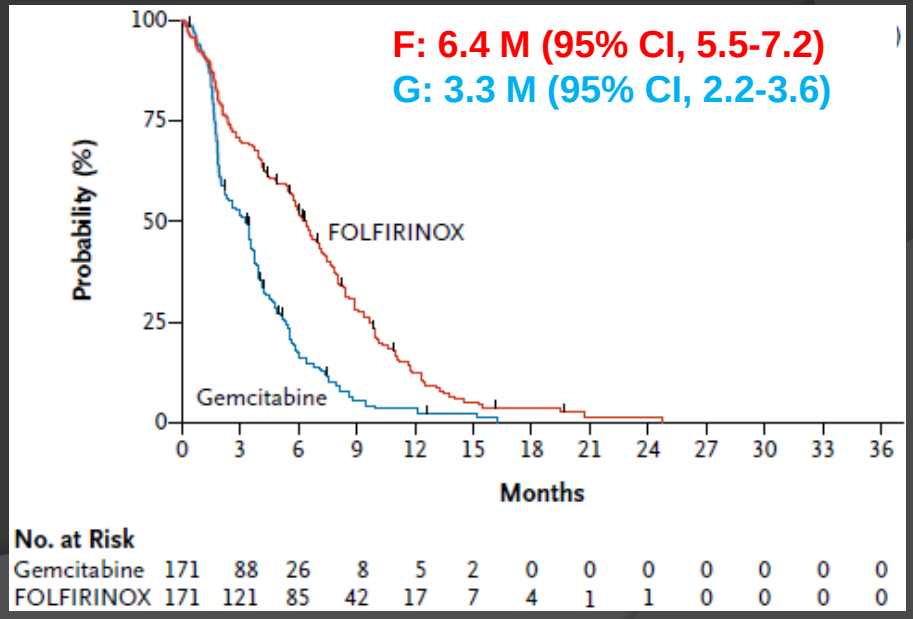
(%)	F	G
CR	0.6	0
PR	31.0	9.4
SD	38.6	41.5

RR: P <0.001

OS *HR =0.57, P<0.001*



PFS *HR =0.47, P<0.001*



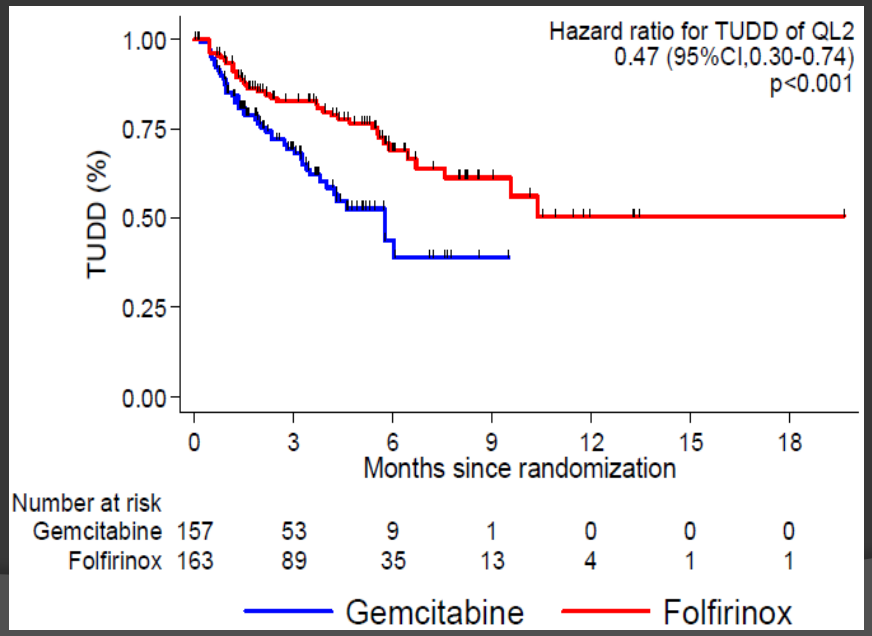
Conroy T et al, N Engl J Med. 2011 May 12;364(19):1817-25

PRODIGE 4/ACCORD 11

- 2nd line:
  - F group: G alone (82.5%), G-com (12.5%)
  - G group:
    - FOLFOX (49.4%), GO (17.6%), PFL (16.5%)
    - **FOLFIRINOX: 4.7%**

Event *Gr 3-4*	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

QoL



time until definitive deterioration (TUDD)

Toxicity

Ox: oxaliplatin
Iri: irinotecan
F: 5-FU
G: gemcitabine

Nab-P: nanoparticle paclitaxel
S-1: tegafur/Gimeracil/Oteracil potassium
Erl: erlotinib

(<1000/mm^3)

DI: dose intensity

Regimen	Age	PS	≥ Gr 3 Neutropenia (%)	(Combination arm) ≥ Gr 3 Other toxicity (%)	DI (%)
Ox + Iri + F	61	0-1	45.7	fatigue (23.6), vomit (14.5) diarrhea (12.7), neuro (7.3)	78/81/82
G	61		21		100
Nab-P + G	62	0-1	38	fatigue (17), diarrhea (6), neuro (17)	81/75
G	63		27		85
S-1 + G	65	0-1	62.2	fatigue (4.9), vomit (4.5), diarrhea (4.5), AST (12)	87/83
G	65		41		83
Erl + G	64	0-2	24	fatigue (15), diarrhea (6), infection (17), rash (6)	NA
G	64		27		

N Engl J Med. 2013;369(18):1691-703

J Clin Oncol 2013;31:1640-8

N Engl J Med 2011;364:1817-25

J Clin Oncol 2007;25:1960-6

Significant toxicity

Key milestone in 1st line tx

Pre-1996	The dark ages. Nothing works
1996	**Gemcitabine** improves survival compared with 5-FU. Gemcitabine is approved for PC
1996-2005	Many agents tested. No drug or drug combination is better than Gemcitabine
2005	**Erlotinib + Gemcitabine** modestly improves survival compared with Gemcitabine. Erlotinib is approved for PC
2005-2009	More drugs tested. Man
2010	**FOLFIRINOX** improves survival compared with Gemcitabine
2012	***nab*-Paclitaxel + Gemcitabine** improves survival compared with Gemcitabine

OS 5-7 m

Gem+ X

OS= 6.24 m, +0.3m

2006:S-1 was approved in Japan

Presented By Hedy Lee Kindler, MD at 2013 ASCO Annual Meeting

Topic

- Epidemiology
- Chemotx in advanced disease
  - 1st line
    - Gemcitabine-based regimens
    - Non-gemcitabine regimens
  - 2nd line

2nd line development

Regimen	Sample size	Median PFS/TTP (months)	Median OS (months)
OFF (oxaliplatin, 5-FU, folinic acid)[1]	76	3.0	6.1
FOLFOX[2]	46	3.7	5.8
CapOx[3]	41	2.3	5.4
FOLFIRI[4]	63	3.0	6.6
Irinotecan[5]	56	2.9	5.3
Capecitabine[6]	39	2.3	7.6
S-1[7]	67	2.1	5.8
MM-398 (nanoliposomal CPT11)[8]	40	2.4	5.2

1. Pelzer, J Clin Oncol 2008 (abstract); 2. Berk, Hepatogastroent 2012; 3. Xiong, Cancer 2008; 4. Neuzillet, World J Gastroent 2012; 5.Takahara, Cancer Chemother Pharmacol 2013; 6. Boeck, Oncology 2007; 7. Todaka, Jpn J Clin Oncol 2010;8. Ko, Br J Cancer 2013.

