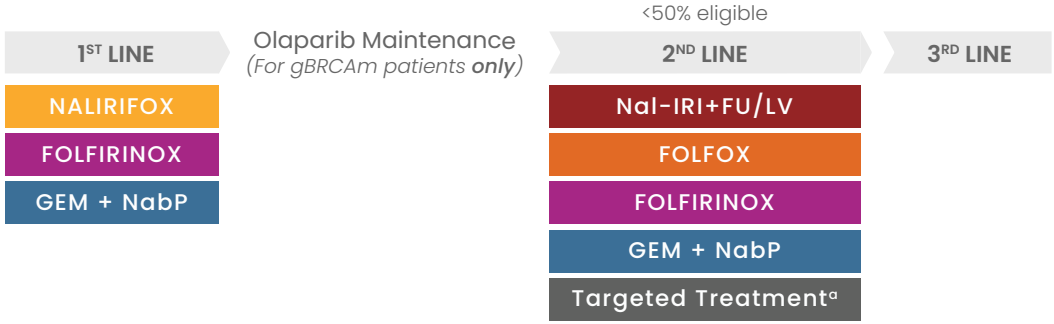
Chemotherapy strategies for metastatic pancreatic ductal adenocarcinoma (mPDAC)

Cytotoxic combination chemotherapy is the cornerstone of treatment for advanced or metastatic PDAC.

Treatment selection depends on factors such as patient performance status and co-morbidities. Treatment strategies can be implemented to manage toxicities associated with the different chemotherapy regimens to enable a patient to stay on treatment for optimal efficacy.

Although newer treatment regimens have improved survival rates, ongoing efforts in risk assessment and early detection remain essential.

Recommended systemic chemotherapy options for mPDAC



Key studies of systemic chemotherapy for mPDAC

Study setting	Study	Study type	Arm (N)	Primary end point	Primary endpoint Months	Primary endpoint HR (95% CI)	Secondary end point	Secondary endpoint Months	Secondary endpoint HR (95% CI)	ORR (%)	Notable adverse events
1st line	PRODIGE (2011)	RCT, phase 2/3	FOLFIRINOX (171) Gemcitabine (171)	OS	11.1 6.8	0.57 (0.45 to 0.73)	PFS	6.4 3.3	0.47 (0.37 to 0.59)	31.6 9.4	FOLFIRINOX vs Gem (G≥3): neutropenia 47.5 vs 21.0%, febrile neutropenia 5.4 vs 1.2%, thrombocytopenia 9.1 vs 3.6%, diarrhoea 12.7 vs 1.8%
1st line	MPACT (2013)	RCT, phase 3	Gem + NabP (431) Gemcitabine (430)	OS	8.5 6.7	0.72 (0.62 to 0.83)	PFS	5.5 3.7	0.69 (0.58 to 0.82)	23.0 7.0	Gem + NabP vs Gem (G≥3): neutropenia 38.0 vs 27.0%, leukopenia 31.0 vs 16.0%, thrombocytopenia 13.0 vs 9.0%, fatigue 17.0 vs 7.0%, and neuropathy 17.0 vs 1.0%
1st line	NAPOLI-3 (2023)	RCT, phase 3	NALIRIFOX (383) Gem + NabP (387)	OS	11.1 9.2	0.83 (0.70-0.99)	PFS	7.4 5.6	0.69 (0.58-0.83)	41.8 36.2	NALIRIFOX vs Gem + NabP (G≥3): hypokalaemia 15.0 vs 4.0%, diarrhoea 20.0 vs 5.0%, nausea 12.0 vs 3.0%. Lower rates of hematological AEs with NALIRIFOX: neutropenia 14.0 vs 25.0%, aneamia 11.0 vs 17.0%
Metastatic maintenance[b]	POLO (2019, 2022)	RCT, phase 3	Olaparib (92) Placebo (62)	PFS	7.4 3.8	0.53 (0.35 to 0.82)	OS	19.0 19.2	0.83 (0.56 to 1.22)	23.1[c] 11.5[c]	Olaparib vs placebo (G≥3): fatigue 5.6 vs 0%, anaemia 12.2 vs 3.3%, decreased appetite 3.3 vs 0%
2nd line	CONKO-003 (2014)	RCT, phase 3	OFF (77) FF (91)	OS	5.9 3.3	0.66 (0.48-0.91)	PFS	2.9 2.0	0.68 (0.50-0.94)	- -	Rates of adverse events were similar between treatment arms, with the exception of grades 1 to 2 neurotoxicity 38.2 vs 7.1% in the OFF and FF groups
2nd line	PANCREOX (2016)	RCT, phase 3	mFOLFOX (54) 5FU/LV (54)	PFS	3.1 2.9	1.00 (0.66-1.53)	OS	6.1 9.9	1.78 (1.08-2.93)	13.2 8.5	Increased toxicity was observed with the addition of oxaliplatin, with grade 3/4 adverse events occurring in 63.0% of patients who received mFOLFOX6 and 11.0% of those who received FU/LV
2nd line	NAPOLI-1 (2016)	RCT, phase 3	Nal-IRI + 5-FU/LV (117) 5-FU/LV (119)	OS	6.1 4.2	0.67 (0.49 to 0.92)	PFS	3.1 1.5	0.56 (0.41 to 0.75)	16.2 0.8	Most frequent grade 3 or 4 AEs for Nal-IRI + 5- FU/LV vs 5-FU/LV: neutropenia 27.0 vs 1.0%, diarrhoea 13.0 vs 4.0%, vomiting 11.0 vs 3.0%, and fatigue 14.0 vs 4.0%

