

Systemic Treatments in Pancreatic cancer Taiwan Pancreas Society Recommendation

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Outline

- Introduction : 陳仁熙
- Patient selection and Initial Assessment: 許劭榮
- Resectable disease:
 - neoadjuvant role: 林欣辰
 - Post-operative adjuvant chemotherapy: 楊陽生
- Locally advanced (include borderline resectable)
 - Induction chemotherapy: 黃千睿
 - CCRT: 黃千睿
- Metastatic disease
 - 1st line chemotherapy : 蘇勇暉 (international) 姜乃榕 (Taiwan local data)
 - 2nd line chemotherapy : 周文其 (international) 邱泰然 (Taiwan local data)
- Treatment beyond 2nd line chemotherapy: 白禮源
- NGS role (targeted and immunotherapy): 陳彥仰
- Novel treatments:
 - Clinical trial : 李重賓
 - Cell therapy: 楊士弘
- Summary : 李重賓

Taiwan Cancer Registry 2020

- 民國109年初次診斷為胰惡性腫瘤者共計3,012人，占消化器官及腹膜(ICD-O-3 C15 - C26，C48)個案數的7.54%；當年死因為胰惡性腫瘤者共計2,450
- 胰惡性腫瘤發生個案數占全部惡性腫瘤發生個案數的2.47%，
 - 發生率的排名於男性為第12位、女性為第13位
- 死亡人數占全部惡性腫瘤死亡人數的4.88%。；
 - 死亡率的排名於男性為第8位、女性為第5位。

首次療程

3,012位胰惡性腫瘤個案接受治療之情形，以化學治療者最多，占55.91%。

申報治療方式*	男性		女性		總計	
	治療人數	百分比	治療人數	百分比	治療人數	百分比
手術治療	427	25.89	356	26.12	783	26.00
放射線治療	154	9.34	142	10.42	296	9.83
化學治療	946	57.37	738	54.15	1,684	55.91
免疫治療	15	0.91	20	1.47	35	1.16
標靶治療	25	1.52	18	1.32	43	1.43
緩和照護	715	43.36	573	42.04	1,288	42.76
其他治療	7	0.42	3	0.22	10	0.33
未有首次治療申報紀錄	260	15.77	229	16.80	489	16.24

申報治療方式：每名個案所接受之治療方式均分別計數。

Patient selection and initial assessment

- Multidisciplinary approaches
- Chemotherapy enhances quality of life, despite its associated toxicities.
- Considering the specific adverse effects associated with each chemotherapy regimen is essential as they can significantly affect patients' quality of life . Thus, informing patients about the potential benefits and limitations of treatment choices is imperative for effectively managing their expectations.
- Engaging in comprehensive evaluations, discussions, and informed decision-making processes are vital for providing optimal care and treatment outcomes for patients with pancreatic cancer.

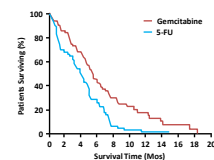
Metastatic Pancreatic Cancer: Pivotal study: GEM vs. 5FU

Median survival :
5.65 vs 4.41 m (P = .0025)

1-year survival:
18% vs 2%

Clinical benefit*:
23.8% vs 4.8% (P = .0022)

Response rate:
5.4% vs 0% (P = NS)



*A composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight. Clinical benefit required a sustained (≥ 4 weeks) improvement in at least 1 parameter without worsening in any others.