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Oettle H et al, J Clin Oncol. 2014 Aug 10;32(23):2423-9

OFF vs. FF (CONKO-003)

1˚ endpoint: OS

Inclusion

- 1st line G alone
- KPS≥70
- Adequate organ function
- >18 y/o

STRATIFICATI

Mets
Duration of 1st line
KPS

RANDOMIZATI

OFF (N=76)

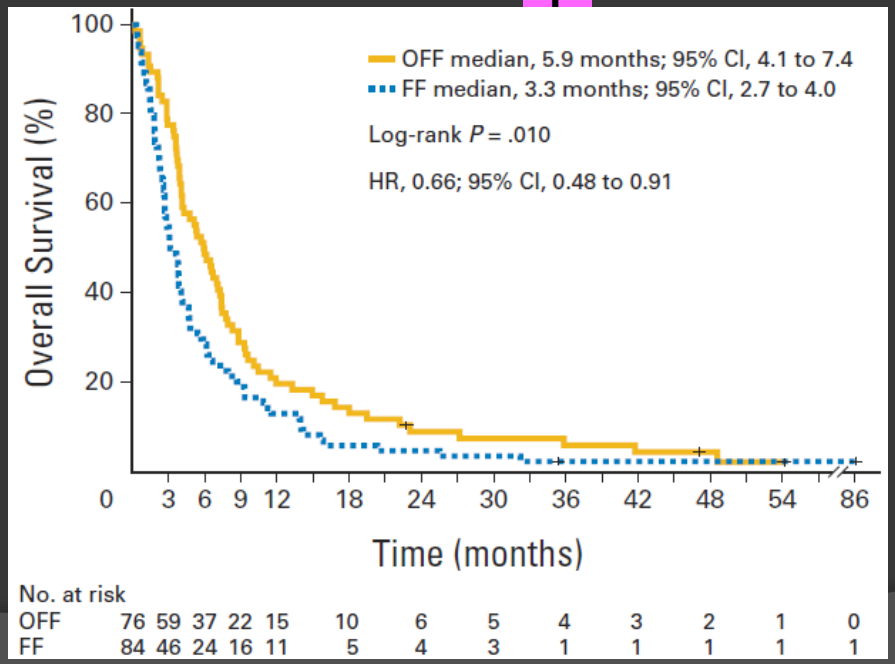
Oxa 85 mg/m², D8/22

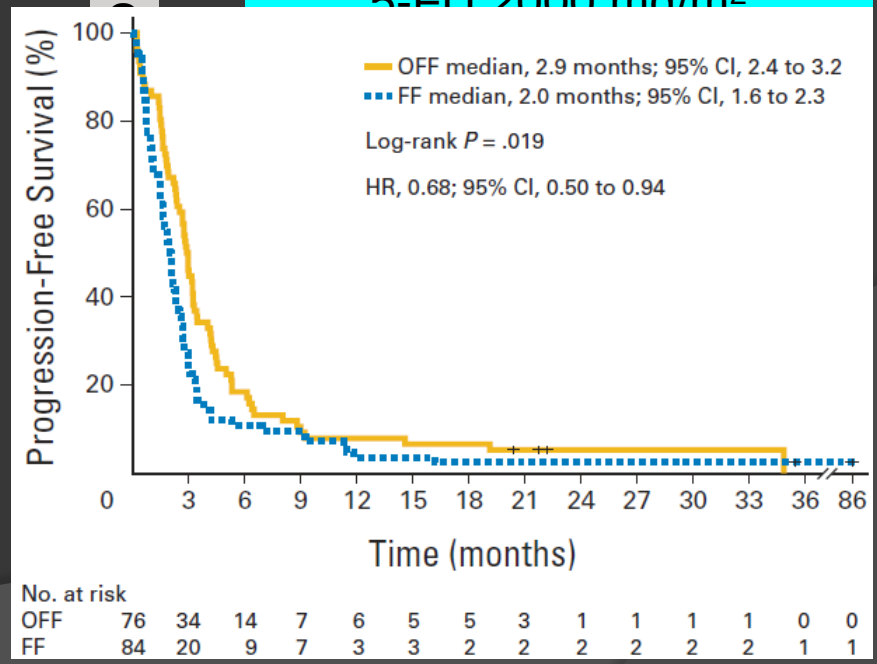
+ FF 4 of 6 wks

FF (N = 84)

