胰臟癌之治療新趨勢

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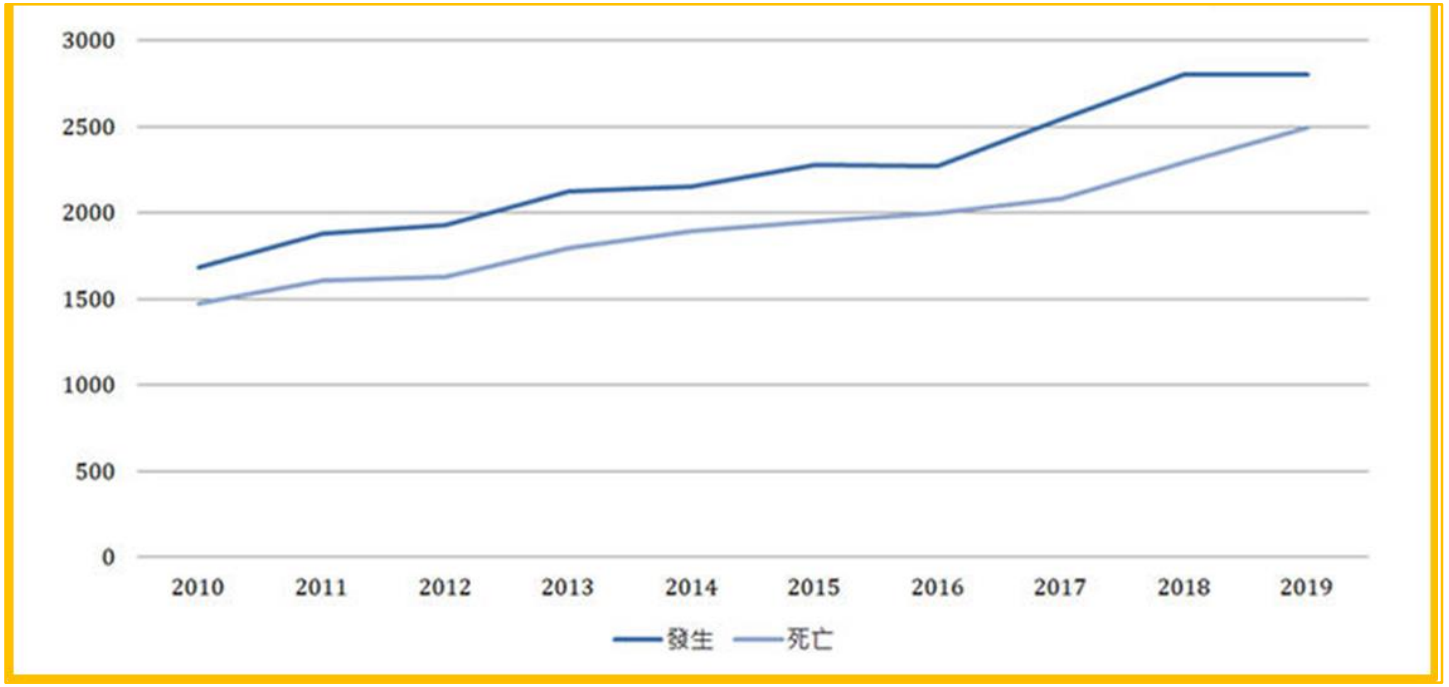
2023/3/18

衛生福利部
國民健康署

歷年胰臟癌發生及死亡人數



（國內每年發生人數與因病死亡人數相近。資料來源／衛福部國健署癌症登記報告）

衛生福利部
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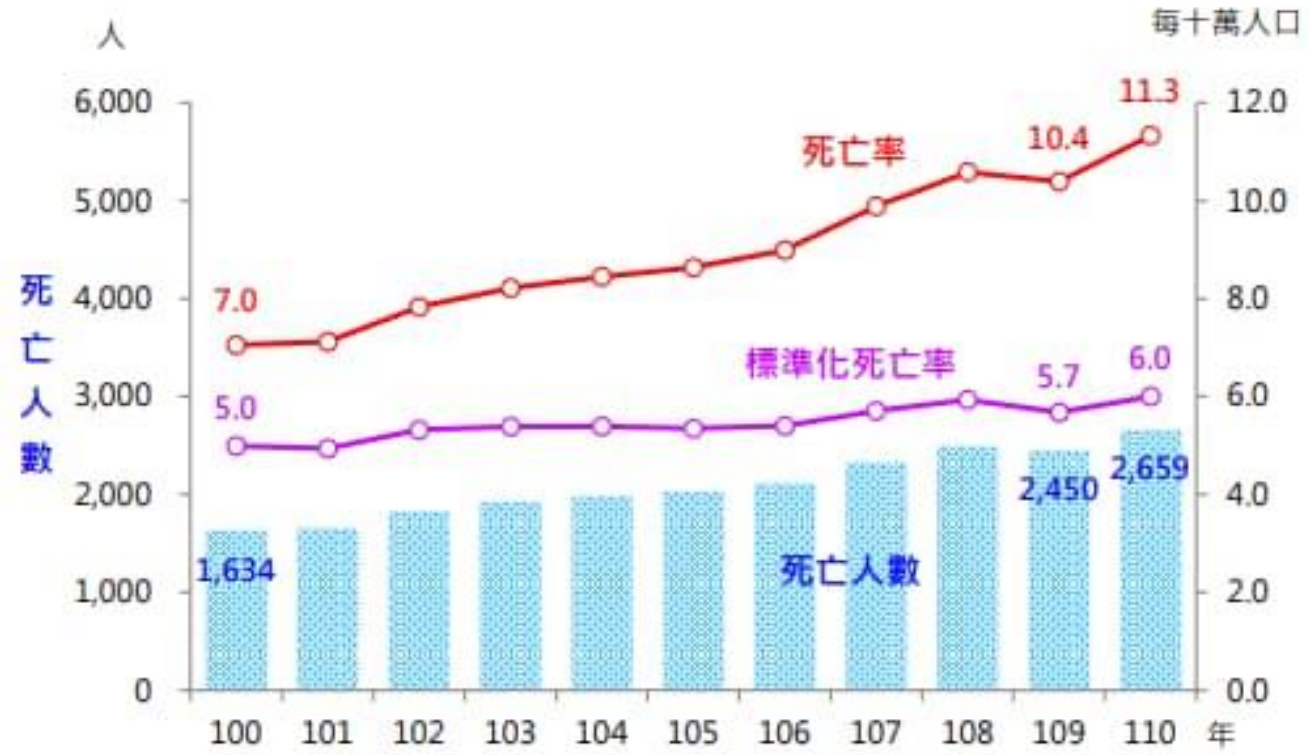
圖 7-2　近年胰臟癌死亡概況



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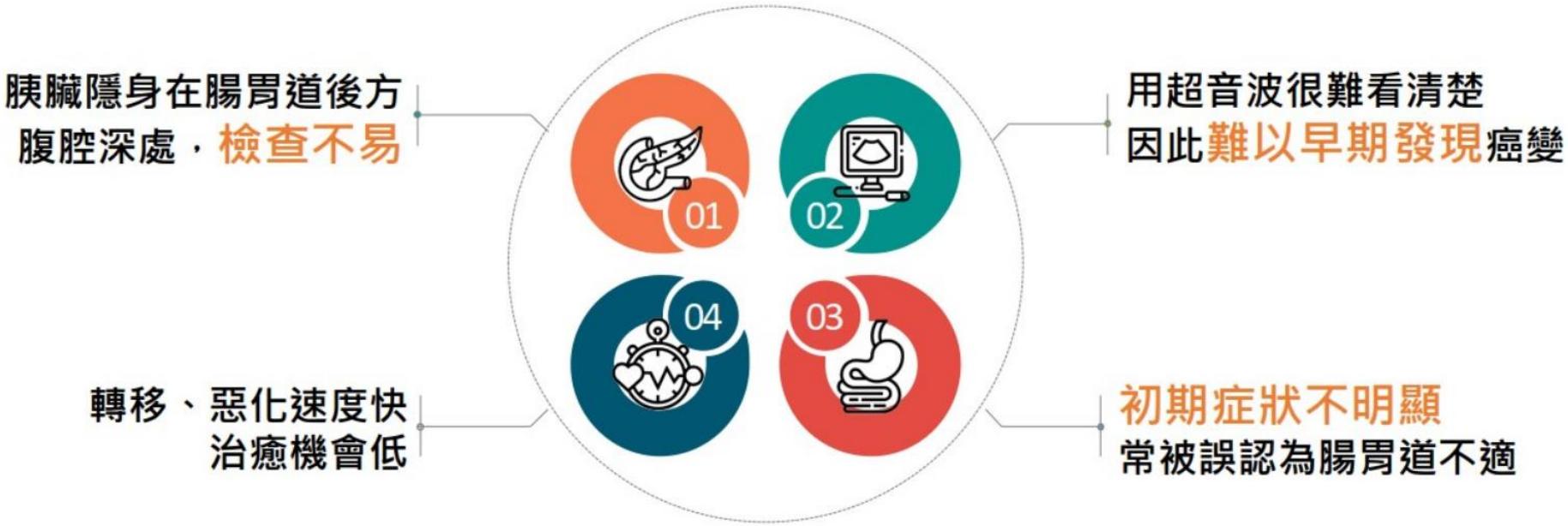
2021年十大致死癌症排名