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

Pooled Survival and Response Data From Phase III Randomized Controlled Trials for Gemcitabine-based Regimes in the Treatment of Advanced Pancreatic Cancer before 2010

- 21 Phase III studies
- GEM vs. GEM + X (3171 vs. 3177)

Results:

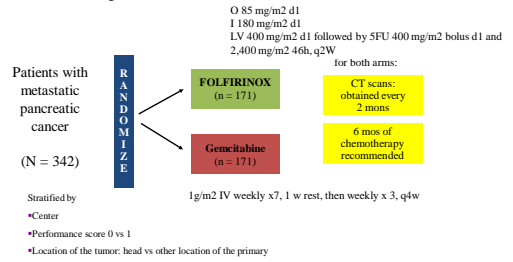
	GEM	GEM + X
Response rate	8.3%	1%-38.5%
PFS	3.3m	3.725m
OS	6.15m	6.55m
1yr	22%	23%

Toxicity:

- Significantly reduce hematological or non-hematological toxicities experienced with GEM alone.
- GEM + X have shown disappointing activity in phase III trials and investigation must continue into novel agents

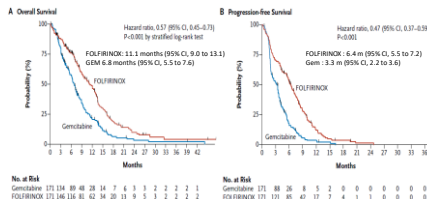
Arshad, A, et al. Am J Clin Oncol 2013;36:411-414

PRODIGE 4/ACCORD 11 Trial Design (The FOLFIRINOX Regimen vs. GEM)



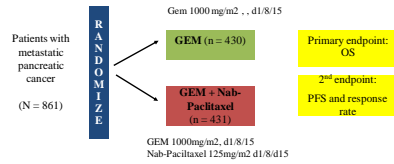
Conroy T, et al. N Engl J Med, 2011; 364(19):1817-25

PRODIGE 4/ACCORD 11 FOLFIRINOX vs. GEM



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

Phase III: GEM vs GEM/Nab-Paclitaxel



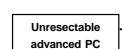
Van Hoff DD, et al. N Engl J Med, 2013; 369:1691-703

Table 1. Overall Survival, Progression-Free Survival, and Response Data in the Intention-to-Treat Population.

Effray Variable	sub-Paclitaxel gem Gemcitabine (n=431)	Gemcitabine alone (n=430)	Hazard Ratio or Response Rate Ratio (95% CI)*	P Value
Overall survival				
Median overall survival—mo (95% CI)	5.1 (4.7-5.5)	6.7 (6.0-7.3)	0.72 (0.63-0.83)	<.001
Survival rate—% (95% CI)				
1 mo	67 (60-71)	71 (60-80)		<.001
12 mo	35 (28-39)	22 (19-27)		<.001
18 mo	18 (13-23)	9 (6-12)		<.001
24 mo	9 (6-13)	4 (2-7)		<.001
Progression-free survival				
Median progression-free survival—mo (95% CI)	3.3 (3.0-3.6)	3.7 (3.0-4.5)	0.69 (0.58-0.82)	<.001
Rate of progression-free survival—% (95% CI)				
1 mo	44 (39-49)	35 (29-39)		<.001
12 mo	18 (13-23)	9 (6-14)		<.001
Response				
Rate of objective response				
Independent review				
No. of patients with a response	58	31	3.19 (2.18-4.66)	<.001
% (95% CI)	13 (10-17)	7 (6-8)		
Investigator review	106	33	3.81 (2.86-5.04)	<.001
% (95% CI)	24 (20-28)	8 (7-10)		
Rate of disease control	266	141	1.46 (1.25-1.72)	<.001
% (95% CI)	61 (55-67)	33 (29-37)		
Best response according to independent review—no. (%)				
Complete response	1 (0.2)	0		
Partial response	56 (13)	31 (7)		
Stable disease	139 (31)	127 (29)		
Progressive disease	162 (38)	120 (28)		
Could not be evaluated	138 (31)	107 (25)		