LV 200 mg/m²

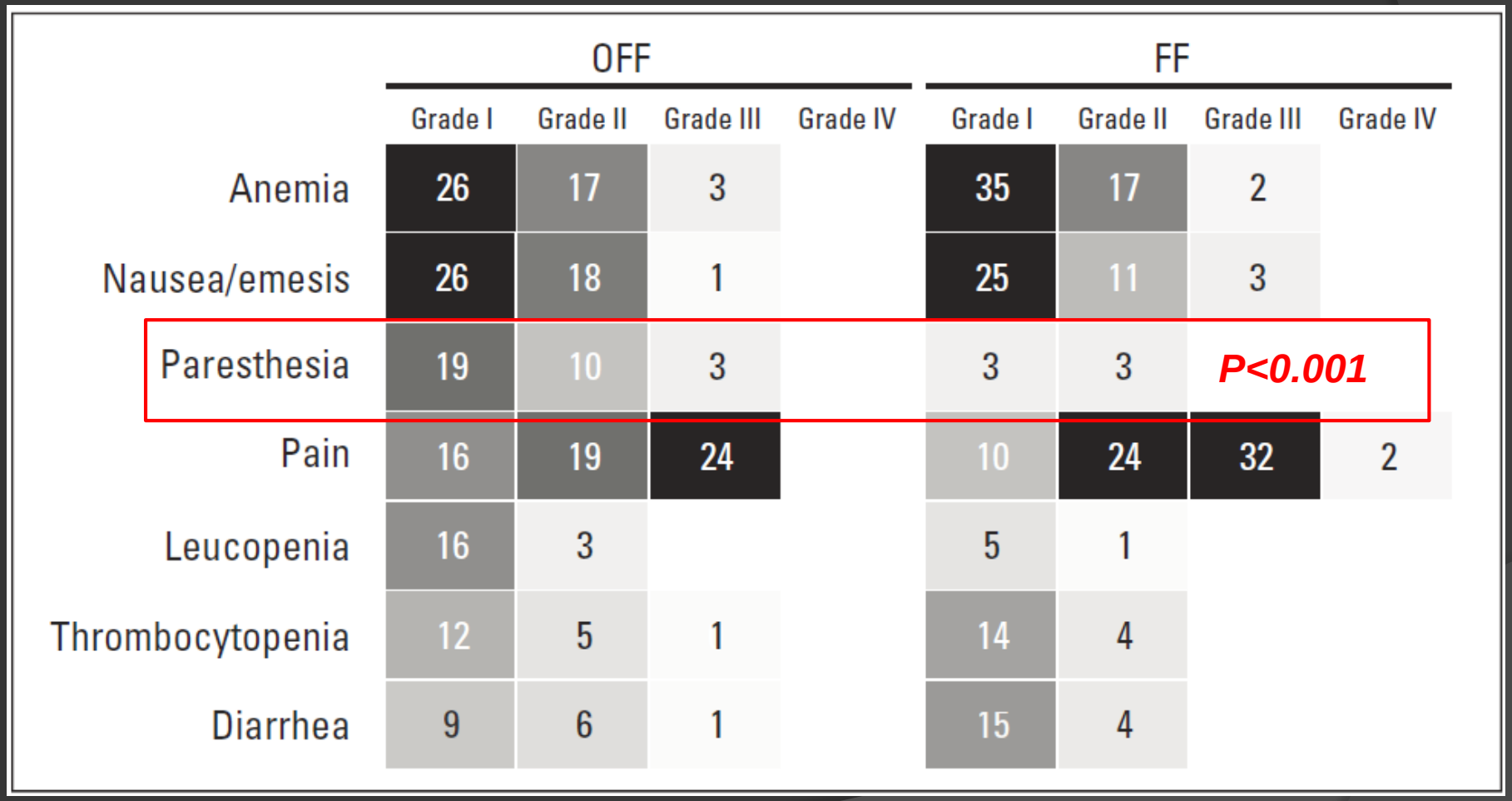
5-FU 2000 mg/m²





Oettle H et al, J Clin Oncol. 2014 Aug 10;32(23):2423-9

AE



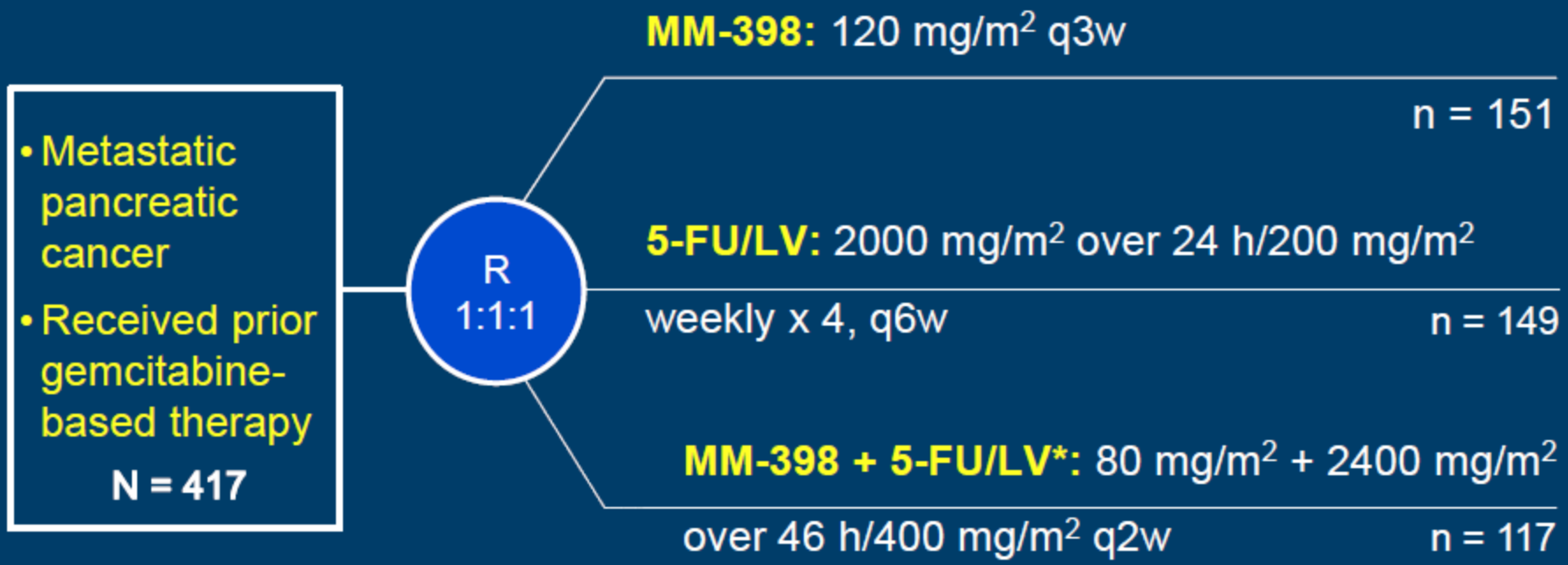
	OFF				FF			
	Grade I	Grade II	Grade III	Grade IV	Grade I	Grade II	Grade III	Grade IV
Anemia	26	17	3		35	17	2	
Nausea/emesis	26	18	1		25	11	3	
Paresthesia	19	10	3		3	3	P<0.001	
Pain	16	19	24		10	24	32	2
Leucopenia	16	3			5	1		
Thrombocytopenia	12	5	1		14	4		
Diarrhea	9	6	1		15	4		

NAPOLI-1: Randomized Phase 3 Study of MM-398 (nal-IRI), With or Without 5-Fluorouracil and Leucovorin versus 5-Fluorouracil and Leucovorin, in Metastatic Pancreatic Cancer Progressed on or following Gemcitabine-Based Therapy

Daniel Von Hoff,[1] Chung-Pin Li,[2] Andrea Wang-Gillam,[3] György Bodoky,[4] Andrew Dean,[5] Gayle Jameson,[1] Teresa Macarulla,[6] Kyung-Hun Lee,[7] David Cunningham,[8] Jean Frédéric Blanc,[9] Richard Hubner,[10] Chang-Fang Chiu,[11] Gilberto Schwartsmann,[12] Jens Siveke,[13] Fadi Braiteh,[14] Victor Moyo,[15] Bruce Belanger,[15] Navreet Dhindsa,[15] Eliel Bayever,[15] Li-Tzong Chen[16]

[1]TGen, Scottsdale Healthcare, Scottsdale, AZ, USA; [2]Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan; [3]Washington University, St. Louis, MO, USA; [4]St László Teaching Hospital, Budapest, Hungary; [5]St John of God Hospital, Subiaco, Western Australia, Australia; [6]Vall d'Hebron University Hospital, Barcelona, Spain; [7]Seoul National University Hospital, Seoul, South Korea; [8]The Royal Marsden Hospital, London, UK; [9]Hôpital Saint-André, Bordeaux, France; [10]The Christie NHS Foundation Trust, Manchester, UK; [11]China Medical University Hospital, Taichung, Taiwan; [12]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [13]Klinikum rechts der Isar der TU München, Munich, Germany; [14]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [15]Merrimack Pharmaceuticals Inc., Cambridge, MA, USA; [16]National Institute of Cancer Research, Tainan, Taiwan