排名	癌症別	死亡率	死亡人數
1	氣管、支氣管和肺癌	42.8%	1萬0040人
2	肝和肝內膽管癌	34.0%	7970人
3	結腸、直腸和肛門癌	28.4%	6657人
4	女性乳癌	24.6%	2913人
5	前列腺（攝護腺）癌	14.5%	1689人
6	口腔癌	14.5%	3395人
7	胰臟癌	11.3%	2695人
8	胃癌	9.8%	2310人
9	食道癌	8.6%	2030人
10	卵巢癌	5.9%	696人

為何胰臟癌致死率這麼高？



由於初期症狀不明顯，難以早期發現癌變，逾8成患者確診已晚期

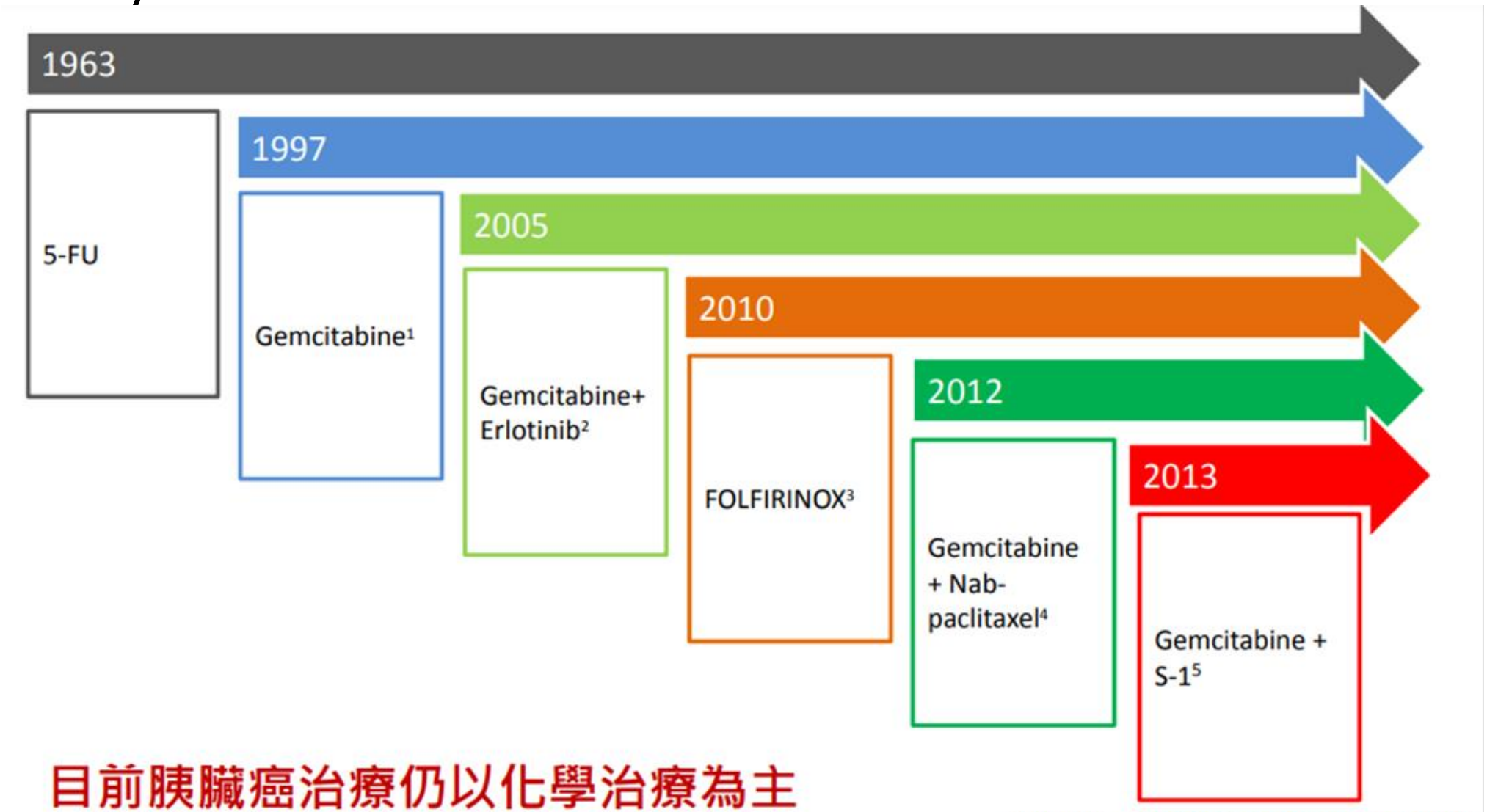
胰臟癌發生率並非最高，但初診即晚期加上易轉移特性導致死亡率高。（圖片來源／葉大森醫師提供）

胰臟癌患者好發於60歲左右，若平時出現腹痛、體重減輕等症狀，就要提高警覺。（圖片來源／葉大森醫師提供）

2015~2020 癌登資料

- 年齡中位數: **68.5**
- 性別比: 男>女(1.22~1.38:1)
- 組織型態分布: 腺癌(70.16%~60.57%)
- 首次治療:化學治療(51.8%), 手術治療(26.5%),緩和照護(42.3%)

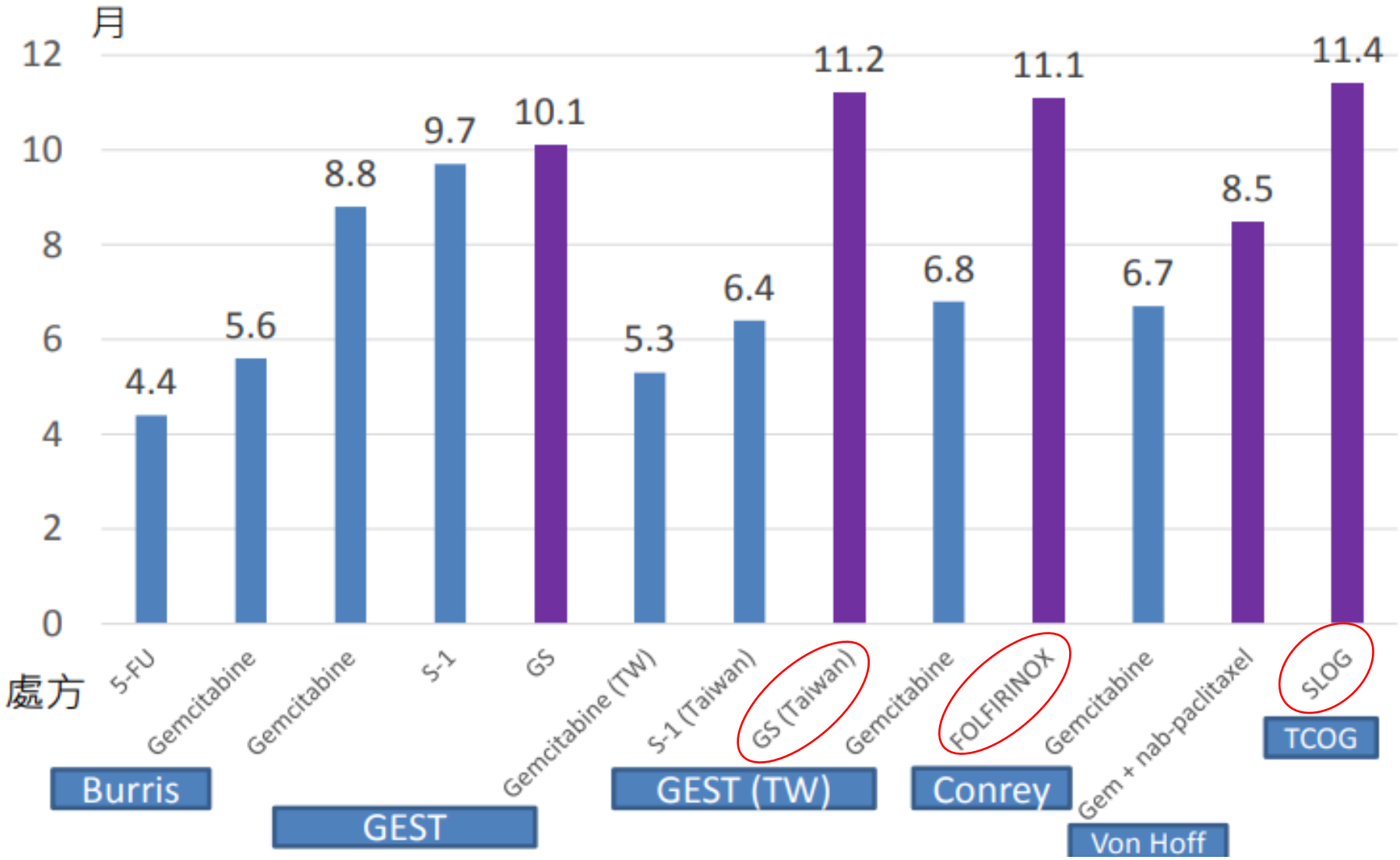
Locally advanced and metastasis



目前胰臟癌治療仍以化學治療為主

1.Burris, JCO 1997; 2. Moore, JCO 2007
3.Conroy, NEJM 2011; 4. von Hoff, NEJM 2013; 5.Ueno H, JCO 2013

