METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (mPDAC): FROM DIAGNOSIS TO TREATMENT

MICRO LEARNING MODULE ONE

DIAGNOSIS AND MANAGEMENT OF mPDAC

Prof. Efrat Dotan
Penn Medicine, Ann B. Barshinger Cancer Institute, PA, USA

Prof. Shubham Pant
MD Anderson Cancer Center, TX, USA

DECEMBER 2024

DEVELOPED BY GI CONNECT

This programme is developed by GI CONNECT, an international group of experts in the field of gastrointestinal oncology.

Acknowledgement and disclosures

This GI CONNECT programme is supported through an independent educational grant from Ipsen USA. The programme is therefore independent, the content is not influenced by the supporter and is under the sole responsibility of the experts.

Please note: The views expressed within this programme are the personal opinions of the experts. They do not necessarily represent the views of the experts' institutions, or the rest of the GI CONNECT group.

Expert disclosures:

- **Prof. Efrat Dotan** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: Amgen, Dragonfly, Gilead, Incyte, Ipsen, Kinnate, Leap therapeutics, Lutris, MedImmune, Merck, MERUS, Olympus, Pfizer, Relay, TME biopharmaceuticals, Zymeworks
- **Prof. Shubham Pant** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: Alligator Bioscience, Amal Therapeutics, Arcus, AskGene Pharma, Astellas, AstraZeneca, BioNTech, Boehringer Ingelheim, BPGBio, Bristol-Myers Squibb, Elicio, Framewave, Immuneering, ImmunoMET, Ipsen, Janssen, Jazz, Lilly, Mirati Therapeutics, NGM Pharmaceuticals, Nihon Medi-Physics Co, Ltd, Novartis, Pfizer, Revolution Medicine, Theriva Biosciences, USWorldmeds, Zymeworks

THIS PROGRAMME HAS BEEN DEVELOPED BY EXPERTS

Prof. Efrat Dotan
Penn Medicine, Ann B. Barshinger Institute, USA

Prof. Shubham Pant
MD Anderson Cancer Center, USA

EDUCATIONAL OBJECTIVES

Educational objectives

1. Be able to identify mPDAC **early signs and symptoms** to engage in the appropriate testing strategy for an **early diagnosis**
2. Be able to **differentiate** the **efficacy and safety profiles** of **chemotherapies** for mPDAC
3. Recognise how to **optimise** chemotherapies for patients with mPDAC, and understand the optimal **combination** of treatments

CLINICAL TAKEAWAYS

- Pancreatic ductal adenocarcinoma (PDAC) is usually diagnosed at an advanced, incurable stage due to non-specific symptoms and has an extremely poor prognosis
- Recognition of symptoms and known risk factors is important for an early diagnosis
- Systemic chemotherapy is the standard treatment for mPDAC but molecularly targeted treatments and immunotherapies may have a role for specific patients
- Choice of treatment depends on several factors, including patients' performance status and co-morbidities

WHAT IS THE ISSUE?

PANCREATIC DUCTAL ADENOCARCINOMA

- Pancreatic ductal adenocarcinoma (PDAC) is a highly devastating disease with poor prognosis and rising incidence and accounts for the majority (90%) of pancreatic neoplasms.[1] Typically after diagnosis, only 13% live for 5 years[2]
- PDAC is the third-leading cause of cancer mortality in the US and the seventh-leading cause worldwide.[2,3] It is projected to become the second-leading cause of cancer-related mortality by 2030[3]
  - Approximately 1.7% of men and women will be diagnosed with pancreatic cancer at some point during their lifetime[2]
- In 2024, estimated numbers in the US are:
  - 66,440 new cases (3.3% of all new cancer cases)[2]
  - 51,750 deaths (8.5% of all cancer deaths)[2]
- Pancreatic cancer is difficult to diagnose due to the lack of early symptoms and 80-90% of patients have unresectable tumours due to the advanced stage at diagnosis[4]
- Surgery, chemotherapy and radiation are the primary treatment options for pancreatic cancer[1]

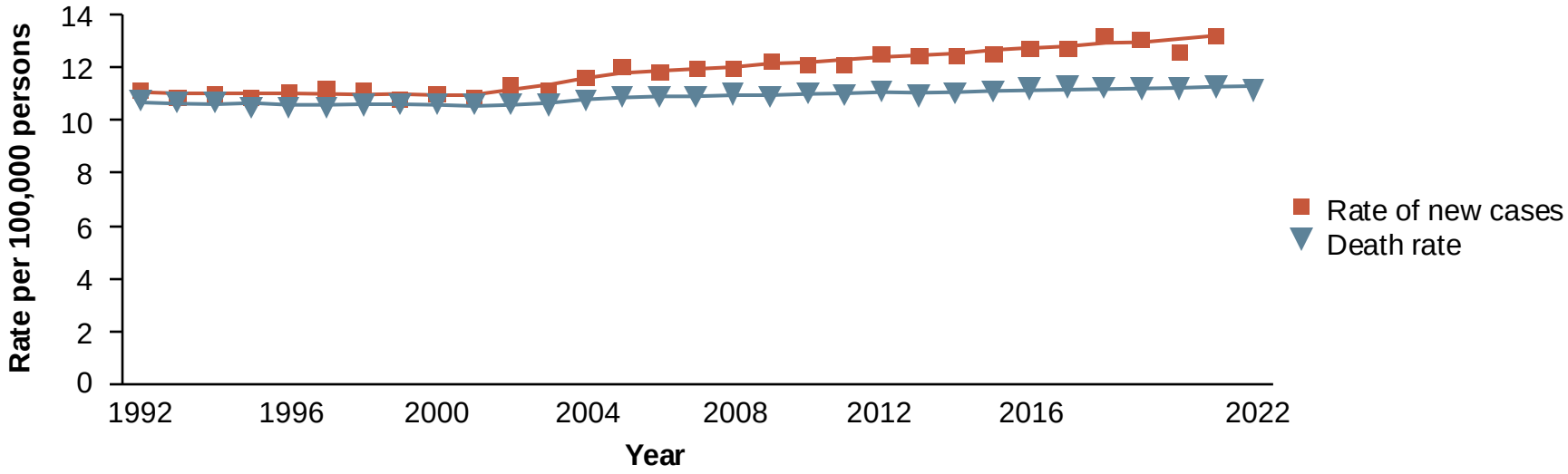
US, United States

1. Orth M, et al. Radiat Oncol. 2019;14:141; 2. Cancer Stat Facts: Pancreatic Cancer. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed October 2024; 3. Park W, et al. JAMA. 2021; 326:851-862; 4. Rawla P, et al. World J Oncol. 2019;10:10-27

PANCREATIC CANCER HAS A LOW 5-YEAR SURVIVAL RATE

Estimated new cases in 2024	66,440
% of all new cancer cases	3.3%
Estimated deaths in 2024	51,750
% of all cancer deaths	8.5%