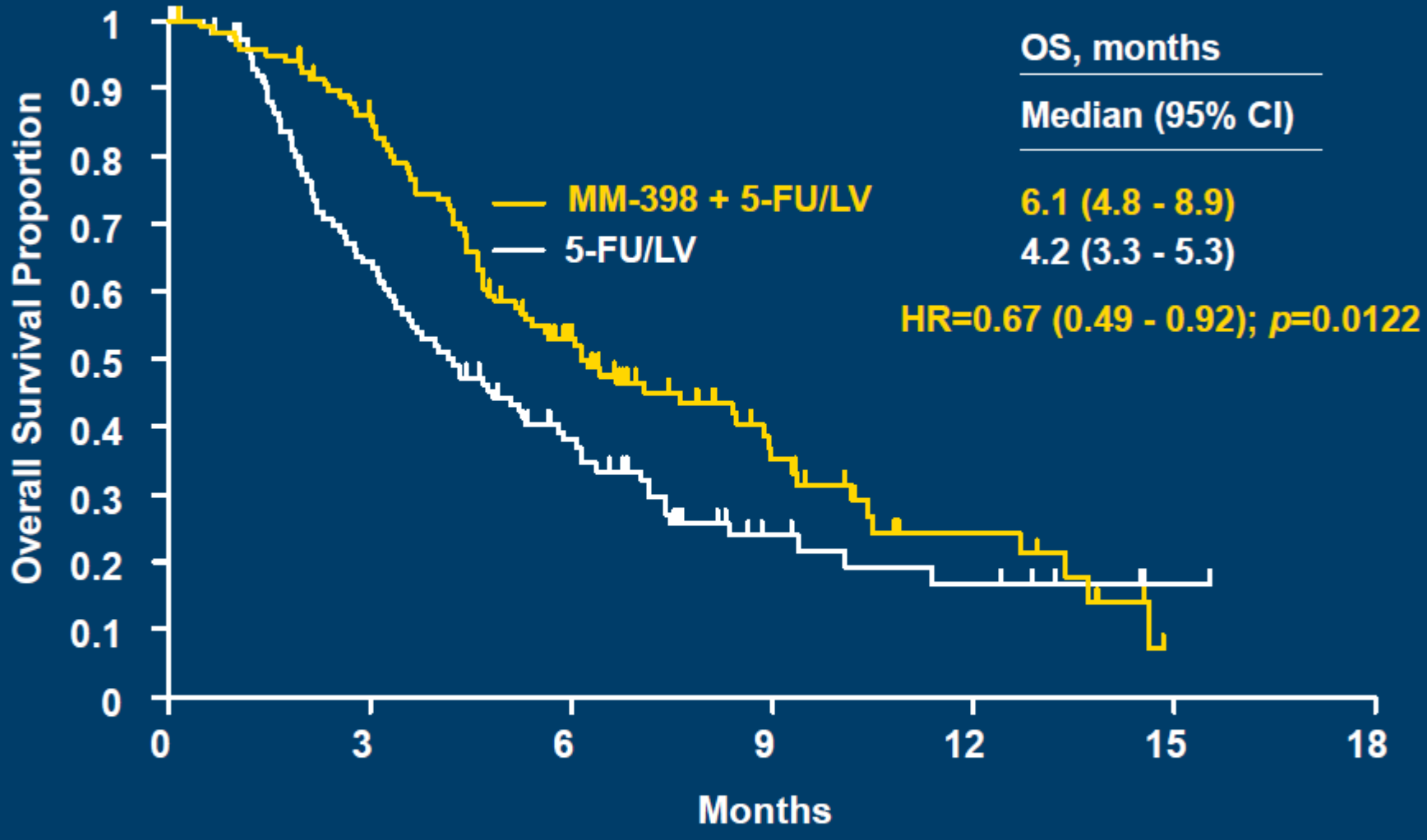
NAPOLI-1 Study Design



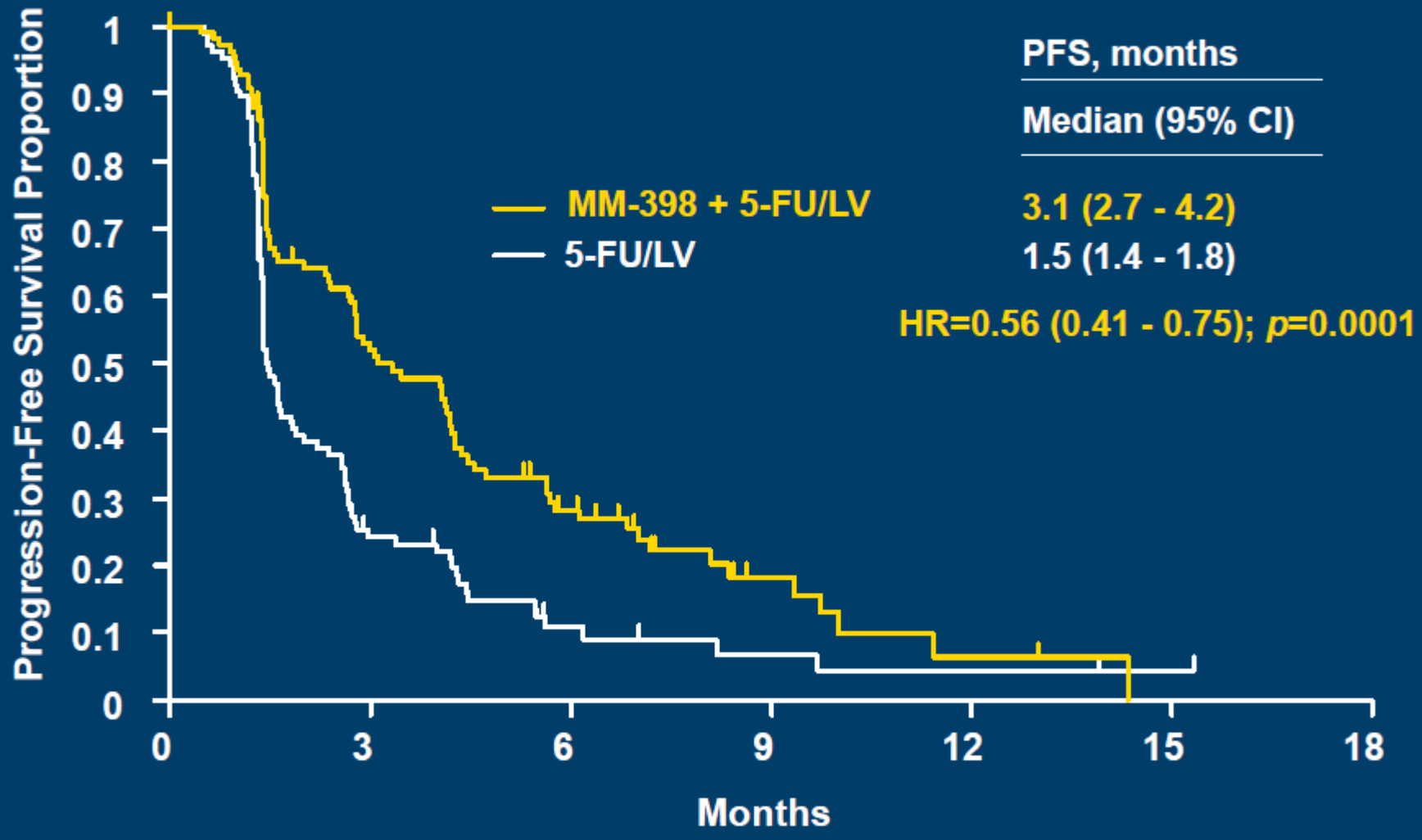
- Primary endpoint: Overall survival
- Secondary endpoints: PFS, ORR, CA19-9 response, and safety
- Stratification factors: Albumin, KPS, and ethnicity

* Study was amended to add the MM-398 + 5-FU/LV arm once safety data on the combination became available; 63 patients already had been enrolled in the original 2-arm study at the time of amendment.