併用化療有更好的存活


月
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處方
5-FU
Gemcitabine
Gemcitabine
S-1
GS
Gemcitabine (TW)
S-1 (Taiwan)
GS (Taiwan)
Gemcitabine
FOLFIRINOX
Gemcitabine
Gem + nab-paclitaxel
SLOG
Burris
GEST
GEST (TW)
Conrey
Von Hoff
TCOG

表一：胰臟癌術後輔助性化療臨床試驗進程

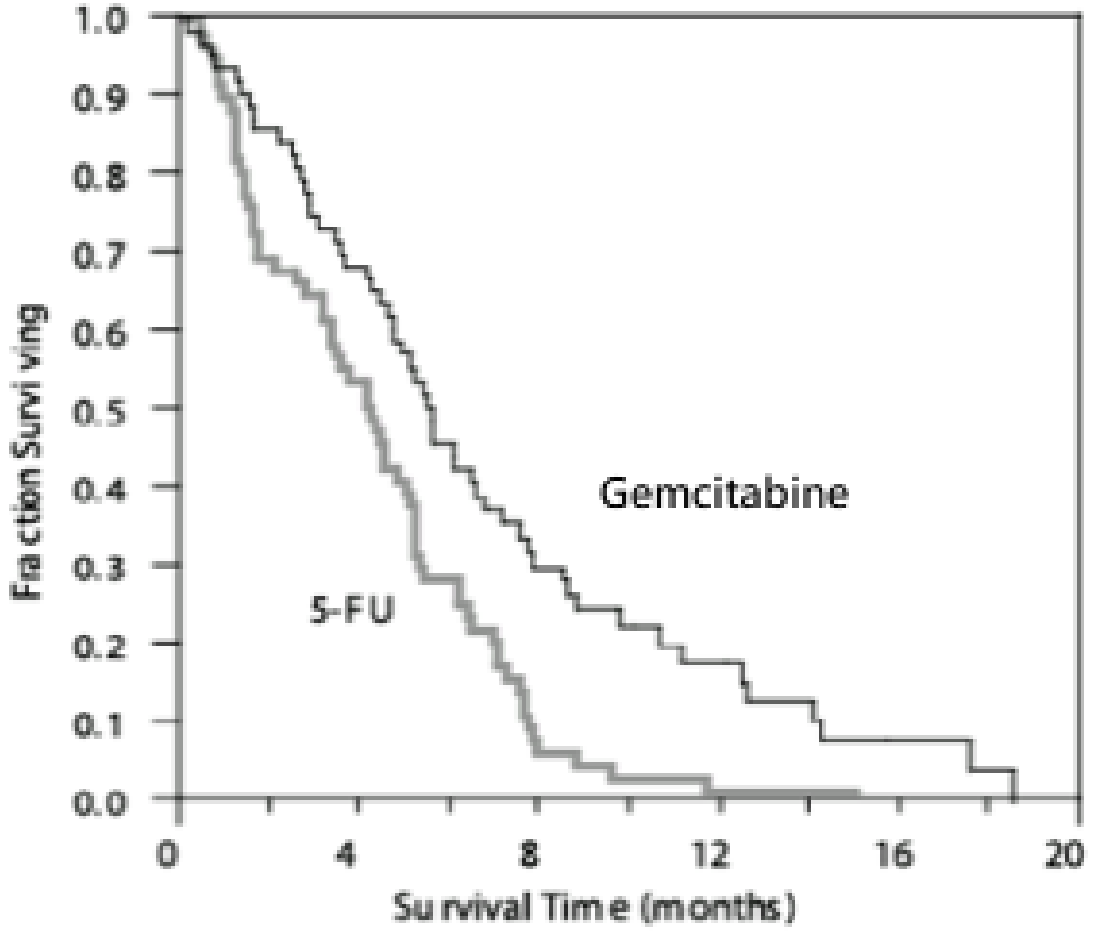
Author/Trial	Number	Treatment	Patient selection	OS(m)	DFS(m)
GITSG study Arch Surg 1986	21	chemoradiation with 5-FU	胰臟癌接受根除性手術	20 (p=0.01)	11 (p=0.01)
	22	surgery alone		11	9
ESPAC-3 JAMA 2010	537	gemcitabine	胰臟癌接受根除性手術	23.6 (p=0.39)	14.3 (p=0.53)
	551	5-FU+covorin		23	14.1
CONKO-001 JAMA 2013	179	gemcitabine	無術前化療之胰臟癌接受根除性手術	22.8 (p=0.01)	13.4 (p<0.001)
	175	surgery alone		20.2	6.7
JASPAC-01 Lancet 2016	192	S1	日本族群胰臟癌接受 R0 切除	46.5 (p<0.001)	22.9 (p<0.001)
	193	gemcitabine		25.5	11.3
ESPAC-04 Lancet 2017	364	gemcitabine+ capecitabine	胰臟癌接受根除性手術	28 (p=0.032)	13.9 (p=0.082)
	366	gemcitabine		25.5	13.1
PRODIGE 24/ CCTG PA6 NEJM 2018	247	mFOLFIRINOX	胰臟癌接受根除性手術，CA-199 <180U/ml	54.4 (p=0.003)	21.6 (p<0.001)
	246	gemcitabine		35	12.8

DOI：10.6314/JIMT.202204_33(2).03　內科學誌 2022：33：102-109

Gemcitabine in Pancreatic Cancer

	Gemcitabine	5-FU	
病患數目	63	63	
年齡中位數	62歲	61歲	
範圍	37-79	36-77	
病程為第四期	71.4%	76.2%	
治療前之KPS指數≤70	69.8%	68.3%	
臨床效益反應率 (Clinical Benefit Response Rate)	22.2%	4.8%	P=0.004
存活期 (Overall Survival)			P=0.0009
中位數	5.7月	4.2月	
6個月之可能性 (6 mo survival rate)	(N=30) 46%	(N=19) 29%	
9個月之可能性 (9 mo survival rate)	(N=14) 24%	(N=4) 5%	
一年之可能性 (1 yr survival rate)	(N=9) 18%	(N=2) 2%	
範圍	0.2-18.6月	0.4-15.1+ [d]月	
中位數之95%信賴區間	4.7-6.9月	3.1-5.1月	
到病程惡化前之時間 (TtPD)			P=0.0013
中位數	2.1月	0.9月	
範圍	0.1+-9.4月	0.1-12.0+ 月	
中位數之95%信賴區間	1.9-3.4月	0.9-1.1月	

Gemcitabine vs 5-FU



Burris HA, et al. J Clin Oncol. 1997;15:2403-2413

台灣日本完成第一個臨床三期試驗證實 S-1與Gemcitabine有相當的PFS, OS, 更好的Response

- Country: Japan/Taiwan
- Period: 2007 July – 2009 Oct
- Patients: 834 patients
  - 66 patients from Taiwan
- Primary endpoint: overall survival
  - Non-inferiority of S-1
  - Superiority of GS

Unresectable advanced PC

R

Control組
針劑 Gemcitabine
1000 mg/m² d1, 8, 15
Repeated every 4 weeks (n=277)
OS: 8.8m
PFS: 4.1m
RR: 13%

試驗組
口服 S-1
80, 100, 120mg*/body d1-28
Repeated every 6 weeks (n=280)
OS: 9.7m*
PFS: 3.8m*
RR: 21%**

試驗組
針劑Gemcitabine + 口服S-1
GEM: 1000mg/m2 d1, 8
S-1: 60, 80, 100mg*/body d1-14
Repeated every 3 weeks (n = 275)
OS: 10.1m
PFS: 5.7m**
RR: 29%**

Stratification factors:
- Metastatic vs. Locally advanced
- Institution

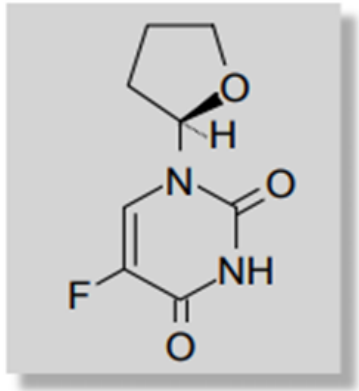
*Initial dose according to body surface area(m²):
BSA < 1.25, 1.25 <BSA <1.5, BSA≥1.5
Secondary endpoint: PFS, response rate, toxicity, QOL (EQ-5D)