5-year relative survival
12.8%
2014-2020

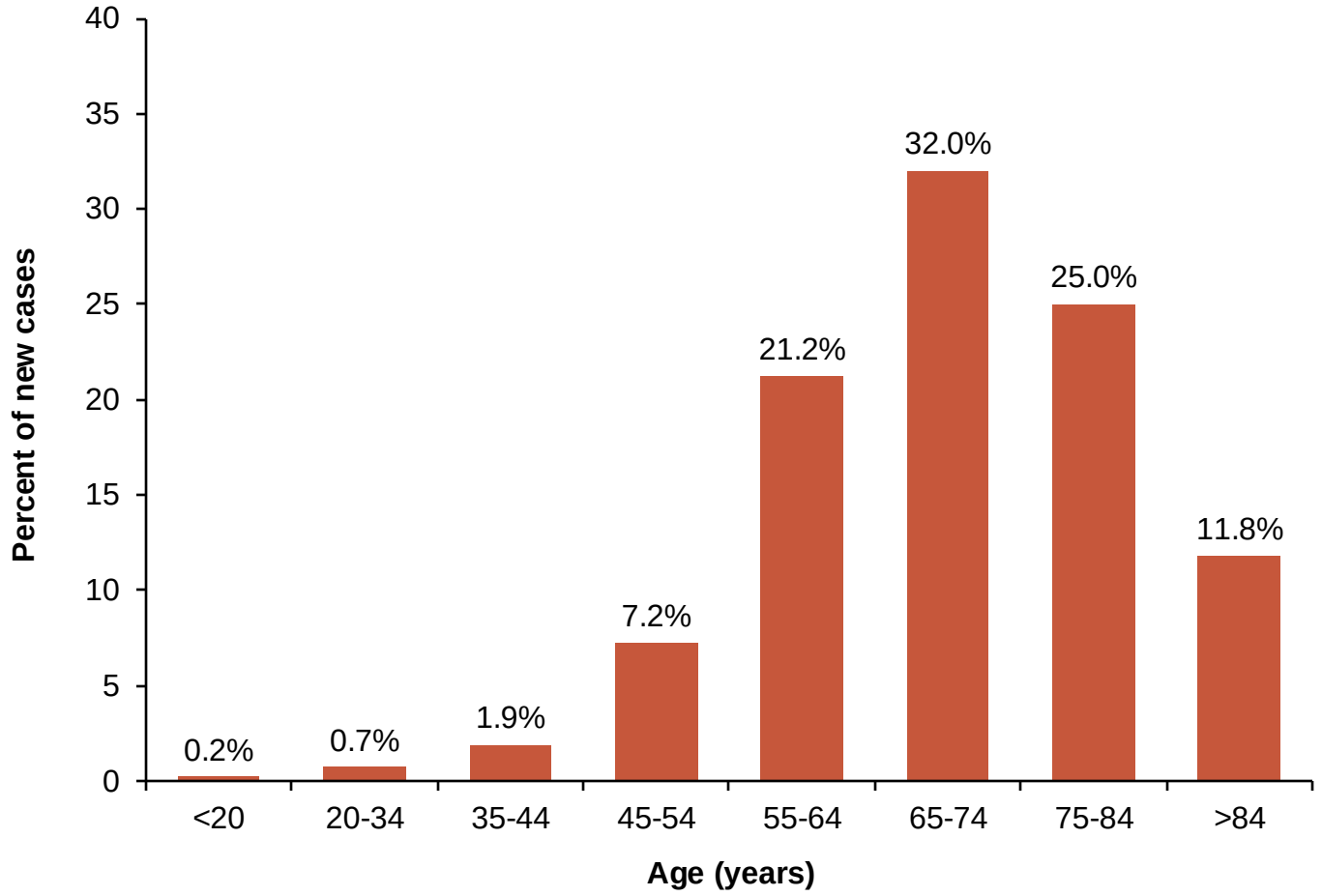


New cases come from SEER 12. Deaths come from U.S. Mortality.
All Races, Both Sexes. Rates are Age-Adjusted

SEER, Surveillance, Epidemiology, and End Results program

Cancer Stat Facts: Pancreatic Cancer. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed October 2024

PANCREATIC CANCER IS MOST FREQUENTLY DIAGNOSED IN PEOPLE AGED 65-74



Pancreatic cancer is most frequently diagnosed among people aged 65-74 years

Median age at diagnosis

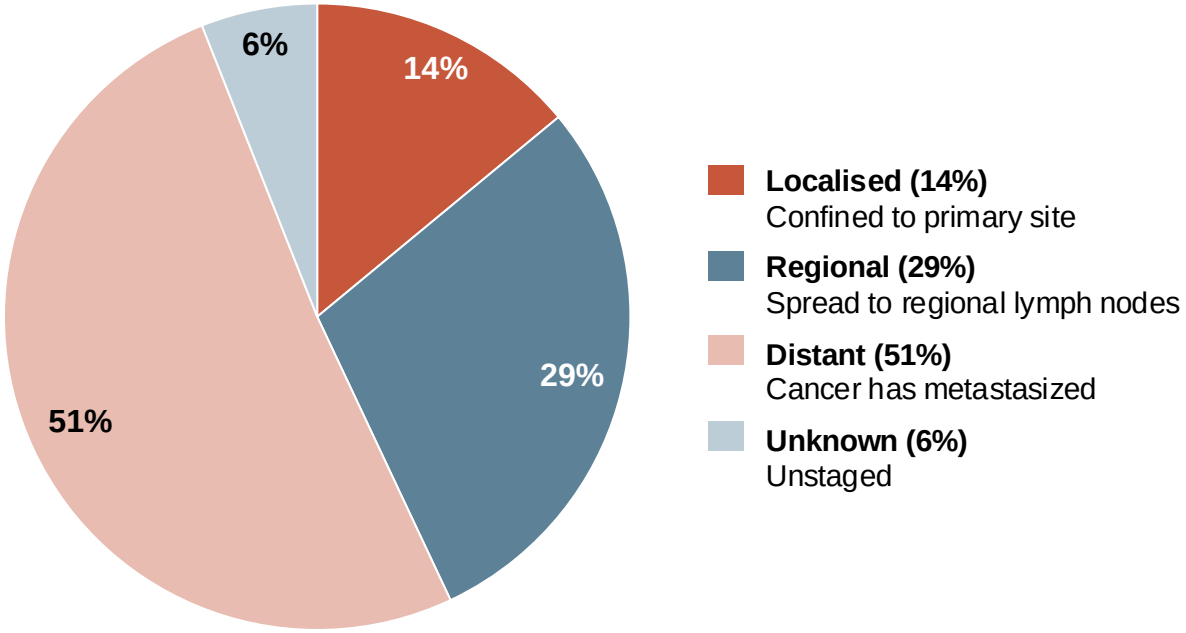
70 years old

SEER, Surveillance, Epidemiology, and End Results program

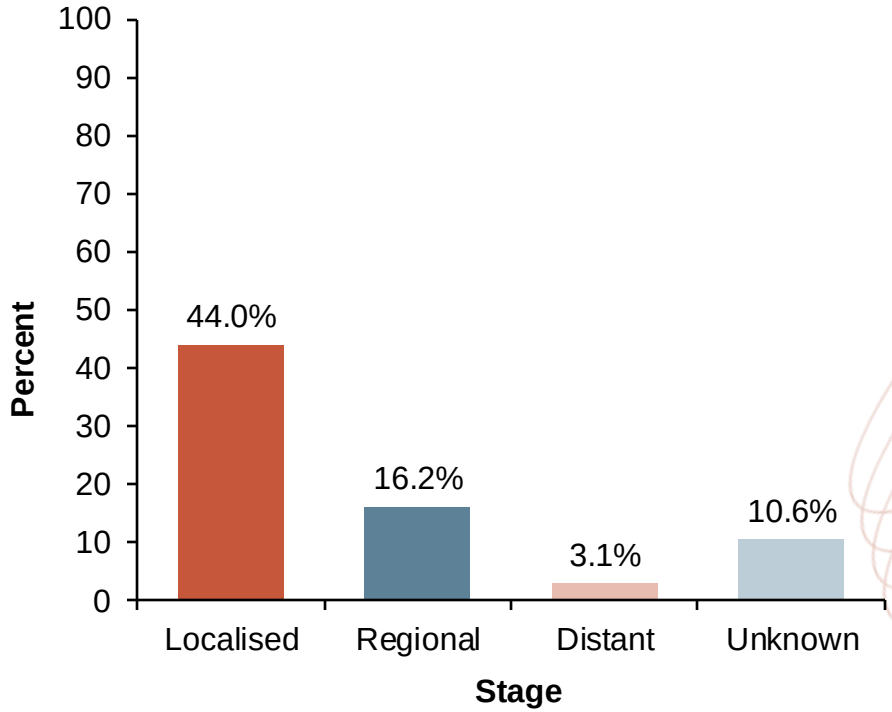
Cancer Stat Facts: Pancreatic Cancer. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed October 2024