[a]if molecular alterations identified
[b]Patients with germline mutations in *BRCA1* or *BRCA2*, who had received at least 16 weeks of continuous platinum-based chemotherapy as 1st-line treatment for metastatic pancreatic cancer, were enrolled; [c]At data cut-off 1

5-FU, fluorouracil; AE, adverse event; BRCA1/2, BReast CAncer 1/2 gene; CI, confidence interval; gBRCAm, germline BRCA mutation; FF, folinic acid (leucovorin calcium) and fluorouracil; FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; FOLFOX, folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin; gem, gemcitabine; HR, hazard ratio; mPDAC, metastatic pancreatic ductal adenocarcinoma; LV, leucovorin calcium (folinic acid); mFOLFOX, modified FOLFOX: folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin; mPFS, median progression-free survival; Nab, nanoparticle albumin-bound; NabP, Nab, nanoparticle albumin-bound paclitaxel; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; OFF, oxaliplatin and FF; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial

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Casolino R, Biankin AV. Camb Prism Precis Med. 2023;1:e14; Conroy T et al, N Engl J Med. 2011;364:1817-25; Gill S, et al. J Clin Oncol. 2016;10;3914-20; Golan T, et al. N Engl J Med. 2019;381:317-27; Kindler H, et al. J Clin Oncol. 2022;40:3929-39; NCCN Guidelines Version 3.2024. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455. Accessed October 2024 NCCN guidelines for pancreatic adenocarcinoma, Version 3.2024: pancreatic.pdf (nccn.org); Oettle H, et al. J Clin Oncol. 2014; 32: 2423-9; Pavlidis N, et al. https://oncologypro.esmo.org/content/download/233711/3944768/file/2019-ESMO-ESO-Course-Valencia-Chemotherapy-Nicholas-Pavlidis.pdf. Accessed: November 2024; Tilsed C, et al. Frontiers in Oncology 2022; 12:960317; Von Hoff D, et al. N Engl J Med. 2013;369:1691-703; Wainberg Z, et al. Lancet 2023;402:1272-81; Wang-Gillam A, et al. Lancet 2016;387:545-57

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