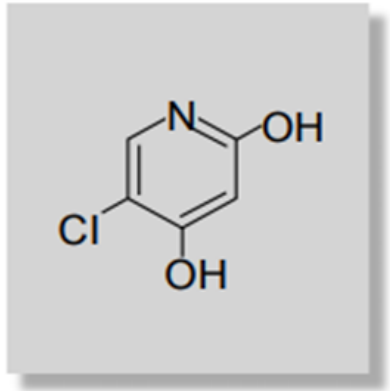
*non-inferiority to Gem, **superiority to Gem

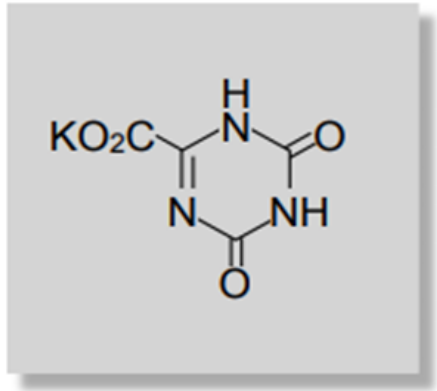
GEST 研究次族群分析

	Treatment (n)	Median overall survival (mon)	1 year survival rate (%)
All (Taiwan and Japan)	GEM (277)	8.8	35.0
	S-1 (280)	9.7	38.4
	GS (275)	10.1	40.4
Taiwan	**GEM (21)**	**5.3**	**23.8**
	S-1 (23)	**6.4**	**29**
	GS (22)	**11.2**	**45.5**

GOLFER 的組成成分







Tegafur **Gimeracil** **Oteracil potassium**

FT **CDHP** **Oxo**

1 : 0.4 : 1

GOLFER CAPSULES

- 成分： TEGAFUR (=FTORAFUR) 、 GIMERACIL 、 OTERACIL POTASSIUM
- 2006 ： S-1 was approved in Japan

健保價

20 mg ：148元/tab

25mg ：168元/tab

適應症

(一) 胃癌：
1. 胃癌術後輔助性化療，golfer用於罹患TNM Stage II (排除TI)、IIIA 或IIIB胃癌且接受過胃癌根除性手術之成年患者。
2. Golfer適用於治療無法切除之晚期胃癌。

(二) 胰臟癌：golfer適用於治療局部晚期或轉移性胰臟癌患者。

(三) 大腸直腸癌：golfer 與 Irinotecan 合併使用於已使用含有 Oxaliplatin 化學療法失敗之轉移性大腸直腸癌患者。

健保給付規定

9.46.Tegafur/gimeracil/oteracil複方製劑(如TS-1）：(103/6/1、105/12/1、109/2/1)

1.治療局部晚期無法手術切除或轉移性胰臟癌病人。

2.胃癌(105/12/1)

(1)胃癌術後輔助性化療，用於罹患TNMS tage Ⅱ(排除T1)、ⅢA或ⅢB胃癌且接受過胃癌根除性手術的成年患者，限用1年。

(2)需經事前審查核准後使用。

3.非小細胞肺癌(109/2/1)

(1)曾使用含鉑之化學藥物治療失敗的局部晚期或轉移性之非小細胞肺癌。

(2)不得與標靶治療、其他化療或免疫檢查點抑制劑併用。

Local advanced and metastasis

Table 1 Comparison of Survival and Toxicities Across the Three Major Positive Clinical Trials in Advanced Pancreatic Cancer

	Gemcitabine vs Gemcitabine/ Erlotinib Phase III trial[3]		ACCORD 11 trial[4]		MPACT[5]	
	Gemcitabine	Gemcitabine/ Erlotinib	Gemcitabine	FOLFIRNOX	Gemcitabine	Gemcitabine/ Nab-Paclitaxel
1-Year survival	17%	23%	20.6%	48.4%	22%	35%
Median OS	5.91 mo	6.24 mo	6.8 mo	11.1 mo	6.7 mo	8.5 mo
Median PFS	3.55 mo	3.75 mo	3.3 mo	6.4 mo	3.7 mo	5.5 mo
ORR	8%	8.6%	9.4%	31.6%	7%	23%
Toxicity						
Neutropenia	–	–	21%	45.7%	27%	38%
Febrile neutropenia	–	–	1.2%	5.4%	1%	3%
Thrombocytopenia	–	–	3.6%	9.1%	9%	13%
Diarrhea	2%	6%	1.8%	12.7%	1%	6%
Sensory neuropathy	–	–	0%	9%	1%	17%
Fatigue	15%	15%	17.8%	23.6%	7%	17%
Rash	6%	1%	–	–	–	–
Stomatitis	<1%	0%	–	–	–	–
Infection	17%	16%	–	–	–	–

FOLFIRINOX = leucovorin, fluorouracil, irinotecan, and oxaliplatin; MPACT = Metastatic Pancreatic Adenocarcinoma Clinical Trial; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

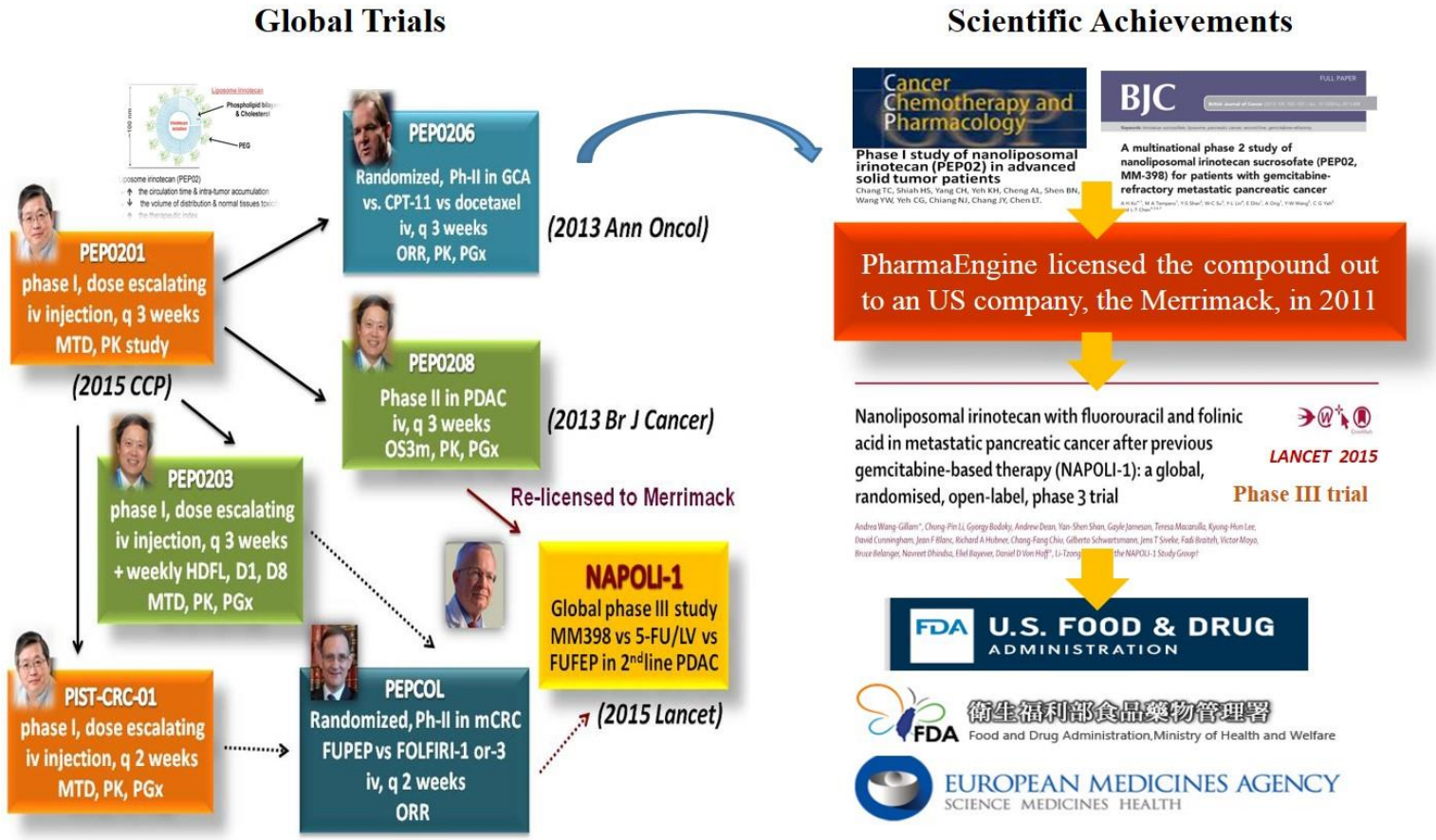
3. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25:1960-6.

4. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817-25.