Phase III: GEST Study

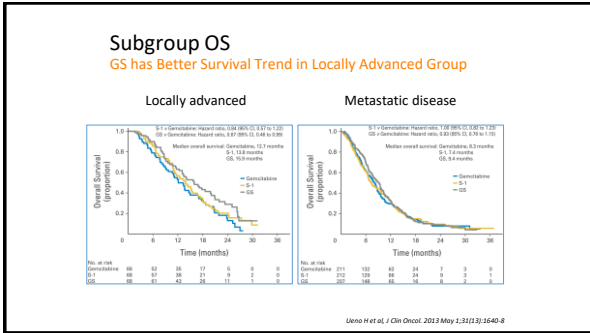
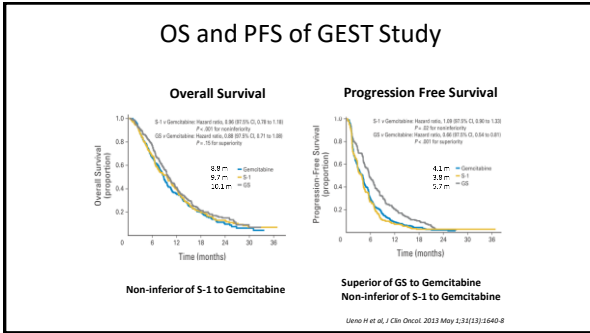
- Japan/Taiwan Collaboration trial
- Accrual: 2007 July - 2009 Oct
- Target enrollment: 750 patients
- Enrolled patients: 834 patients
 - Taiwan enrolled 66 patients
- Primary endpoint: overall survival
 - Superiority of GS to Gem
 - Non-inferiority of S-1 to Gem



- GEM**
1000 mg/m² d1, 8, 15
Repeated every 4 weeks (n = 277)
- S-1**
80, 100, 120mg²/body d1-28
Repeated every 6 weeks (n = 282)
- GEM + S-1**
GEM: 1000mg/m²d1, 8
S-1: 60, 80, 100mg²/body d1-14
Repeated every 3 weeks (n = 275)

Stratification factors:
 - Metastatic vs. Locally advanced
 - Institution
 *Initial dose according to body surface area(m²)
 BSA <1.25: 1.25-BSA <1.5, 85kg; 1.5, dose may be reduced due to CBC result, liver and renal function
 Secondary endpoint: PFS, RR, toxicity, QoL (EQ-5D)

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



Taiwan experience of first-line treatment

- GOFL¹:
 - gemcitabine, oxaliplatin, fluorouracil, and LV every 2 weeks
 - ORR was 33.3%; median PFS : 5.1m; median OS: 8.7m
 - grade 3–4 toxicities of neutropenia (28.9%) and diarrhea (6.7%)
- SLOG²:
 - gemcitabine, oxaliplatin, TS1/LV, every 2 weeks
 - ORR of 40.7%, median PFS : 7.6 m; median OS 11.4 m.
 - grade 3–4 toxicities included neutropenia (40.7%), diarrhea (7.4%), and oral mucositis (5.6%)

1. Ch'ang HJ, et al. *Cancer Chemother Pharmacol.* 2009;64(6):1173-1179.
2. Chiang NJ, et al. *Eur J Cancer.* 2020;124:123-130.

Taiwan experience of first-line treatment

- Modified GSL
 - aged ≥ 70 years and ECOG performance score ≤ 2
 - ORR of 26.5%, median PFS: 6.6 m; median OS 12.5 months.
 - The common grade 3–4 toxicities were
 - neutropenia (18.4%) and mucositis (12.2%),
 - with improved quality of life, indicating that a modified GSL regimen is valuable for Asian elderly patients with advanced pancreatic cancer

Bai LY, et al. *Eur J Cancer.* 2022;173:123-132. 16

Recommendations

- Chemotherapy remains the standard of care in metastatic pancreatic cancer.
- Gemcitabine- or fluorouracil-based combination chemotherapy is recommended for fit patients, whereas monotherapy is recommended for fragile patients.
 - GEM/Nab-Paclitaxel, FOLFIRINOX, Gem/TS1, Gem, TS1,
- Alternative first-line treatments for Taiwanese patients with pancreatic cancer, depending on physicians' choices, patient requests, reimbursement policies, and the balance between efficacy and toxicities.
 - GFOL, SLOG, GSL

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Second-line treatment for advanced and metastatic pancreatic cancer