MAJORITY OF PATIENTS HAVE ADVANCED DISEASE AT DIAGNOSIS AND A POOR PROGNOSIS

PERCENT OF CASES BY STAGE AT DIAGNOSIS



5-YEAR RELATIVE SURVIVAL



SEER, Surveillance, Epidemiology, and End Results program

Cancer Stat Facts: Pancreatic Cancer. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed October 2024

RISK FACTORS AND CLINICAL PRESENTATION

RISK FACTORS

MODIFIABLE/CLINICAL[1-4]

- Smoking
- Alcohol consumption
- Being overweight
- Dietary factors
- Personal history of chronic pancreatitis
- Personal history of diabetes

NON-MODIFIABLE[1-3,5,6]

- Age
  - most frequently diagnosed: 65-74 years of age
  - median age at diagnosis of 70 years
- Family history of pancreatic cancer
- Hereditary conditions (~10-15% of PDAC cases):
  - hereditary pancreatitis
  - Lynch syndrome
  - mutations in the genes such as *BRCA2, PALB2, ATM*

ATM, ataxia-telangiectasia mutated; BRCA2, BReast CAncer 2 gene; PALB2, partner and localiser of BRCA2, PDAC, pancreatic ductal adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results program

1. Ushio J, et al. Diagnostics (Basel) 2021;11(3): 562. doi: 10.3390/diagnostics11030562; 2. Gupta N, et al. World J Gastroenterol. 2021;27:3158-81; 3. Wood L, et al. Gastroenterology 2022;163:386-402; 4. Dong-Mei M, et al. Technol Cancer Res Treat. 2023; 22: doi: 10.1177/15330338231164875; 5. Cancer Stat Facts: Pancreatic Cancer. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed October 2024; 6. Copur MS, et al. Oncology (Williston Park). 2020;34:196-201.

PDAC SYMPTOMS AND CLINICAL PRESENTATION

- **Early-stage disease is usually clinically silent** and can present as an incidental finding or symptoms related to local tumour effect (ie. painless jaundice)[1]
- **Symptoms are generally non-specific**
  - **Abdominal pain is the most frequently reported clinical symptom**
  - Other symptoms typically present when the tumour has grown and metastasised. These include:
    - Weight loss[1,2]
    - Fatigue[3]
    - Floating stools[2]
    - Pain[1]
    - Pruritus[1]
    - Jaundice[1,2]
    - Nausea and vomiting[2]

NCCN, National Comprehensive Cancer Network; PDAC, pancreatic ductal adenocarcinoma

1. Schawkat K, et al. Radiographics 2020; 40:1219-1239; 2. NCCN Guidelines Version 3.2024. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455. Accessed October 2024. 3. Rawla P, et al. World J Oncol. 2019;10:10-27

DIAGNOSIS AND EVALUATION

DIAGNOSTIC MODALITIES

Imaging is the main tool for diagnosis[1,2]

- **Computed tomography** (CT) and **Magnetic Resonance Imaging** (MRI) – gold standard
- **Endoscopic ultrasound** – obtain tissue for cytological diagnosis
- **Endoscopic retrograde cholangiopancreatography** (ERCP)
- **Positron emission tomography–computed tomography** (PET/CT)
- **Magnetic resonance cholangiopancreatography** (MRCP)

Tumour markers

- **CA19-9:** biomarker tool for monitoring and diagnosis of PDAC, however:
  - up to 10% of the PDAC population is a CA19-9 non-secretor[1]
  - sensitivity of biomarker test approx. 80%[1]
  - useful in symptomatic patients but not in asymptomatic patients as not tumour specific[2]
- **CEA:** can be useful in the diagnosis of pancreatic cancer when paired with CA19-9[3]

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; PDAC, pancreatic ductal adenocarcinoma

1. Bugazia D, et al. Front Oncol. 2024;14:1386699; 2. Rawla P, et al. World J Oncol. 2019;10:10-27;
3. Meng Q, et al. Onco Targets Ther. 2017;10:4591-4598

MICROENVIRONMENT OF PDAC

PATHOLOGY AND MOLECULAR ALTERATIONS OF PANCREATIC DUCT LESIONS

Normal duct
- Low cuboidal cells
- Single cell layer

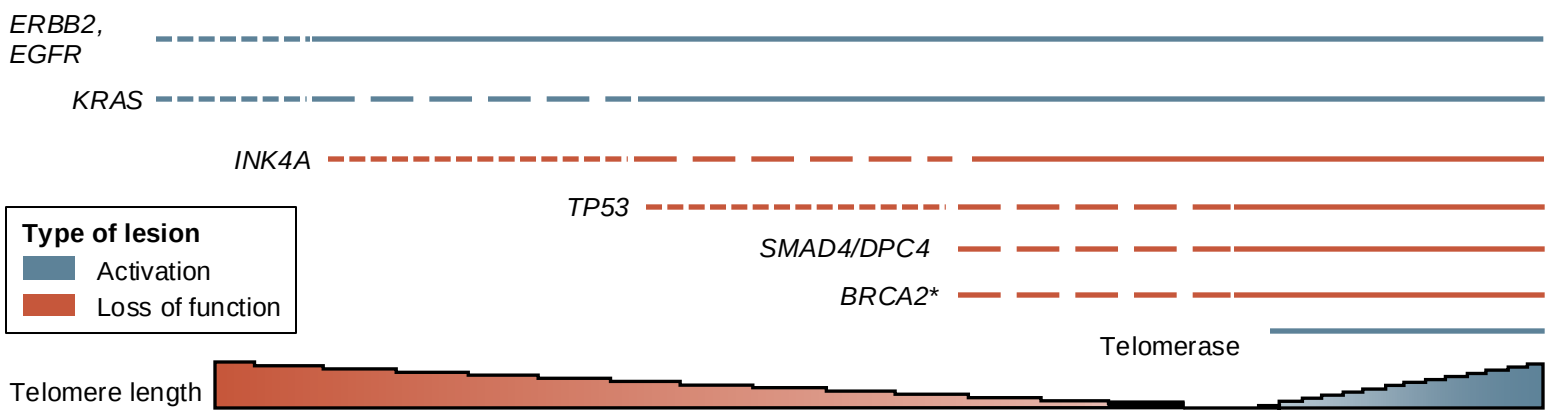
PanIN-1A
- Elongated cells
- Mucin production

PanIN-1B
- Papillary architecture

PanIN-2
- Nuclear abnormalities: e.g. enlargement, some loss of polarity, crowding

PanIN-3
- Budding into lumen
- Severe nuclear atypia
- Mitosis, some abnormal

AdenoCA
- Invasive growth
- Marked stromal reaction (desmoplasia)



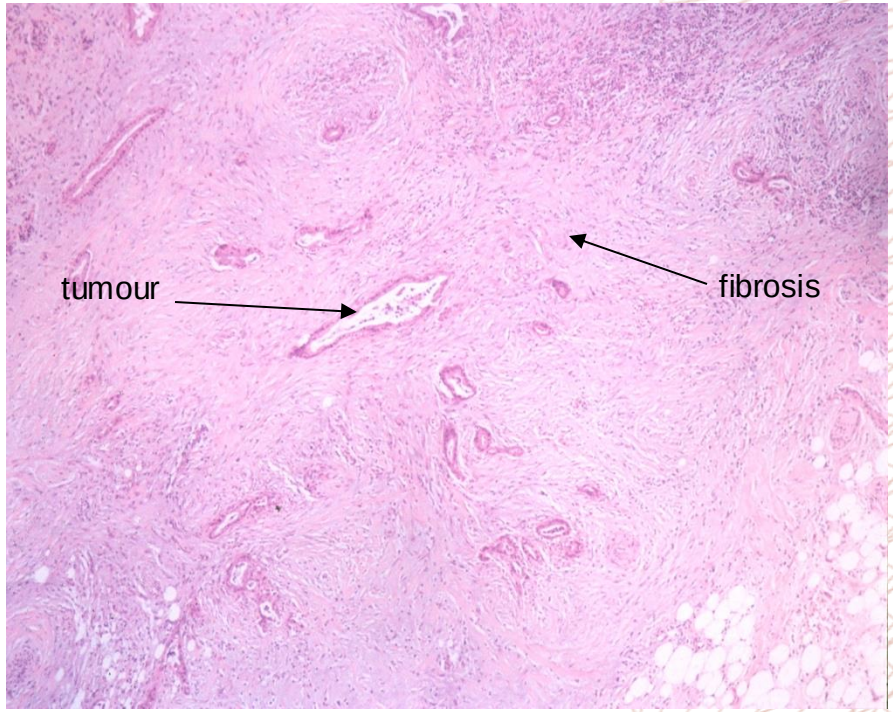


Image provided by Dr Efrat Dotan

Solid lines correspond to alterations that are detected at significant levels at the indicated stages. Broken lines correspond to alterations that may occur at the indicated stages but require further validation.