5. Von Hoff D, Ervin T, Arena F, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691-1703.

國家衛生研究院
National Health Research Institutes

胰臟癌藥物 ONIVYDETM（安能得®）



國家衛生研究院
National Health Research Institutes

胰臟癌藥物 ONIVYDETM（安能得®）

- 2014 年完成全球收案，NAPOLI-1是全世界第一個登錄的第3期臨床試驗 (本試驗收案數最多者為台灣)，臨床試驗結果成功顯示MM-398 (PEP02) 加上5-FU/LV合併療法能延長第一線化學治療失敗之轉移性胰腺癌患者的整體存活期 [ESMO GI 2014, plenary, last-breaking abstract.]。
- 2015年取得美國(FDA)與台灣(TFDA)藥證、2016年取得歐盟(EMEA)藥證，為台灣新藥開發史上第一個獲得美國FDA核准通過的癌症新藥
- 2016年安能得®併用5-FU/LV療法並獲得美國國家癌症資訊網 (NCCN) 列入最新版中對於胰腺癌*第二線治療指引*的第一級(Category1)治療建議。

NAPOLI-1 phase 3 study of liposomal irinotecan in metastatic pancreatic cancer: Final overall survival analysis and characteristics of long-term survivor

Table 3
Baseline characteristics of all patients and long-term survivors.[a]

Characteristic	All patients					Long-term survivors				
	nal-IRI (n = 151)	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV combination control (n = 119)	All 5-FU/LV monotherapy control (n = 149)	Total (N = 417)	nal-IRI (n = 15)	nal-IRI+5-FU/ LV (n = 29)	5-FU/LV combination control (n = 17)	All 5-FU/LV monotherapy control (n = 20)	Total (N = 64)
Age										
Mean (SD), y	64 (10)	63 (9)	61 (9)	62 (10)	63 (10)	63 (13)	60 (10)	56 (12)	58 (12)	60 (11)
Median (IQR, range), y	65 (58–70, 31–87)	63 (57–70, 41–81)	62 (55–69, 34–80)	63 (55–69, 34–83)	63 (57–70)	67 (58–71, 31–80)	59 (55–66, 41–81)	57 (44–63, 34–76)	58.5 (47–67, 34–76)	59.5 (54–68)
≤65 y	82 (54)	65 (56)	81 (68)	94 (63)	241 (58)	6 (40)	21 (72)	14 (82)	14 (70)	40 (63)
>65 y	69 (46)	52 (44)	38 (32)	55 (37)	176 (42)	9 (60)	8 (28)	3 (18)	6 (30)	24 (38)
Sex										
Female	64 (42)	48 (41)	52 (44)	68 (46)	180 (43)	6 (40)	13 (45)	9 (53)	11 (55)	30 (47)
Race										
White	89 (59)	72 (62)	76 (64)	92 (62)	253 (61)	10 (67)	19 (66)	8 (47)	10 (50)	39 (61)
East Asian	52 (34)	34 (29)	36 (30)	50 (34)	136 (33)	4 (27)	10 (34)	7 (41)	8 (40)	22 (34)
Black	3 (2)	4 (3)	3 (3)	3 (2)	10 (2)	0	0	2 (12)	2 (10)	2 (3)
Other	7 (5)	7 (6)	4 (3)	4 (3)	18 (4)	1 (7)	0	0	0	1 (2)
Region										
Asia	50 (33)	34 (29)	35 (29)	48 (32)	132 (32)	3 (20)	10 (34)	6 (35)	7 (35)	20 (31)
Europe	54 (36)	47 (40)	49 (41)	55 (37)	156 (37)	8 (53)	13 (45)	5 (29)	5 (25)	26 (41)
North America	26 (17)	19 (16)	19 (16)	25 (17)	70 (17)	2 (13)	2 (7)	4 (24)	6 (30)	10 (16)
Other	21 (14)	17 (15)	16 (13)	21 (14)	59 (14)	2 (13)	4 (14)	2 (12)	2 (10)	8 (13)
KPS										
≥90	85 (56)	66 (56)	67 (56)	84 (56)	235 (56)	13 (87)	22 (76)	13 (76)	16 (80)	51 (80)
<90	66 (44)	51 (44)	52 (44)	65 (44)	182 (44)	2 (13)	7 (24)	4 (24)	4 (20)	13 (20)
Neutrophil-to-lymphocyte ratio										
≤5	107 (71)	83 (71)	81 (68)	102 (68)	292 (70)	12 (80)	25 (86)	10 (59)	13 (65)	50 (79)
>5	44 (29)	33 (28)	38 (32)	47 (32)	124 (30)	3 (20)	3 (10)	7 (41)	7 (35)	13 (21)
Albumin										
≥40 g/L	63 (42)	53 (45)	54 (45)	66 (44)	182 (44)	9 (60)	16 (55)	13 (76)	14 (70)	39 (61)
<40 g/L	88 (58)	64 (55)	65 (55)	83 (56)	235 (56)	6 (40)	13 (45)	4 (24)	6 (30)	25 (39)
CA19-9 level[b]										
Median (IQR), U/mL	2189 (195–17,678)	1278 (120–9001)	1292 (99–16,381)	1019 (80–12,765)	1542 (120–12,815)	478 (83–4002)	334 (18–2264)	108 (16–475)	117 (22–1545)	344 (31–2078)
≥40 U/mL, n/N (%)	125/146 (86)	92/114 (81)	91/114 (80)	116/144 (81)	333 (82)	13/15 (87)	19/27 (70)	10/16 (63)	13/19 (68)	45 (74)
<40 U/mL, n/N (%)	21/146 (14)	22/114 (19)	23/114 (20)	28/144 (19)	71 (18)	2/15 (13)	8/27 (30)	6/16 (38)	6/19 (32)	16 (26)
<59x ULN, n/N (%)	73/146 (50)	64/114 (56)	61/114 (54)	79/144 (55)	216/404 (53)	11/15 (73)	20/27 (74)	14/16 (88)	16/19 (84)	47/61 (77)
Pancreatic tumour location										
Head	99 (66)	76 (65)	69 (58)	81 (54)	256 (61)	11 (73)	20 (69)	12 (71)	13 (65)	44 (69)
Not head	52 (34)	41 (35)	50 (42)	68 (46)	161 (39)	4 (27)	9 (31)	5 (29)	7 (35)	20 (31)
Site of metastatic lesions										
Liver	101 (67)	75 (64)	84 (71)	109 (73)	285 (68)	8 (53)	12 (41)	8 (47)	9 (45)	29 (45)
Lung	49 (32)	36 (31)	36 (30)	44 (30)	129 (31)	7 (47)	9 (31)	8 (47)	10 (50)	26 (41)
Distant lymph nodes	44 (29)	32 (27)	31 (26)	40 (27)	116 (28)	3 (20)	10 (34)	5 (29)	6 (30)	19 (30)
Regional lymph nodes	19 (13)	13 (11)	14 (12)	20 (13)	52 (12)	4 (27)	6 (21)	2 (12)	3 (15)	13 (20)
Peritoneum	48 (32)	28 (24)	32 (27)	39 (26)	115 (28)	3 (20)	11 (38)	3 (18)	4 (20)	18 (28)
Pancreas	99 (66)	75 (64)	72 (61)	97 (65)	271 (65)	10 (67)	18 (62)	7 (41)	9 (45)	37 (58)
Other	38 (25)	27 (23)	39 (33)	48 (32)	113 (27)	2 (13)	7 (24)	5 (29)	7 (35)	16 (25)
Measurable metastatic lesions										
1	36 (24)	19 (16)	22 (18)	26 (17)	81 (19)	7 (47)	7 (24)	8 (47)	8 (40)	22 (34)
2	63 (42)	49 (42)	58 (49)	72 (48)	184 (44)	3 (20)	10 (34)	3 (18)	4 (20)	17 (27)
3	22 (15)	22 (19)	15 (13)	21 (14)	65 (16)	2 (13)	4 (14)	2 (12)	3 (15)	9 (14)
>3	7 (5)	7 (6)	8 (7)	10 (7)	24 (6)	0	1 (3)	0	0	1 (2)
Prior therapy										
Gemcitabine monotherapy only	67 (44)	53 (45)	55 (46)	66 (44)	186 (45)	8 (53)	13 (45)	9 (53)	10 (50)	31 (48)
Gemcitabine in combination	84 (56)	64 (55)	64 (54)	83 (56)	231 (55)	7 (47)	16 (55)	8 (47)	10 (50)	33 (52)
5-FU	70 (46)	50 (43)	52 (44)	63 (42)	183 (44)	5 (33)	14 (48)	6 (35)	6 (30)	25 (39)
Platinum	54 (36)	38 (32)	41 (34)	45 (30)	137 (33)	5 (33)	10 (34)	5 (29)	5 (25)	20 (31)
Irinotecan	17 (11)	12 (10)	17 (14)	17 (11.4)	46 (11)	1 (7)	0	2 (12)	2 (10)	3 (5)
Radiotherapy	40 (26)	24 (21)	27 (23)	33 (22)	97 (23)	5 (33)	9 (31)	7 (41)	8 (40)	22 (34)
Whipple procedure	47 (31)	30 (26)	33 (28)	36 (24)	113 (27)	5 (33)	8 (28)	9 (53)	9 (45)	22 (34)
Biliary stent	13 (9)	15 (13)	8 (7)	9 (6)	37 (9)	0	3 (10)	1 (6)	1 (5)	4 (6)
Prior lines of metastatic therapy										
0[c]	17 (11)	15 (13)	15 (13)	19 (13)	51 (12)	1 (7)	1 (3)	3 (18)	4 (20)	6 (9)
1	86 (57)	62 (53)	67 (56)	86 (58)	234 (56)	10 (67)	18 (62)	9 (53)	10 (50)	38 (59)
>1	48 (32)	40 (34)	37 (31)	44 (30)	132 (32)	4 (27)	10 (34)	5 (29)	6 (30)	20 (31)