- The choice of second-line chemotherapy depends on the chemotherapy used in the first-line regimen, adverse effects, PS, age, and comorbidities.
- NAPOLI-1 phase III randomized trial
 - who previously received gemcitabine-based therapy were randomized
 - nal-IRI with 5-FU/LV vs. 5-FU/LV
 - Median PFS (3.1 vs. 1.5 months; HR, 0.56; 95% CI, 0.41–0.75; P < 0.001)
 - Median OS (6.1 vs. 4.2 months; HR, 0.67; P = 0.012)
 - The most frequent grade 3–4 side effects of combination therapy were neutropenia, diarrhea, emesis, and fatigue

Wang-Gillam A, et al. *Lancet.* 2016;387(10018):545-557
Eur J Cancer. 2019;Feb;108:78-87. 18

Recommendations

- In patients with preserved PS (ECOG PS 0–1) without relevant comorbidities, proposing second-line treatment with a 5-FU- or gemcitabine-based treatment is reasonable, depending on the first-line chemotherapy used.
- Within 5-FU-based regimens, any residual toxicities of the first-line treatment can lead to the choice of another chemotherapy regimen.

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Taiwan experience of 2nd line treatment

- Taiwan real-world data support the use of the NAPOLI-1 nomogram for risk stratification to predict the OS with metastatic pancreatic cancer ¹.
- Moreover, the starting dose, pre-emptive dose, dose pattern, early cumulative dose, preoperative albumin combined with neutrophil-to-lymphocyte ratio, spleen volume and previous conventional irinotecan treatment also affect the treatment results of nal-IRI in real-world practice ²⁻⁶

¹ Su YV, et al. *Cancer: Cancers (Basel)*. 2023;15(4)
² Chiang NJ, et al. *Am J Cancer Res*. 2022;12(11):5062-5073.
³ Su YV, et al. *Front Oncol*. 2022;12:800842.
⁴ Chen YV, et al. *Am J Cancer Res*. 2022;12(9):4367-4378.
⁵ Yang SH, et al. *Am J Cancer Res*. 2022;12(4):8884-8898.
⁶ Chiu TJ, et al. *J Hepatobiliary Pancreat Sci*. 2022;29(6):670-681.

Treatment beyond second-line regimens

- Currently, there is no standard chemotherapy regimen
- Recommendations
 - In addition to hospice care, fit patients should be encouraged to participate in clinical trials after disease progression.
 - NGS, immunotherapy, and other emerging reports may provide treatment choices for certain populations.

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NGS, targeted therapy, and immune therapy

- Maintenance of olaparib is an option for germline BRCA1/BRCA2 mutations, especially for patients who prefer chemotherapy holidays.
- Currently, there is no standard treatment beyond second-line regimens, and enrollment in clinical trials is recommended.
- NGS testing may be considered for the potential detection of druggable mutations, despite their rarity. Genetic counseling should be considered in patients with familial pancreatic cancer.
- ICIs are not recommended for routine use alone or in combination with standard treatments for pancreatic cancer, except in patients with MSI-H.
- Cell therapy using autologous immune cells may be optimal in patients with pancreatic cancer with stage IV or refractory stage I–III disease under the regulation of the “Regulations Governing the Application or Use of Specific Medical Techniques or Examinations, or Medical Devices” in Taiwan.

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Neoadjuvant therapy for resectable pancreatic cancer

- Neoadjuvant therapy for resectable pancreatic cancer can be considered in patients with high-risk features.
- Multidisciplinary discussions and a definitive diagnosis before initiating neoadjuvant therapy for resectable pancreatic cancer are mandatory.
- There is no standard neoadjuvant regimen for resectable pancreatic cancer, and the choices include chemoradiation with gemcitabine or combination chemotherapy. Therefore, the participation of well-designed clinical trials is recommended.