AdenoCA, adenocarcinoma; BRCA2, BReast CAncer 2 gene; EGFR, epidermal growth factor receptor; ERBB2, erb-b2 receptor tyrosine kinase 2; INK4A, inhibitor of CDK4 (cyclin-dependent kinase 4); KRAS, Kirsten rat sarcoma viral oncogene homolog; PanIN-1A/1B/2/3, pancreatic intraepithelial neoplasia 1A/1B/2/3; PDAC, pancreatic ductal adenocarcinoma; TP53, tumour protein p53 gene

Hruban R, et al. Am J Surg Pathology. 2001;25:579-586; Chiao P and Ling J. Cancer Discovery 2011; 1: 103-5

GENOMIC TESTING

Germline Genetic Testing[1,2]

- Recommended to test for inherited mutations for any patients with confirmed pancreatic cancer diagnosis
- Comprehensive gene panels for hereditary cancer syndromes
- Genetic counseling is recommended for patients who test positive for a pathogenic mutation (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2*, *MSH6, PALB2, PMS2, STK11,* and *TP53*) or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status.

Tumour/Somatic Molecular Profiling[1,2]

- Recommended for locally advanced/metastatic disease who are suitable for anti-cancer therapy
- Panels should include but not be limited to: fusions (*ALK, NRG1, NTRK, ROS1, FGFR2*, and *RET*), mutations (*BRAF, BRCA1/2, HER2, KRAS*, and *PALB2*), amplifications (*HER2*), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumour mutational burden (TMB)
- Next generation sequencing is the gold standard method of detection. RNA sequencing assays are preferred for detecting RNA fusions and immunohistochemistry to detect HER2 overexpression

ATM, ataxia-telangiectasia mutated; BRAF, B-Raf proto-oncogene serine/threonine kinase; BRCA1/2, BReast CAncer 1/2 gene; DNA, deoxyribonucleic acid; FGFR2, fibroblast growth factor receptor 2; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; NCCN, National Comprehensive Cancer Network; NRG1, neuregulin-1; PALB2, partner and localiser of BRCA2; PDAC, pancreatic ductal adenocarcinoma; RET, rearranged during transfection; RNA, ribonucleic acid; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase

1. NCCN Guidelines Version 3.2024. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455. Accessed October 2024; 2. Zhen DB, et al. Therap Adv Gastroenterol 2023;16:17562848231171456

OVERVIEW OF SYSTEMIC TREATMENTS FOR mPDAC

mPDAC, metastatic pancreatic ductal adenocarcinoma

OVERVIEW OF TREATMENT FOR mPDAC

- Chemotherapy is the mainstay of treatment for mPDAC patients
- Enrolment on clinical trials should always be encouraged

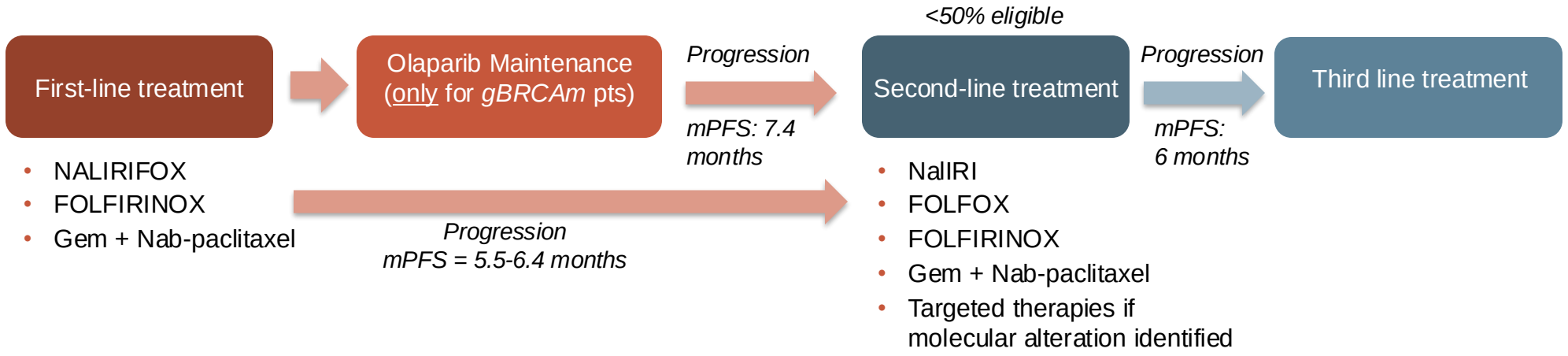


Figure adapted from Casolino 2022

FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; FOLFOX, folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin; gBRCAm, germline BReast CAncer (BRCA) gene mutation; gem, gemcitabine; mPDAC, metastatic pancreatic ductal adenocarcinoma; mPFS, median progression-free survival; Nab, nanoparticle albumin-bound; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; mPDAC, metastatic pancreatic adenocarcinoma; mPFS, median progression-free survival

Casolino R, Biankin AV. Camb Prism Precis Med. 2023;1:e14

KEY STUDIES OF 1L SYSTEMIC THERAPY FOR mPDAC

Study setting	Study	Study type	Arm (N)	Primary endpoint	Primary endpoint		Secondary endpoint	Secondary endpoint		ORR (%)	Notable adverse events (Grade ≥3)
					Months	HR (95% CI)		Months	HR (95% CI)		
First-line	PRODIGE[1] (2011)	RCT, phase 2/3	FOLFIRINOX (171)	OS	11.1	0.57 (0.45 to 0.73)	PFS	6.4	0.47 (0.37 to 0.59)	31.6	FOLFIRINOX vs Gem: 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%
			Gemcitabine (171)		6.8			3.3		9.4	
First-line	MPACT[2] (2013)	RCT, phase 3	Gem + NabP (431)	OS	8.5	0.72 (0.62 to 0.83)	PFS	5.5	0.69 (0.58 to 0.82)	23.0	Gem + NabP vs Gem: 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%
			Gemcitabine (430)		6.7			3.7		7.0	
First-line	NAPOLI-3[3] (2023)	RCT, phase 3	NALIRIFOX (383)	OS	11.1	0.83 (0.70-0.99)	PFS	7.4	0.69 (0.58-0.83)	41.8	NALIRIFOX vs Gem + NabP: hypokalaemia 15.0 vs 4.0%, diarrhoea 20.0 vs 5.0%, nausea 12.0 vs 3.0%. Lower rates of hematological AE's with NALIRIFOX: neutropenia 14.0 vs 25.0%, anaemia 11.0 vs 17.0%
			Gem + NabP (387)		9.2			5.6		36.2	
Metastatic maintenance[a]	POLO[4,5] (2019, 2022)	RCT, phase 3	Olaparib (92)	PFS	7.4	0.53 (0.35 to 0.82)	OS	19.0	0.83 (0.56 to 1.22)	23.1[b]	Olaparib vs placebo: Fatigue 5.6 vs 0%, anaemia 12.2 vs 3.3%, decreased appetite 3.3 vs 0%
			Placebo (62)		3.8			19.2		11.5[b]	