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Table 1
Summary of updated efficacy.[a]

End-point	nal-IRI+5-FU/LV (n = 117)[b]	5-FU/LV combination control (n = 119)[b]	Treatment effect[c]	nal-IRI monotherapy (n = 151)	5-FU/LV monotherapy control (n = 149)	Treatment effect[a]
OS, mo, median (95% CI)	6.2 (4.8–8.4)	4.2 (3.3–5.3)	HR: 0.75 P = 0.039	4.9 (4.2–5.6)	4.2 (3.6–4.9)	HR, 1.07 P = 0.568
OS rate at 6 mo, % (95% CI)[d]	53 (44–62)	38 (29–47)	–	39 (31–46)	35 (27–43)	–
OS rate at 12 mo, % (95% CI)[d]	26 (18–35)	16 (10–24)	–	11 (6–16)	15 (9–21)	–
PFS, mo, median (95% CI)	3.1 (2.7–4.2)	1.5 (1.4–1.8)	HR: 0.57 P = 0.0001	2.7 (2.1–2.9)	1.6 (1.4–1.8)	HR, 0.81 P = 0.105
ORR, % (95% CI)[e]	17 (10–24)	1 (0–2)	P < 0.0001	6 (3–11)	1 (0–4)	P = 0.020
Disease control rate (CR + PR + SD), % (95% CI)	52 (43–61)	24 (17–33)	–	44 (36–52)	26 (19–33)	–
Best overall response, n (%)[e]						
PR	20 (17)	1 (1)	–	9 (6)	1 (1)	–
SD[f]	38 (32)	26 (22)	–	54 (36)	35 (23)	–
PD	34 (29)	56 (47)	–	51 (34)	71 (48)	–
Other[g]	3 (3)	2 (2)	–	3 (2)	2 (1)	–
Not evaluable	22 (19)	34 (29)	–	34 (23)	40 (27)	–
CA19-9						
20% reduction from baseline, n/N[g] (%)	38/95 (40)	11/82 (13)		41/124 (33)	16/106 (15)	
50% reduction from baseline, n/N[h] (%)	27/95 (28)	8/82 (10)	–	29/124 (23)	13/106 (12)	–

5-FU, 5-fluorouracil; CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; CR, complete response; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease.

[a] Confidence intervals are based on the exact method.

[b] In nal-IRI+5-FU/LV and 5-FU/LV combination control arms, 36% and 42%, respectively, received any post-study drug; corresponding percentages among long-term survivor subgroups were 59% and 76%, respectively.

[c] HRs derived using Cox proportional hazards model with treatment as the independent variable; P values based on unstratified log-rank test.

[d] Survival function estimate and 95% CI at each time point are from Kaplan–Meier analysis.

[e] Designation of response did not require confirmation and was based solely on the investigator's assessment using RECIST v1.1.

[f] Minimum duration for stable disease from the baseline is 6 weeks from date of randomisation.

[g] Patients without measurable (target) disease at baseline may have a best overall response of non-CR/non-PR.

[h] N = patients with baseline CA19-9 >30 IU/mL.

Eur J Cancer. 2019 Feb;108:78-87. doi: 10.1016/j.ejca.2018.12.007. Epub 2019 Jan 14.

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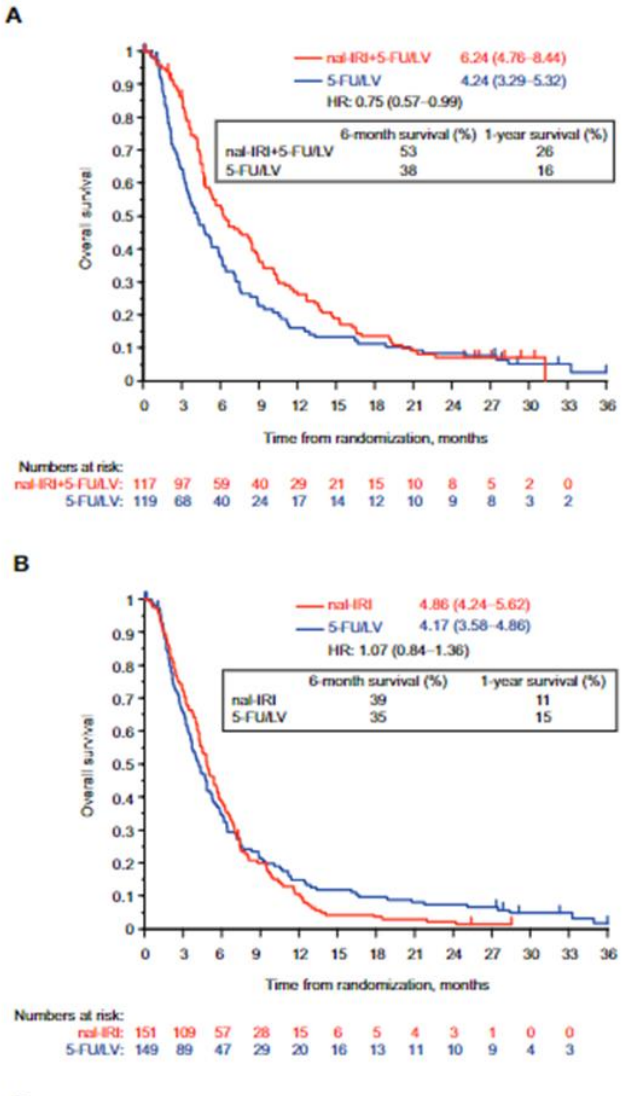
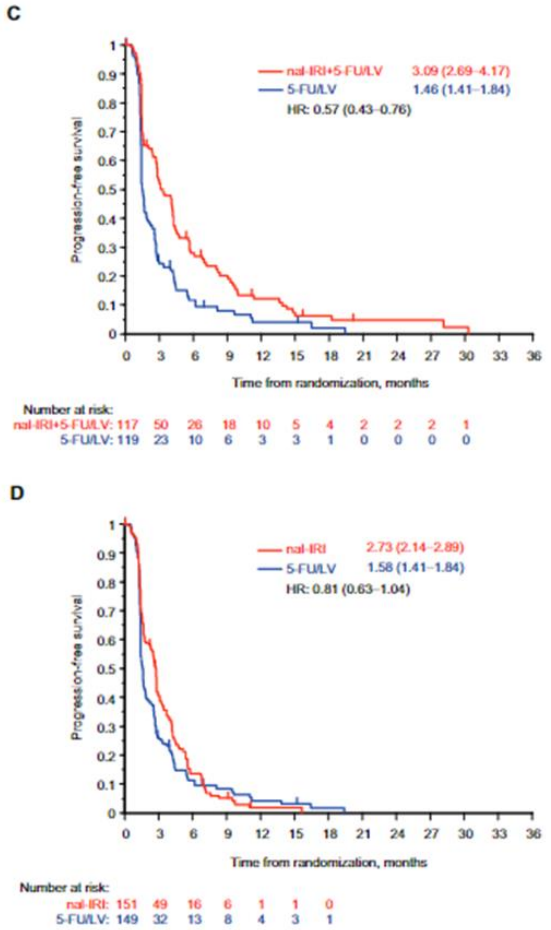
OS



PFS



表二：胰臟癌緩解性化療臨床試驗進程

Author/Trial	Number	Treatment	Patient selection	OS(m)	1-year OS
Burris et al. J Clin Oncol 1997	63	gemcitabine	未曾接受治療，不適合開刀之晚期胰臟癌	5.7 (p=0.0025)	18%
	63	5-FU		4.4	2%
Moore MJ, et al. J Clin Oncol 2007	285	gemcitabine+ erlotinib	晚期胰臟癌	6.24 (p=0.038)	23% (p=0.023)
	284	gemcitabine		5.91	13%
PRODIGE study NEJM 2011	171	FOLFIRINOX	未曾接受治療之轉移性胰臟癌	11.1 (p<0.001)	48.4%
	171	gemcitabine		6.8	20.6%
MPACT trial NEJM 2013	431	gemcitabine+ nab-paclitaxel	未曾接受治療之轉移性胰臟癌	8.5 (p<0.001)	35%
	430	gemcitabine		6.7	22%
J Cancer Res Clin Oncol 2017	277	gemcitabine	未曾接受治療之晚期胰臟癌	8.8	23.8%
	280	S-1		9.7	29%
	275	gemcitabine+ S-1		10.1	45.5%
TCOG T1211 (phase II) EJC 2020	51	SLOG	未曾接受治療之轉移性胰臟癌	11.4	46%

DOI：10.6314/JIMT.202204_33(2).03　　內科學誌 2022：33：102-109

A multicenter, phase I/II trial of biweekly S-1, leucovorin, oxaliplatin and gemcitabine in metastatic pancreatic adenocarcinoma-TCOG T1211 study

- 73 patients
- 19 patients in phase I , the MTD of S-1 was 35 mg/m2 twice daily.
- 54 patients in phase II, the ORR was 40.7% (95% confidence interval [CI], 28%–55%).
- The median progression-free survival and overall survival were 7.6 (95% CI, 5.6–11.0) and 11.4 (95% CI, 8.1–16.3) months, respectively.
- Grade III/IV adverse event was neutropenia (40.7%).
- 24% patients for more than 1 year.
- The mean relative dose intensities of gemcitabine(92%), oxaliplatin(92%), and S-1(89%).