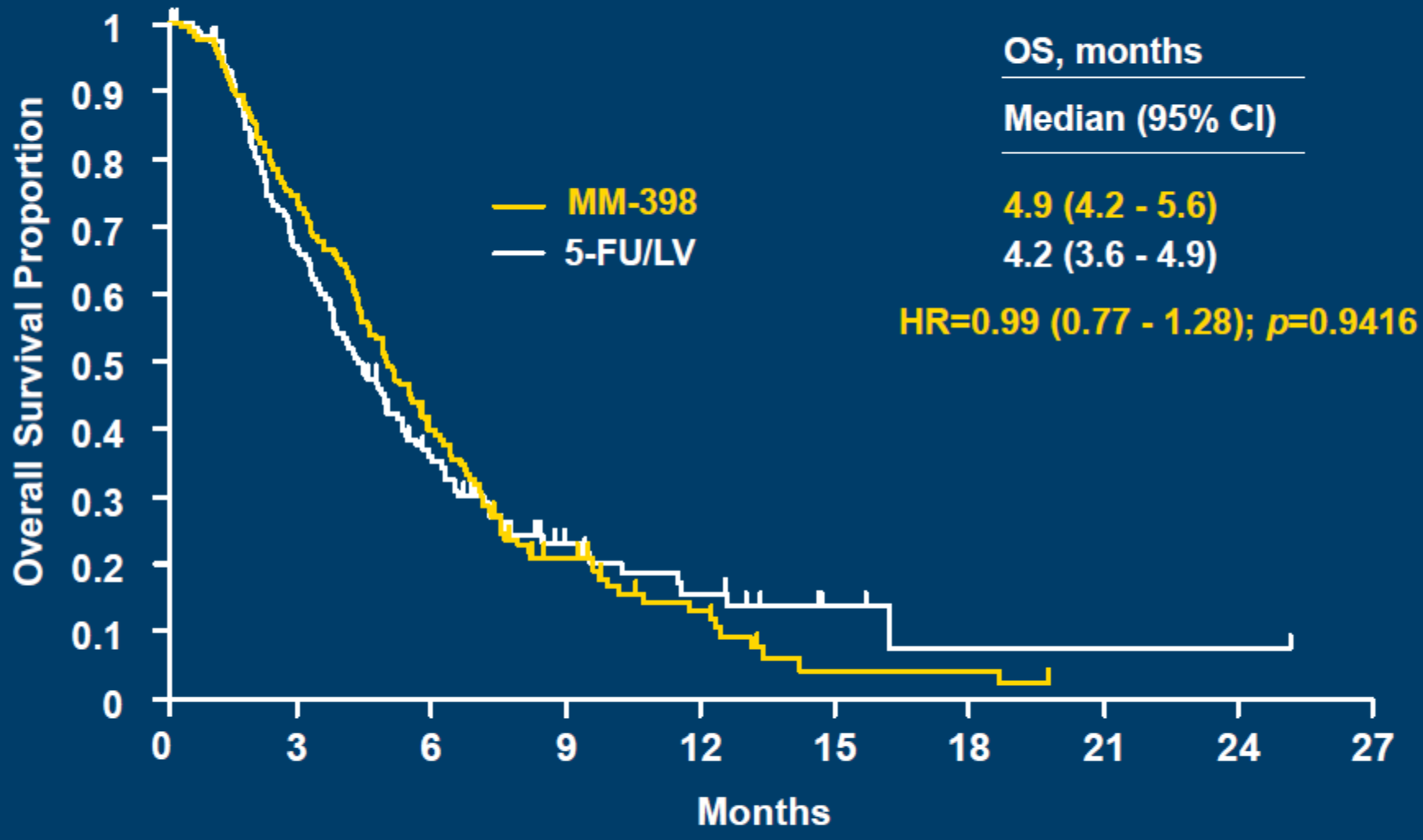
OS: MM-398 + 5-FU/LV



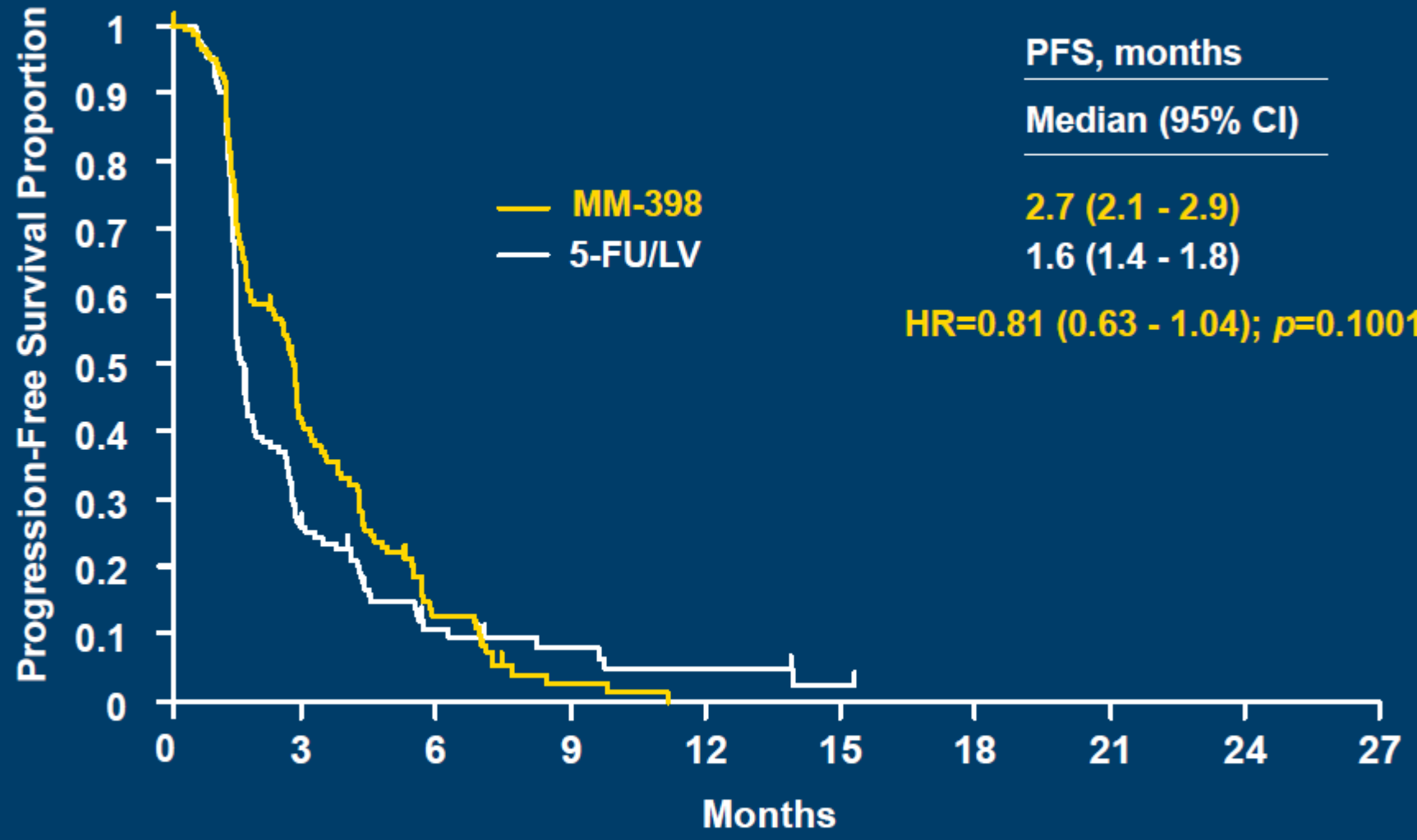
PFS: MM-398 + 5-FU/LV



OS: MM-398 Monotherapy



PFS: MM-398 Monotherapy



PFS, months	
Median (95% CI)	
2.7 (2.1 - 2.9)	
1.6 (1.4 - 1.8)	

HR=0.81 (0.63 - 1.04); *p*=0.1001

Summary - Survival

Disease Stage	Percent of Patients at Diagnosis	Treatment	Median Survival, mos
Resectable	15%	Surgery+ adjuvant	15 - 20m
Locally advanced	25%	CT/CCRT	9 - 12m
Metastatic	60%	CT	6 - 10 m