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

AE, adverse event; BRCA1/2, BReast CAncer 1/2 gene; CI, confidence interval; FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; Gem+ Nab-P, gemcitabine and nab (nanoparticle albumin-bound)-paclitaxel; HR, hazard ratio; mPDAC, metastatic pancreatic ductal adenocarcinoma; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial

1. Conroy T et al, N Engl J Med. 2011;364:1817-25; 2. Von Hoff D, et al. N Engl J Med. 2013;369:1691-703; 3. Wainberg Z, et al. Lancet 2023;402:1272-81;
4. Golan T, et al. N Engl J Med. 2019;381:317-27; 5. Kindler H, et al. J Clin Oncol. 2022;40:3929-39

KEY STUDIES OF 2L SYSTEMIC THERAPY FOR MPDAC

Study setting	Study	Study type	Arm (N)	Primary endpoint	Primary endpoint		Secondary endpoint	Secondary endpoint		ORR (%)	Notable adverse events
					Months	HR (95% CI)		Months	HR (95% CI)		
Second-line	CONKO-003[1] (2014)	RCT, phase 3	OFF (77)	OS	5.9	0.66 (0.48-0.91)	PFS	2.9	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% and 7.1% in the OFF and FF groups
			FF (91)		3.3			2.0		–	
Second-line	PANCREOX[2] (2016)	RCT, phase 3	mFOLFOX (54)	PFS	3.0	1.00 (0.66-1.53)	OS	6.1	1.78 (1.08-2.93)	13.2	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.
			5FU/LV (54)		2.8			9.9		8.5	
Second-line	NAPOLI-1[3] (2016)	RCT, phase 3	Nal-IRI + 5-FU/LV (117)	OS	6.1	0.67 (0.49 to 0.92)	PFS	3.1	0.56 (0.41 to 0.75)	16.2	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%
			5-FU/LV (119)		4.2			1.5		0.8	

5-FU, fluorouracil; AE, adverse event; CI, confidence interval; FF, folinic acid (leucovorin calcium) and fluorouracil; HR, hazard ratio; LV, leucovorin calcium (folinic acid); mFOLFOX, modified FOLFOX: folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin; mPDAC, metastatic pancreatic ductal adenocarcinoma; Nal-IRI, nanoliposomal irinotecan; OFF, oxaliplatin and FF; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial

1. Oettle H, et al. J Clin Oncol. 2014; 32: 2423-9; 2. Gill S, et al. J Clin Oncol. 2016;10;3914-20; 3. Wang-Gillam A, et al. Lancet 2016;387:545-57

CONSIDERATIONS FOR TREATMENT SELECTION

- Patient performance status is key factor for treatment selection
- Age and frailty
- Co-morbidities
- Molecular profile
- Patient preference
- Supportive system

Jiang Y, et al. JCO Oncol Pract. 2023;19(1):19-32

SYSTEMIC THERAPIES FOR GOOD PS 0-1

BASED ON NCCN GUIDELINES

First-line

- FOLFIRINOX / mFOLFIRINOX
- NALIRIFOX

Gemcitabine-based therapy:
- Gemcitabine + Nab-paclitaxel
- Gemcitabine + cisplatin for known *BRCA1/2* or *PALB2* mutations)

Maintenance

Olaparib maintenance, only for patients with germline *BRCA1/2* mutations

Subsequent therapy

- Liposomal irinotecan (Nal-IRI) +FU/LV *(if no prior irinotecan)*
- Gemcitabine
- Gemcitabine-based therapy

- Liposomal irinotecan (Nal-IRI) +FU/LV
- Fluoropyrimidine-based therapy

Targeted therapies
Useful in certain circumstances

- Entrectinib, Larotrectinib, Repotrectinib (*NTRK* fusion)
- Dabrafenib + trametinib (*BRAF* V600E mutation)
- Selpercatinib (*RET* fusion)
- Pembrolizumab (MSI-H, dMMR, or TMB-H)

Chemotherapy is recommended as front-line therapy for mPDAC patients, but targeted therapies may be useful in certain circumstances (e.g. if a patient can no longer tolerate chemotherapy)

- Entrectinib, Larotrectinib, Repotrectinib (*NTRK* fusion)
- Dabrafenib + trametinib (*BRAF* V600E mutation)
- Selpercatinib (*RET* fusion)
- Adagrasib, sotorasib (*KRAS* G12C)
- Trastuzumab deruxtecan (*HER2*)

If no prior immunotherapy:

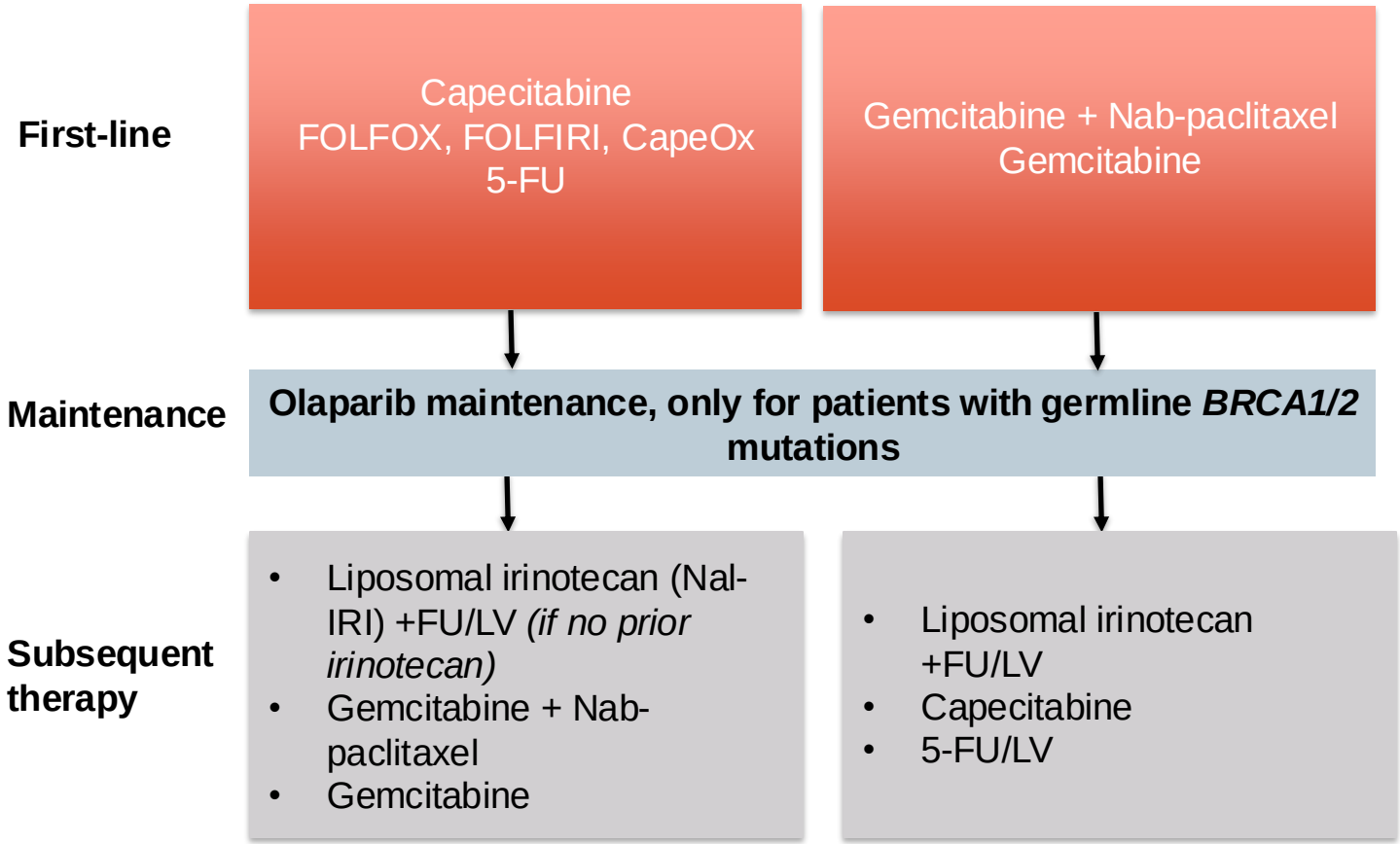
- Pembrolizumab (MSI-H, dMMR, or TMB-H)
- Dostarlimab (MSI-H or dMMR)
- Nivolumab + ipilimumab (TMB-H)