- Eur J Cancer. 2020 Jan;124:123-130. doi: 10.1016/j.ejca.2019.10.023. Epub 2019 Nov 22.

TCOG T1211 study

Table 1
Baseline demographics and clinical characteristics.

Characteristic	Phase I (19)	Phase II (54)	Phase I/II (73)
	n (%)		
Age (yrs)			
Median (range)	54 (33–75)	59 (32–74)	59 (32–75)
<65	16 (84.2)	41 (75.9)	57 (78.1)
≥65	3 (15.8)	13 (24.1)	16 (21.9)
Gender			
Male	12 (63.2)	31 (57.4)	43 (58.9)
Female	7 (36.8)	23 (42.6)	30 (41.1)
ECOG performance status			
0	7 (36.8)	10 (18.5)	17 (23.3)
1	12 (63.2)	44 (81.5)	56 (76.7)
Pancreatic tumour location*			
Head	7 (36.8)	21 (38.9)	26 (35.6)
Body	7 (36.8)	20 (35.2)	25 (34.3)
Tail	7 (36.8)	19 (35.2)	25 (34.3)
Metastatic sites			
Liver	17 (89.4)	36 (66.7)	52 (71.2)
Lymph nodes	12 (63.2)	25 (46.3)	37 (50.7)
Peritoneum	2 (10.5)	5 (9.3)	7 (9.6)
Others	5 (26.3)	31 (57.4)	36 (49.3)
Number of metastatic sites			
0	0 (0.0)	1 (1.9)	1 (13.7)
1	7 (36.8)	22 (40.7)	29 (39.7)
2	8 (42.1)	20 (37.0)	28 (75.7)
3	3 (15.8)	10 (18.5)	13 (17.8)
>3	1 (5.3)	1 (1.9)	2 (2.7)
Stent or drainage			
No	15 (79.0)	47 (87)	62 (84.9)
Yes	4 (21.1)	7 (13)	11 (15.1)
Pancreatic resection			
No	18 (94.7)	47 (87)	65 (89.0)
Yes	1 (5.3)	7 (13)	8 (11.0)
Baseline CA199 (U/mL)			
Median (min–max)	700.35 (1.5–65765)	612 (1.5–39515)	700.35 (1.5–65765)

ECOG, Eastern Cooperative Oncology Group.

Table 2
Dose escalation scheme of S-1 in phase I part.

Level	S-1 (mg/m^2)	Patients (*n*)	Number of DLT (*n*)	DLTs
I	20	3	0	–
II	30	7[a]	1	grade III diarrhoea
III	35	3 + 3	0 + 0	–
IV	40	3	2	grade III diarrhoea and grade III allergy[b]

DLT, dose-limiting toxicity.
[a] One patient only received one cycle treatment and withdrew early from this study.
[b] Skin rash over trunk and extremities with face swelling, leading to hospitalisation.

Table 3
Efficacy results in phase II part alone or plus phase I MTD part.

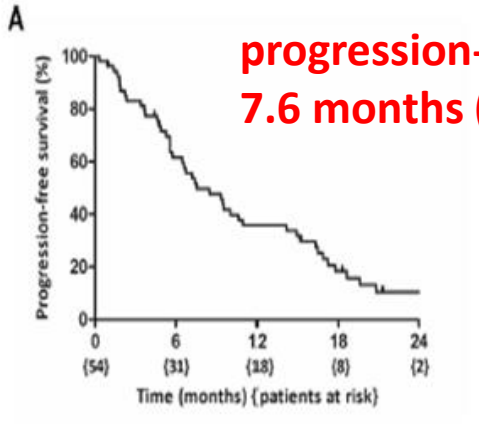
Best overall response	Phase II (*n* = 54)		Phase I + phase II (*n* = 60)	
	n	%	*n*	%
Complete response (CR)	0	0	0	0
Partial response (PR)	22	40.7	26	43.3
Stable disease (SD)	19	35.2	21	35
Progressive disease	8	14.8	8	13.3
Not evaluated	5	9.3	5	8.3
Long-term DCR*	35	64.8	39	65

MTD, maximum tolerated dose; DCR, disease control rate; *CR + PR + SD ≥ 16 weeks.

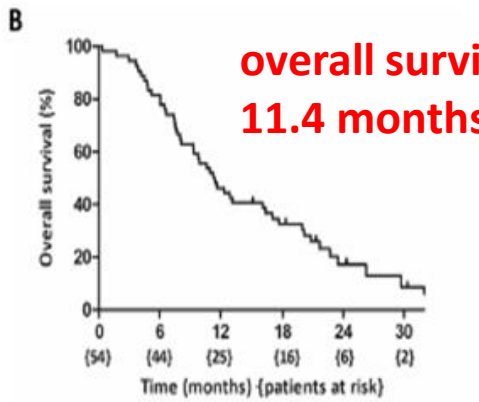
ORR 40.7%
(95% confidence interval [CI], 28%–55%).

TCOG T1211 study

Grade III/IV neutropenia (40.7%)



progression-free survival
7.6 months (95% CI, 5.6–11.0)



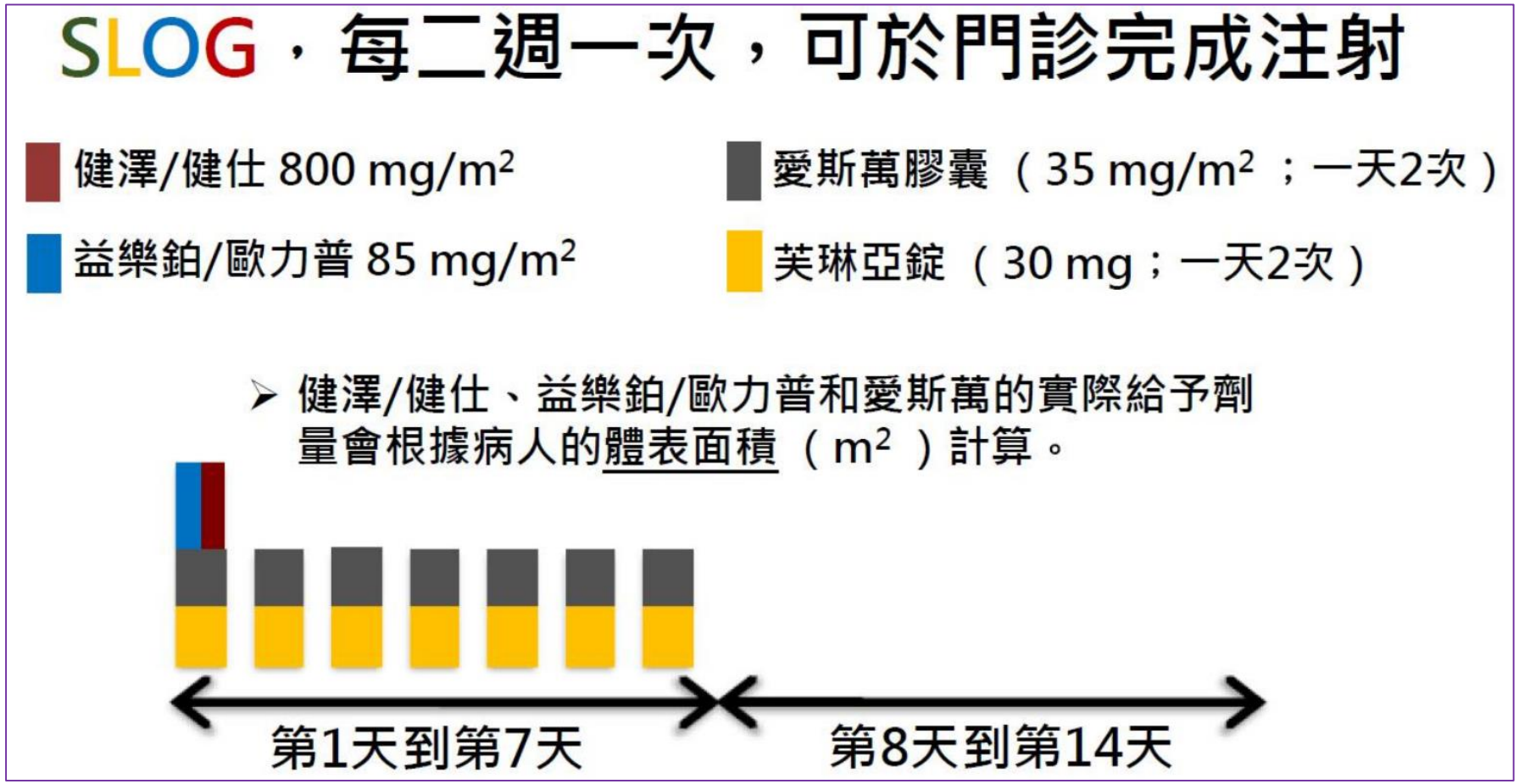
overall survival
11.4 months (95% CI, 8.1–16.3)

Fig. 1. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) in phase II part.