1. Geer RJ, Brennan MF. Am J Surg 1993; 165:68-72.
2. Willett CG, et al. J Clin Oncol. 2005;23:4538-4544.s

總結

- 併用藥物往往增加毒性
- 化學治療仍然是目前主要的治療方式
- 鼓勵參加臨床試驗
- 尋找預測因子是可行的

CHEMOTHERAPY IN BILIARY TRACT CANCER

Pooled Analysis

- Looked at mostly phase II trials
  - RR (N=2,810 pts, 104 trials) 22.6%
  - TTP (N=1,543pts, 60 trials) 4.1 m
  - OS (N=2,197 pts, 82 trials) 8.2 m
- Most important drugs: gemcitabine, fluoropyrimidines, platinums
  - Gemcitabine alone is not superior to fluoropyrimidines
  - Platinums increase the activity of both fluoropyrimidines and gemcitabine
  - Trend towards better OS comparing two drug combination over monotherapy (9.0 vs 7.5 m, p=0.086)
  - Gemcitabine and platinums had highest RRs

Eckel F, et al. Br J Cancer 2007;96:896-902

Phase III Study: UK ABC-02

Eligible cholangiocarcinoma, gallbladder, ampullary carcinoma patients (n=410)

Randomized 1:1

(stratified by centre, primary site, PS, prior therapy and locally advanced vs. metastatic)

Arm A n=206

Gem 1000 mg/m^2 D1,8,15 q 28d

24 weeks (6 cycles)

Arm B n=204

Cisplatin 25 mg/m^2

+ Gem 1000 mg/m^2

D1,8 q 21d

24 weeks (8 cycles)

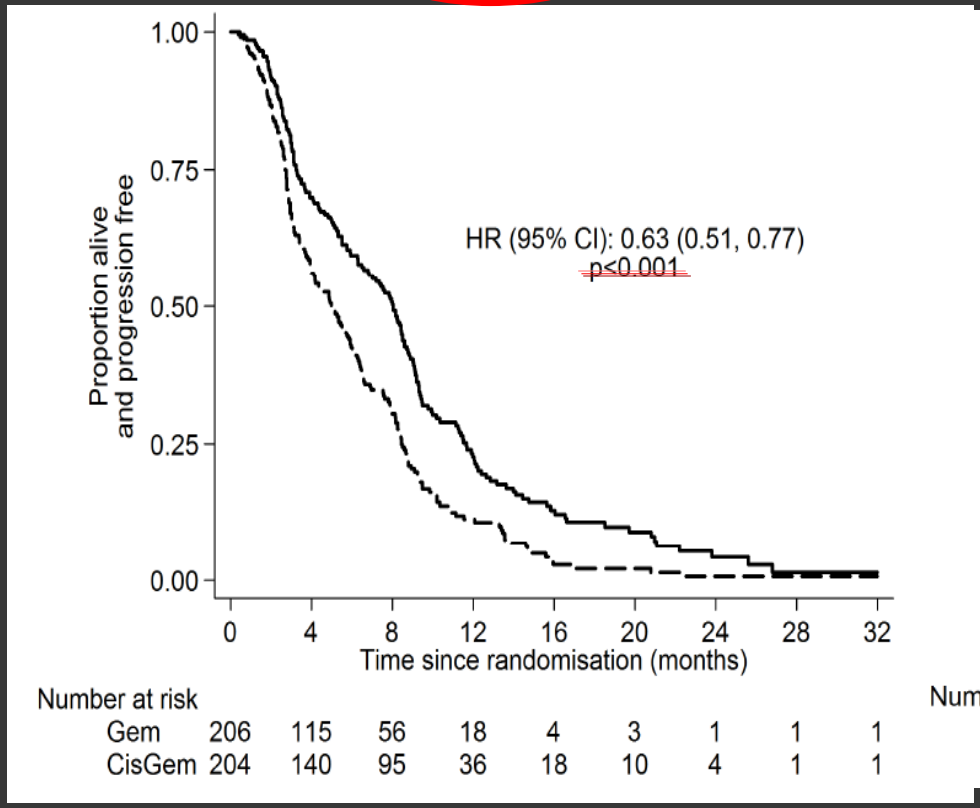
Primary endpoint OS

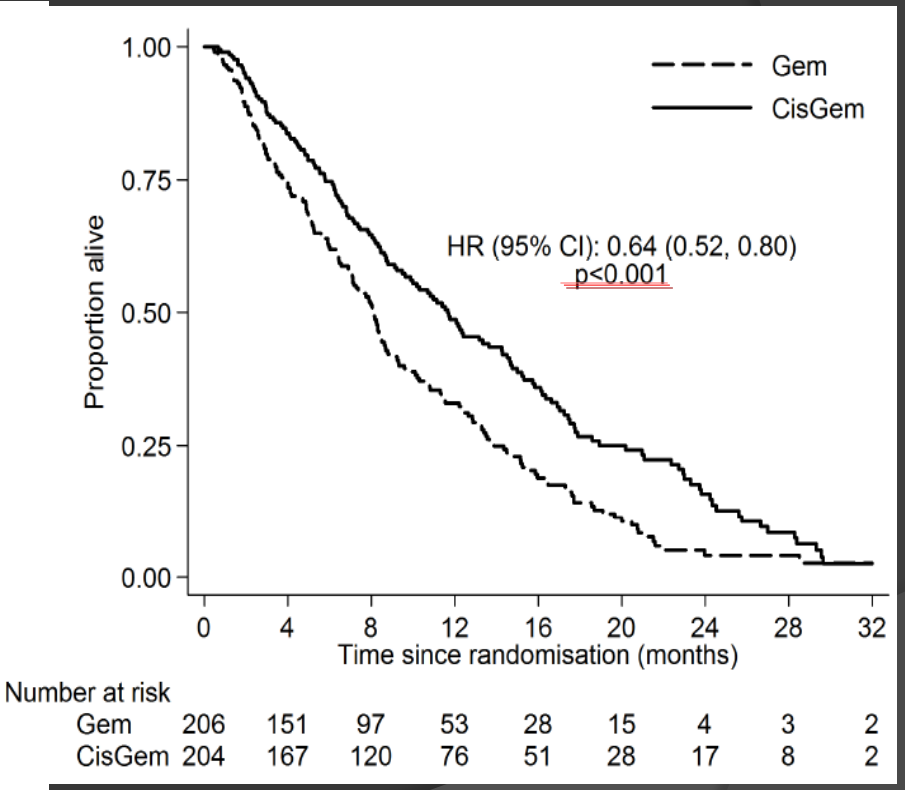
Valle et al, NEJM 2010;362:1273

ABC-02 Results: PFS & OS (ITT)