5-FU, fluorouracil; BRAF, B-Raf proto-oncogene serine/threonine kinase; BRCA1/2, BReast CAncer 1/2 gene; dMMR, deficient DNA mismatch repair; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; LV, leucovorin calcium (folinic acid); (m)FOLFIRINOX, (modified) FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; MSI-H, microsatellite instability-high; Nab, nanoparticle albumin-bound; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; NCCN, National Comprehensive Cancer Network; NRG1, neuregulin-1; NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localiser of BRCA2; PS, performance status; RET, rearranged during transfection; TMB-H, tumour mutational burden-high

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)

SYSTEMIC THERAPIES FOR INTERMEDIATE PS 2 OR HIGHER

BASED ON NCCN GUIDELINES



Targeted therapies
Useful in certain circumstances

- Entrectinib, Larotrectinib, Repotrectinib (*NTRK* fusion)
- Dabrafenib + trametinib (*BRAF* V600E mutation)
- Selpercatinib (*RET* fusion) [ECOG PS 2 only for first-line]
- Pembrolizumab (MSI-H, dMMR, or TMB-H)

Chemotherapy is recommended as front-line therapy for mPDAC patients, but targeted therapies may be useful in certain circumstances (e.g. if a patient can no longer tolerate chemotherapy)

- Entrectinib, Larotrectinib, Repotrectinib (*NTRK* fusion)
- Dabrafenib + trametinib (*BRAF* V600E mutation)
- Selpercatinib (*RET* fusion) [ECOG PS 2 only for first-line]
- Adagrasib, sotorasib (*KRAS* G12C)

If no prior immunotherapy:

- Pembrolizumab (MSI-H, dMMR, or TMB-H)
- Dostarlimab (MSI-H or dMMR)
- Nivolumab + ipilimumab (TMB-H)

5-FU, fluorouracil; BRAF, B-Raf proto-oncogene serine/threonine kinase; BRCA1/2, BReast CAncer 1/2 gene; CapeOX, capecitabine and oxaliplatin; dMMR, deficient DNA mismatch repair; FOLFOX, folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin; FOLFIRI, folinic acid (leucovorin calcium), fluorouracil and irinotecan; KRAS, Kirsten rat sarcoma viral oncogene homolog; LV, leucovorin calcium (folinic acid); MSI-H, microsatellite instability-high; Nab, nanoparticle albumin-bound; NCCN, National Comprehensive Cancer Network; NRG1, neuregulin-1; NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localiser of BRCA2; PS, performance status; RET, rearranged during transfection; TMB-H, tumour mutational burden-high

NCCN Guidelines Version 3.2024. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455. Accessed October 2024;

PATIENTS WITH POOR PERFORMANCE STATUS AND PROGRESSIVE DISEASE

PALLIATIVE CARE

- **Single agent chemotherapy** *(gemcitabine)*
- **Targeted therapy** *(based on molecular profiling and as clinically indicated)*
- **Palliative radiotherapy**
  - To relieve pain, bleeding and/or local obstructive symptoms

NCCN, National Comprehensive Cancer Network

NCCN Guidelines Version 3.2024. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455. Accessed October 2024

BEST SUPPORTIVE CARE

mPDAC PATIENTS MAY REQUIRE BEST SUPPORTIVE CARE ALONGSIDE SYSTEMIC TREATMENT

- Biliary stent
  - To treat biliary obstruction
- Pain management
- Pancreatic enzyme replacement
  - In patients with symptoms of exocrine enzyme deficiency
- Physical therapy
  - To improve QoL by controlling symptoms of pain, reducing fatigue, and strengthening weak muscles

mPDAC, metastatic pancreatic ductal adenocarcinoma; NCCN, National Comprehensive Cancer Network; QoL, quality of life

NCCN Guidelines Version 3.2024. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455. Accessed October 2024; van Weert E, et al. Physical Therapy 2010; 90: 1413-1425

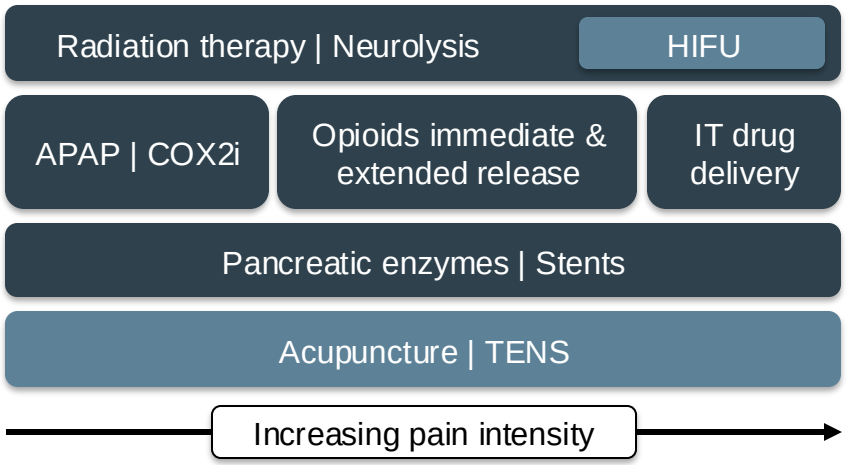
PAIN MANAGEMENT

- Many patients continue to have cancer-related pain despite responding to chemotherapy
- Pain management modalities can be used throughout the patient's clinical course and to achieve optimal relief, can be switched or added to

CURRENT PAIN TREATMENTS

Treatment modalities	Barriers
Systemic chemotherapy	Performance status of patients at presentation
Opioids	Side effects, concern for abuse, provider comfort on required dosing
Radiation therapy	Performance status, minimal barriers outside of locations of radiation therapy centers
Neurolysis/HIFU	Interventional gastroenterologists, although available at academic centers, may not be available in the general community
Intrathecal drug delivery	• Limited availability of pain specialists • Resource intensive • Unclear benefit and cost effectiveness in those expected to live less than 6 months
CAM (CBD, cannabis, acupuncture)	Lack of data and lack of coverage