Table 4
Treatment-related adverse events in phase II part (n = 54).

Adverse events	Grade I-II		Grade III		Grade IV	
Haematological toxicities						
Leucopenia	15	27.4	14	25.9	2	3.7
Neutropenia	10	18.5	20	37	2	3.7
Febrile neutropenia	0	0	1	1.9	0	0
Thrombocytopenia	29	53.7	2	3.7	4	7.4
Anaemia	37	68.5	3	5.6	1	1.9
Non-haematological toxicities						
Fatigue	44	81.5	3	5.6	0	0
Anorexia	35	64.8	8	14.8	0	0
Nausea	32	59.2	6	11.1	0	0
Vomiting	26	48.1	4	7.4	0	0
Diarrhoea	26	48.1	4	7.4	0	0
Elevated AST	15	27.8	1	1.9	0	0
Elevated ALT	12	22.3	2	3.7	0	0
Elevated GGT	9	16.7	2	3.7	0	0
Oral mucositis	20	37.0	3	5.6	0	0
Sepsis	1	1.9	0	0	2[a]	3.8
Alopecia	15	27.8	0	0	0	0
Skin rash	8	14.8	1	1.9	0	0
Pruritus	8	14.8	0	0	0	0
Skin hyperpigmentation	31	57.5	0	0	0	0
Peripheral sensory neuropathy	33	61.1	0	0	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase.
[a] One patient suffered from grade V sepsis leading to death finally.



SLOG為一種有效的新穎化學複方，用於轉移性胰臟癌的治療。在每個療程的第一天施打2種靜脈注射藥物，於第1天到第7天服用另外2種藥物，第8天到第14天則為休息時間。（圖片來源／國衛院提供）

NCCN Guidelines Version 1.2022

Pancreatic Adenocarcinoma

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Pancreatic Adenocarcinoma

General Principles:

- Systemic therapy is used in all stages of pancreatic cancer. This includes neoadjuvant therapy (resectable or borderline resectable), adjuvant therapy, and first-line or subsequent therapy for locally advanced, metastatic, and recurrent disease.
- Goals of systemic therapy should be discussed with patients prior to initiation of therapy, and enrollment in a clinical trial is strongly encouraged.
- Close follow-up of patients undergoing chemotherapy is indicated.
- For regimens where RT or chemoradiation is included, see Principles of Radiation Therapy (PANC-G) for more details related to radiation delivery, including recommended technique and dose.
- To optimize the care of older adults, see NCCN Guidelines for Older Adult Oncology.
- Squamous/adenosquamous carcinomas are treated the same as adenocarcinoma. There is no data supporting the efficacy of any of the recommended regimens for squamous/adenosquamous carcinomas.

Neoadjuvant Therapy (Resectable/Borderline Resectable Disease)

- There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and radiation. Subsequent chemoradiation is sometimes included. If neoadjuvant therapy is considered or recommended, treatment at or coordinated through a high-volume center is preferred, when feasible. Participation in a clinical trial is encouraged.

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• FOLFIRINOX or modified FOLFIRINOX[a] ± subsequent chemoradiation[b] • Gemcitabine + albumin-bound paclitaxel ± subsequent chemoradiation[b] Only for known *BRCA1/2* or *PALB2* mutations: • FOLFIRINOX or modified FOLFIRINOX[a] ± subsequent chemoradiation[b] • Gemcitabine + cisplatin (≥2–6 cycles) ± subsequent chemoradiation[b]	• None	• None

NCCN Guidelines Version 1.2022
Pancreatic Adenocarcinoma

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Adjuvant Therapy

- The CONKO-001 trial demonstrated significant improvements in disease-free survival (DFS) and overall survival (OS) with use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.[1]
- ESPAC-3 study results showed no significant difference in OS between 5-FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.[2]
- Data from ESPAC-4 support the use of gemcitabine combined with capecitabine (1,660 mg/m^2/day days 1–21 every 4 weeks) with superiority demonstrated compared to gemcitabine alone (HR, 0.82; 95% CI, 0.68, 0.98; P = .032).[3]
- No significant differences were observed in the RTOG 97-04 study comparing pre- and post-chemoradiation 5-FU with pre- and post-chemoradiation gemcitabine for postoperative adjuvant treatment.[4]
- Recommended adjuvant therapy options apply to patients who did not receive prior neoadjuvant therapy. For those who received prior neoadjuvant therapy, the adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Modified FOLFIRINOX (category 1)[a] • Gemcitabine + capecitabine (category 1)	• Gemcitabine (category 1) • 5-FU + leucovorin (category 1) • Continuous infusion 5-FU • Capecitabine (category 2B) • Induction chemotherapy (gemcitabine, 5-FU + leucovorin, or continuous infusion 5-FU) followed by chemoradiation[b,c] • Induction chemotherapy (gemcitabine, 5-FU + leucovorin, or continuous infusion 5-FU) followed by chemoradiation[b,c] followed by subsequent chemotherapy:[4] ‣ Gemcitabine followed by chemoradiation[b,c] followed by gemcitabine ‣ Bolus 5-FU + leucovorin followed by chemoradiation[b,c] followed by bolus 5-FU + leucovorin ‣ Continuous infusion 5-FU followed by chemoradiation[b,c] followed by continuous infusion 5-FU	• None

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NCCN Guidelines Version 1.2022
Pancreatic Adenocarcinoma

Locally Advanced Disease (First-Line Therapy)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS	• FOLFIRINOX or modified FOLFIRINOX[a,d,e,5] • Gemcitabine + albumin-bound paclitaxel[d,f,6] Only for known *BRCA1/2* or *PALB2* mutations: • FOLFIRINOX or modified FOLFIRINOX[a,d,e,5] • Gemcitabine + cisplatin[7,8]	• Gemcitabine + erlotinib[9,9] • Gemcitabine + capecitabine[10] • Gemcitabine • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)[11] (category 2B) • Fluoropyrimidine + oxaliplatin (5-FU + leucovorin + oxaliplatin [OFF][12] or CapeOx[13]) (category 2B) • Gemcitabine + albumin-bound paclitaxel + cisplatin[14,15] (category 2B)	• Induction chemotherapy with any of the preferred/other regimens (≥4–6 cycles) followed by chemoradiation[b,h] or SBRT[16] in selected patients (locally advanced disease without systemic metastases)[17] • Chemoradiation[b,i] or SBRT[i] (in patients who are not candidates for induction chemotherapy)
Poor PS	• Gemcitabine ▸ 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B)	• None	• None

See Subsequent Therapy on PANC-F (6 of 9)

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NCCN Guidelines Version 1.2022
Pancreatic Adenocarcinoma

Metastatic Disease (First-Line Therapy)

- Patients who progress with metastatic disease are not candidates for radiation unless required for palliative purposes.

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS	• FOLFIRINOX (category 1) or modified FOLFIRINOX[a,e,5] • Gemcitabine + albumin-bound paclitaxel[1,6] (category 1) Only for known *BRCA1/2* or *PALB2* mutations: • FOLFIRINOX (category 1) or modified FOLFIRINOX[a,e,5] • Gemcitabine + cisplatin[7,8]	• Gemcitabine + erlotinib[g,9] (category 1) • Gemcitabine (category 1) • Gemcitabine + capecitabine[10] • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)[11] (category 2B) • Fluoropyrimidine + oxaliplatin (eg, 5-FU + leucovorin + oxaliplatin [OFF][12] or CapeOx[13]) (category 2B) • Gemcitabine + albumin-bound paclitaxel + cisplatin[14,15]	• Pembrolizumab[j,18] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb])
Poor PS	• Gemcitabine ▸ 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B)	• None	• Pembrolizumab[j,18] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Larotrectinib (if *NTRK* gene fusion positive) • Entrectinib (if *NTRK* gene fusion positive) (category 2B)

Thank You for being here!