PFS 5 → 8m

OS 8.1 → 11.7m

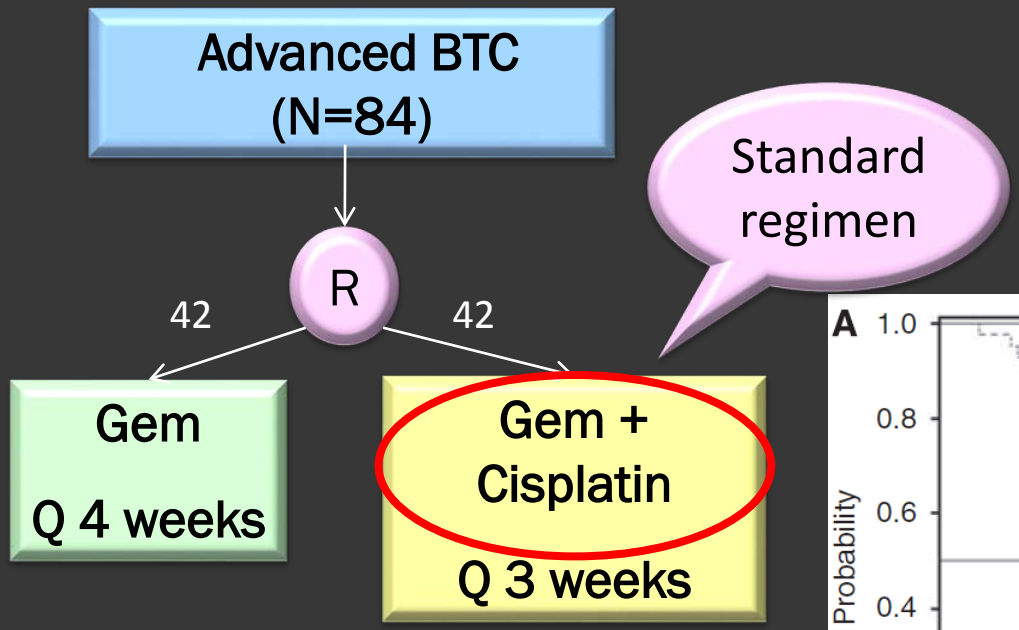




RR: 26.1 v 15.5%
DCR: 81.4 v 71.8% (p=0.049)

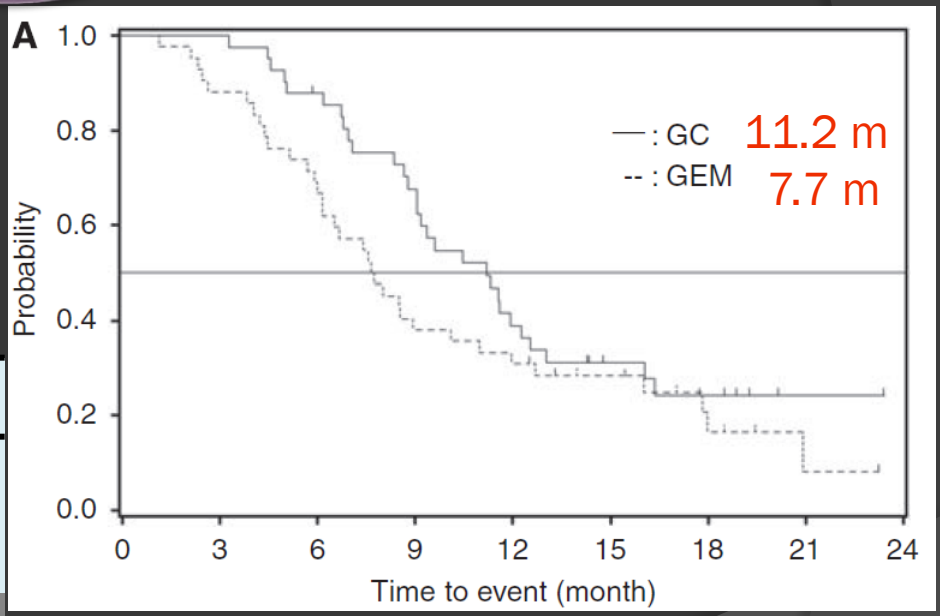
Valle et al, NEJM 2010;362:1273

Randomized Phase II Study: Japan BT-22



	Gem	Gem + Cisplatin
Intrahepatic/Extra- GB/Ampullary	34/20/ 37/10	33/26/ 41/0
Response Rate/DCR	11.9/38.1%	19.5/48.8%
1-yr survival rate	31%	39%
PFS	3.7m	5.8m

Overall Survival



Okusaka T, et al. Br J Cancer 2010;103:469-474.

Second line therapy

Regimen	Patients Treated	Patients Treated and Evaluated	Objective Response Rate	Disease Control Rate
FOLFIRI/XELIRI, No. (%)	64 (32.7)	61 (32.8)	7 (11.5)	25 (41.0)
LV5FU2 plus cisplatin, No. (%)	38 (19.4)	37 (19.9)	5 (13.5)	23 (62.2)
5-FU/capecitabine, No. (%)	40 (20.4)	37 (19.9)	4 (10.8)	17 (45.9)
FOLFOX/XELOX, No. (%)	21 (10.7)	20 (10.8)	2 (10.0)	9 (45.0)
Sunitinib, No. (%)	10 (5.1)	9 (4.8)	1 (11.1)	6 (66.7)
Other, No. (%)[a]	23 (11.7)	22 (11.8)	2 (12)	12 (54.5)
All regimens, No. (%)	196 (100)	186 (100)	22 (11.8)	92 (49.5)
P	–	–	.99	.41

Cancer 2015

Molecular-targeted Agents

- No survival benefit was achieved until now

	Line	Phase	Number of patients	ORR	mPFS (months)	mOS (months)
EGFR						
GemOx ± erlotinib	1st	III	268	16% versus 30%	4.2 versus 5.8	9.5 versus 9.5
GemOx ± cetuximab	1st	II	150	29% versus 23%	5.3 versus 6	12.4 versus 11
GemOx/cetuximab	1st	II	30	63%	8.8	15.2
GemOx/cape/Pmab	1st	II	46	33%	8.3	10
GemIrino/Pmab	1st	II	26/42			12.7
Erlotinib	2nd	II	42	8%	2.6	7.5
VEGF						
GemOx/bevacizumab	1st	II	35	40%	7	12.7
Sorafenib	Any	II	46	2%	2.3	4.4
Sorafenib	1st	II	31	0%	3	9
Sunitinib	2nd	II	56	8.9%		4.8
MEK						
Selumitinib	2nd	II	56	12%	3.7	9.8
HER-2						
Lapatinib	2nd	II	17	0%	1.8	5.2
Combination						
Erlotinib/bevacizumab	1st	II	53	12%		9.9
Gemcitabine ± S-1	1st	II	101		7.1 versus 4.2	12.5 versus 9

Noel M, et al. OncoTargets and Therapy 2013:6 1545–1552

S-1 IN BILIARY TRACT CANCER

S-1: Japanese Phase II Trials for Approval

- Patients with pathologically confirmed advanced BTC

	S-1 (N=19) [1]	S-1 (N=40) [2]
S-1 dosage	80-120mg/day for 28 days, followed by 14 days rest, q6w	
ORR	21.1% (4/19)	35% (14/40)
OS mos	8.3	9.4
PFS mos	3.7	3.7
Grade 3/4 ANC	5.3%	5%
Grade 3/4 anorexia	10.5%	7.5%
Grade 3/4 diarrhea	5.3%	0%
Grade 3/4 fatigue	10.5%	7.5%