CURRENT PAIN TREATMENTS

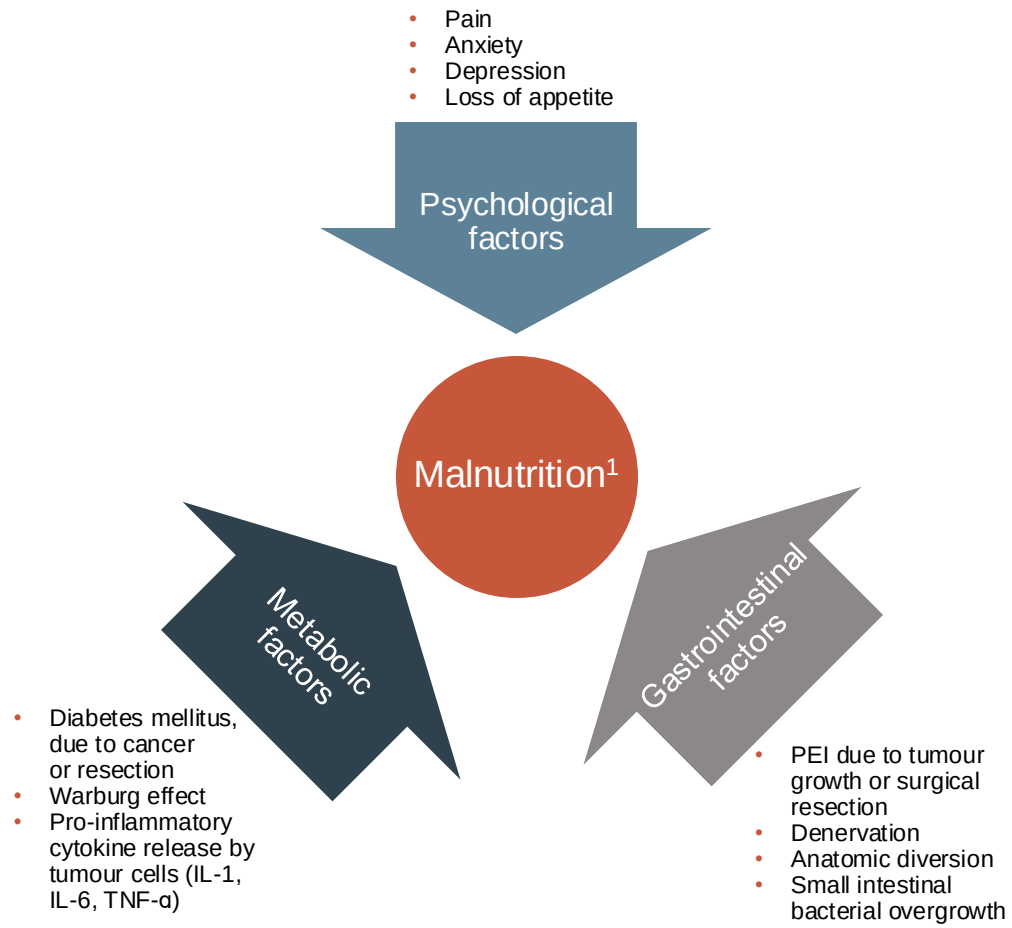


Dark coloured boxes, current standard of care;
light coloured boxes, experimental modalities

APAP, acetaminophen; CAM, complementary and alternative medicine; CBD, cannabidiol; COX-2i, cyclooxygenase-2 inhibitor; HIFU, high-intensity focused ultrasound; IT, intrathecal; TENS, transcutaneous electrical nerve stimulation.

Coveler AL, et al. Oncologist. 2021;26:e971-e982

MANAGING MALDIGESTION AND MALABSORPTION



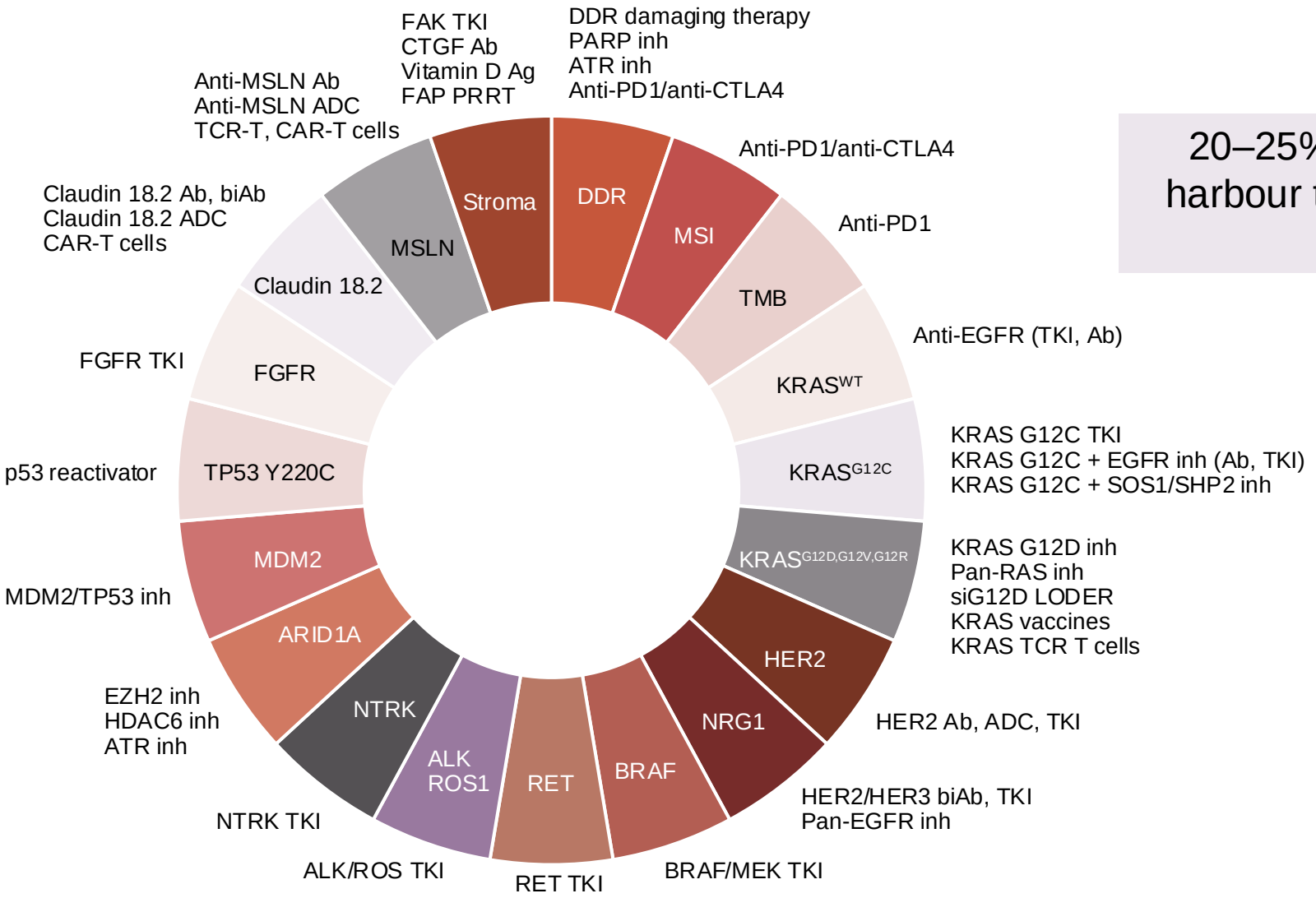
- Pancreatic tumours often result in occlusion of the main pancreatic duct, impeding production of pancreatic enzymes or the transportation into the duodenum and resulting in pancreatic exocrine enzyme deficiency leading to malabsorption and postprandial pain[1,2]
- Pancreatic enzyme replacement therapy (PERT) may enhance nutritional status, helping the patient to undergo chemotherapy, increase quality of life and overall survival[1]

IL-1/6, interleukin 1/6; PEI, pancreatic exocrine insufficiency; TNF- α, tumour necrosis factor alpha

1. Pezzilli R, et al. Cancers (Basel). 2020;12:275; 2. Coveler AL, et al. Oncologist 2021;26:e971-e982

TARGETED THERAPY IN PANCREATIC CANCER

POTENTIAL MOLECULAR TARGETS IN PDAC



20–25% of PDAC patients harbour targetable molecular alterations

ADC, antibody-drug conjugate; ALK, anaplastic lymphoma kinase; ARID1A, AT-rich interaction domain 1A; ATR, ataxia telangiectasia and Rad3-related protein; (bi)Ab, (bi-specific) antibody; BRAF, B-Raf proto-oncogene serine/threonine kinase; CAR-T, chimeric antigen receptor T-cell therapy; CTLA-4; cytotoxic T-lymphocyte-associated protein 4; DDR, DNA damage repair; EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; FAP, fibroblast activation protein; FGFR, fibroblast growth factor receptor; HDAC, histone deacetylase 6; inh, inhibitor; HER2/3, human epidermal growth factor receptor 2/3; KRAS, Kirsten rat sarcoma viral oncogene homolog; MEK, mitogen-activated protein kinase kinase; MSI, microsatellite instability; MSLN, mesothelin; NRG1, neuregulin-1; NTRK, neurotrophic tyrosine receptor kinase; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; PRRT, peptide receptor radionuclide therapy; RAS, rat sarcoma; RET, rearranged during transfection; ROS, ROS proto-oncogene receptor tyrosine kinase; siG12D LODER, small interfering RNA G12D Local Drug EluteR; TCR, T-cell receptor; TKI, tyrosine kinase inhibitor; TMB, tumour mutational burden; TP53, tumour protein p53 gene; WT, wild-type