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Adjuvant treatments after surgical resection				
Study	C/T regimen	Patient No	PFS	OS
ESAPC ¹	Obs vs C/T vs. CCRT vs. RT	142 vs. 147	na	20.1 vs. 15.5m; HR: 0.71; [95% CI], 0.55-0.92; P = 0.009.
CONKO-001 ²	Gem vs. Obs	179 vs. 175	13.4 m (95%CI, 11.6-15.3) vs. 6.7m (95%CI, 6.0-7.5)	5-y OS 20.7% vs. 10.4%
ESPAC-3 ³	Gem vs. 5-FU/LV	5-FU/LV: 143 Gem: 141 Obs: 144		43.1m 43.1m 35.2 m; HR: 0.76 (95% CI, 0.57-0.98); Wald Z ² = 4.93; P = .023.
ESPAC-4 ⁴	Gem/CAP vs Gem	366 vs. 364		28.0 m vs. 25.5m HR 0.82 (95% CI 0.68-0.98) p=0.025.
PRODIGE 24-ACCORD ⁵	mFOLFIRINOX vs Gem	246 vs 247	21 m vs 12m	54.4 m vs 35.0 m HR: 0.6 (95% CI, 0.48 to 0.86; P=0.003)
JSPAC-01 ⁶	S-1 vs Gem	193 vs 192		5-y OS 44.1 % vs 24.4%; HR: 0.57 (95% CI 0.44-0.72 p<0.0001)

¹ Neoptolemos JP, et al. *N Engl J Med*. 2004;350(21):1200-1210. ² Dettle H, et al. *JAMA*. 2013;309(14):1473-1481. ³ Neoptolemos JP, et al. *JAMA*. 2012;307(14):1757-1764. ⁴ Neoptolemos JP, et al. *Lancet*. 2017; Mar 11;389(10073):1011-1024. ⁵ Conroy T, et al. *N Engl J Med*. 2018; 379:2395-2406. ⁶ Uesaka K, et al. *Lancet*. 2016 Jul 16;388(10041):248-57.

Recommendations: post-op adjuvant

- A multidisciplinary team is necessary.
- Adjuvant treatment with modified FOLFIRINOX, S-1, and gemcitabine plus capecitabine is recommended for fit patients, and gemcitabine monotherapy or 5-FU/LV is reserved for less fit patients.
- Routine chemoradiation is not recommended to patients after surgery, except in clinical trials.

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Treatment of borderline resectable and locally advanced unresectable diseases

- Short courses of neoadjuvant therapy, including chemotherapy alone or gemcitabine-based chemoradiotherapy, are recommended for borderline resectable disease.
- Neoadjuvant chemotherapy may be more preferred than neoadjuvant chemoradiotherapy based on current evidence.
- No definite preference for chemotherapy regimens has been suggested. FOLFIRINOX, gem/nab-P, and gemcitabine alone are reasonable choices.

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Locally advanced disease

- Up to 4–6 months of induction chemotherapy combined with chemoradiotherapy is recommended for locally advanced disease.
- Surgical exploration should be considered if the disease is under control after induction therapy.
- Both FOLFIRINOX and gem/nab-P, or sequential therapy, are safe and tolerable for locally advanced disease. No preference suggestions can be made based on the current evidence.
- Some new radiotherapy treatment choices, including proton and carbon, may be considered.

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Conclusion

- This review provides an overview of the medical treatment for pancreatic cancer, covering various disease stages and therapeutic approaches.
- It emphasizes the importance of patient selection and initial assessment.
- Postoperative adjuvant chemotherapy is recommended for resectable diseases, whereas neoadjuvant therapy is recommended for borderline resectable diseases. Induction chemotherapy and concurrent chemoradiotherapy have been used to treat locally advanced tumors.
- Systemic therapies are pivotal for improving patient outcomes in metastatic diseases. It incorporates data from international and Taiwan-specific studies to guide first- and second-line treatment choices. Additionally, it explores treatment options beyond second-line treatment and highlights the potential role of NGS in identifying targeted immunotherapies.
- Furthermore, novel treatments, including clinical trials and cell therapy, offer promising avenues for future advancements in pancreatic cancer management.

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