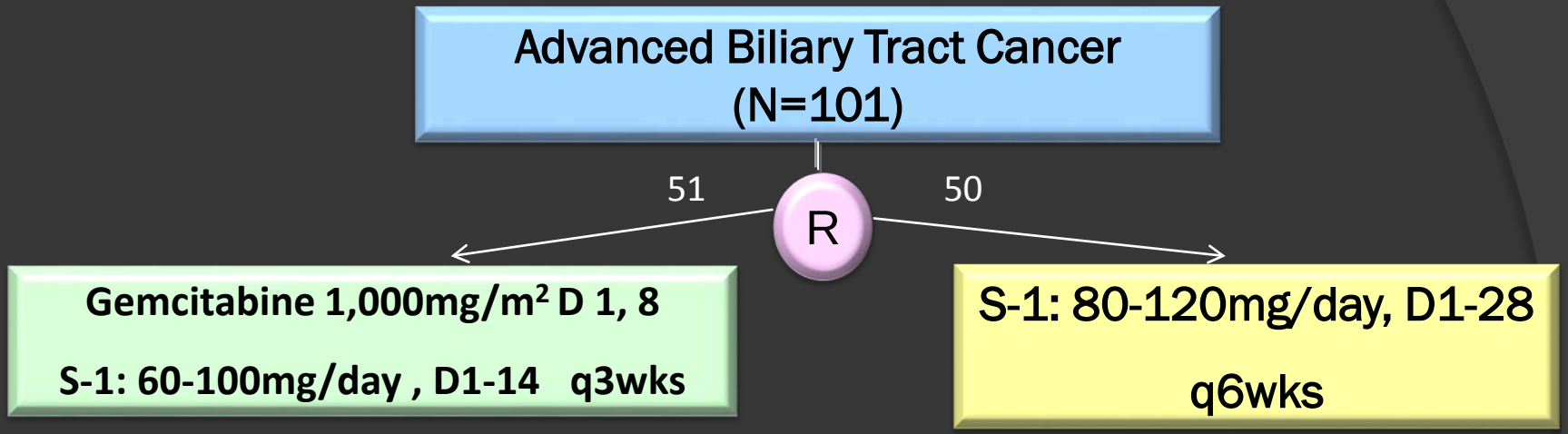
1. Ueno H, et al. Br J Cancer 2004; 91:1769–14 *2. Furese J, et al. Cancer Chemother Pharmacol 2008; 62:849–55*

S-1 and Gemcitabine Combination Therapy Phase II Study

	Phase II Study (N=35) [1]	Phase II Study (N=25) [2]
S-1+Gemcitabine dosage	S-1: 80-120mg/day d1-14 Gemcitabine: 1,000mg/m^2 D 1, 15 Q4wks	S-1: 60-100mg/day d1-14 Gemcitabine: 1,000mg/m^2 D 1, 8 Q3wks
ORR	34.3%	30.4%
OS mos	11.6	12.7
PFS mos	5.9	3.7
Grade 3/4 ANC	34%	56%
Grade 3/4 leukopenia	23%	24%
Grade 3/4 anemia	20%	8%
Grade 3/4 diarrhea	-	4%

1. Sasaki T, et al.Cancer Chemother Pharmacol 2010;65:1101-07 2. Kanai M, et al. Cancer Chemother Pharmacol 2011;67:1429-34

S-1 and Gemcitabine Combination Therapy Randomized Phase II Study JCOG 0805



	G+S	S-1	
1-year survival rate	52.9%	40%	Primary end point
ORR	36.4%	17.4%	
Median PFS	7.1m	4.2m	P<0.0001 HR=0.44
Median OS	12.5m	9.0m	P=0.52 HR=0.86
Grade 3-4 ANC	60.7%	4%	

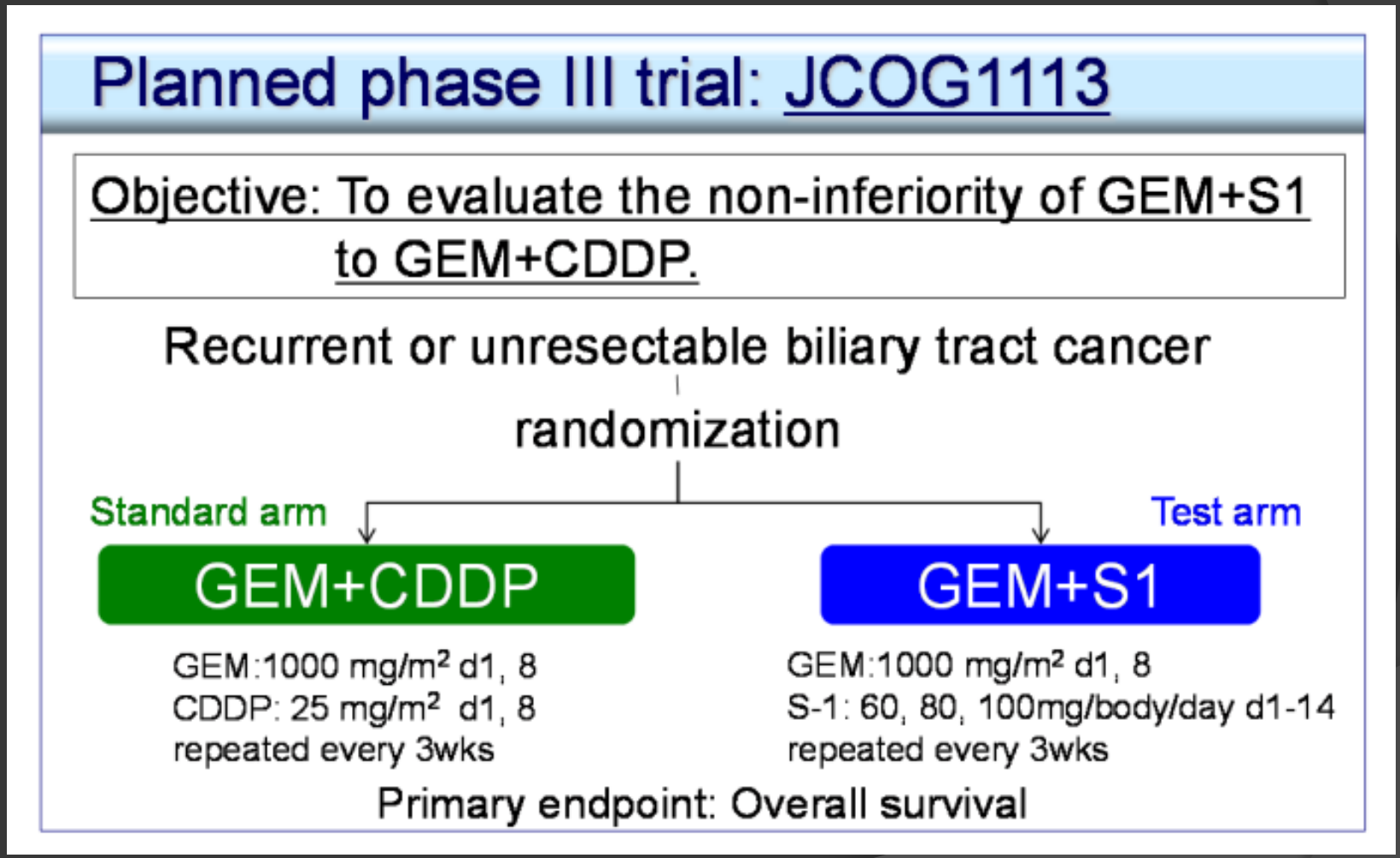
Morizane C et al. Cancer Sci. 2013 ;104:1211-6

JCOG 0805 versus BT-22 Study

Trial/ Regimen	JCOG 0805[1] Gemcitabine+S-1	BT-22[2] Gemcitabine+ Cisplatin
1-year survival rate	52.9%	39%
ORR	36.4%	19.5%
Median PFS	7.1m	4.2m
Median OS	12.5m	11.2m
Grade 3-4 ANC	60.7%	56.1%
All-grade Nausea	35.3%	68.3%
All-grade Vomiting	13.7%	48.8%
All-grade Anorexia	51%	80.5%

1. Morizane C et al. Cancer Sci. 2013 ;104:1211-6 2.Okusaka T, et al. Br J Cancer 2010;103:469-474

Japan Ongoing Phase III Study in Unresectable Biliary Tract Cancer: JCOG 1113



Conclusions

- BTC: Gemcitabine and S-1 combination chemotherapy has promising efficacy and good tolerability in patients with advanced biliary tract cancer.


謝謝聆聽