Zhen DB, et al. Therap Adv Gastroenterol 2023;16:17562848231171456

TARGETED THERAPY FOR PANCREATIC ADENOCARCINOMA

Molecular Target	Targeted Therapy	NCCN panel recommendations
NTRK gene fusions	Larotrectinib	1st line and subsequent treatment options for pts with *NTRK* gene fusion-positive locally advanced or metastatic pancreatic adenocarcinoma and for recurrent disease
	Entrectinib	
	Repotrectinib	Category 2B recommendation as 1st line for patients with metastatic disease (PS 3) and subsequent therapy or therapy for recurrent disease for patients with intermediate/poor PS (PS 2-3)
RET gene fusions	Selpercatinib	1st line: pts with locally advanced/metastatic disease (PS 0–2) and as subsequent therapy for pts with good PS (0–1)
NRG1 gene fusions	Zenocutuzumab-zbco	FDA approved for advanced, unresectable, or metastatic pancreatic adenocarcinoma harboring a NRG1 gene fusion with disease progression on or after prior systemic therapy. Awaiting incorporation into the NCCN guidelines
KRAS G12C mutations	Adagrasib	Subsequent therapy options for patients with any PS (category 2B for poor PS)
	Sotorasib	
BRAF V600E mutations	Dabrefenib/trametinib	1st line: metastatic disease (category 2B) and as subsequent line options (category 2A) for pts with good/poor PS and BRAF V600E mutations
HER2-positive	Fam-trastuzumab-deruxtecan-nxki	As a subsequent therapy option only for patients with good PS and HER2 IHC 3+ expression
	Pembrolizumab	In the advanced disease setting for first-line and subsequent treatment (if no prior immunotherapy)
	Dostarlimab-gxly	As a subsequent treatment option (if no prior immunotherapy) for patients with MSI-H or dMMR locally advanced, metastatic, or recurrent pancreatic adenocarcinoma and any PS
	Nivolumab/Ipilimumab	Category 2B, subsequent therapy option for patients with good or intermediate PS and those who did not receive prior immunotherapy

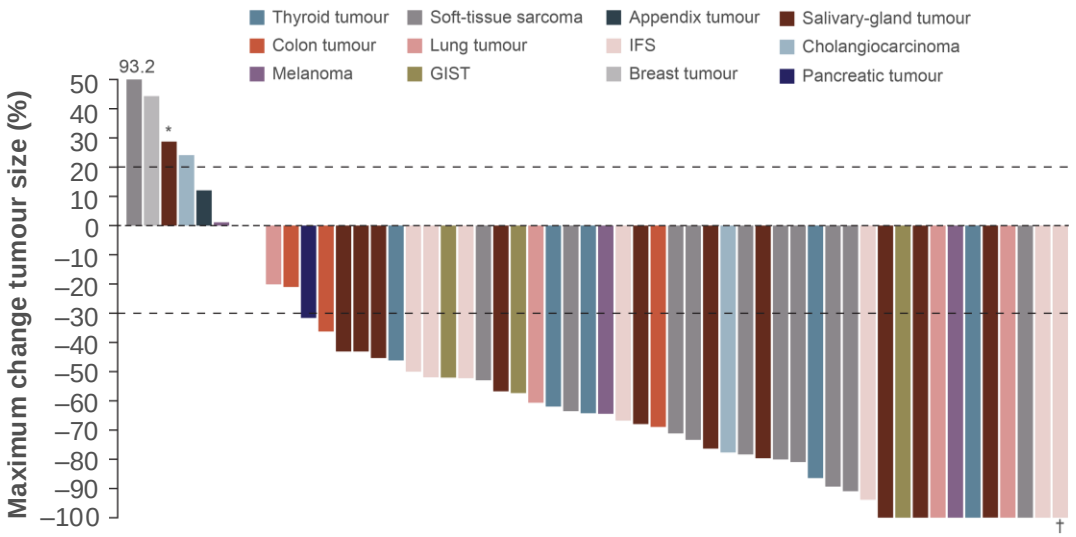
BRAF, B-Raf proto-oncogene serine/threonine kinase; dMMR, deficient DNA mismatch repair; HER2, human epidermal growth factor receptor 2; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; MSI-H, microsatellite instability-high; *NTRK*, neurotrophic tyrosine receptor kinase; PDAC, pancreatic ductal adenocarcinoma; PS, performance status; *RAS*, rat sarcoma; *RET*, rearranged during transfection; TMB-H, tumour mutational burden-high

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)

INITIAL EFFICACY RESULTS OF APPROVED *TRK* INHIBITORS: RESPONSES BY TUMOUR TYPE

Larotrectinib[1]

Data cut-off: 17 July 2017

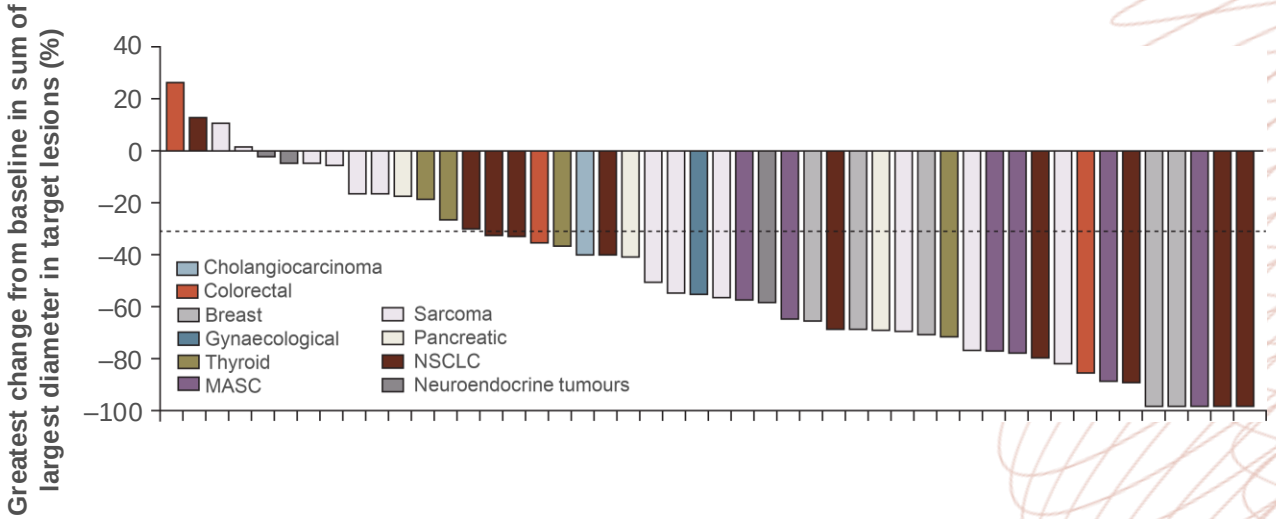


Objective responses with larotrectinib are seen in multiple tumour types and in most of the patients:

80%, 95% CI: 67-90

Entrectinib[2]

Data cut-off: 31 May 2018



Objective responses with entrectinib are seen in multiple tumour types and in most of the patients:

57%, 95% CI: 43.2-70.8

* Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline owing to previous therapy
† Patient had a pathological complete response

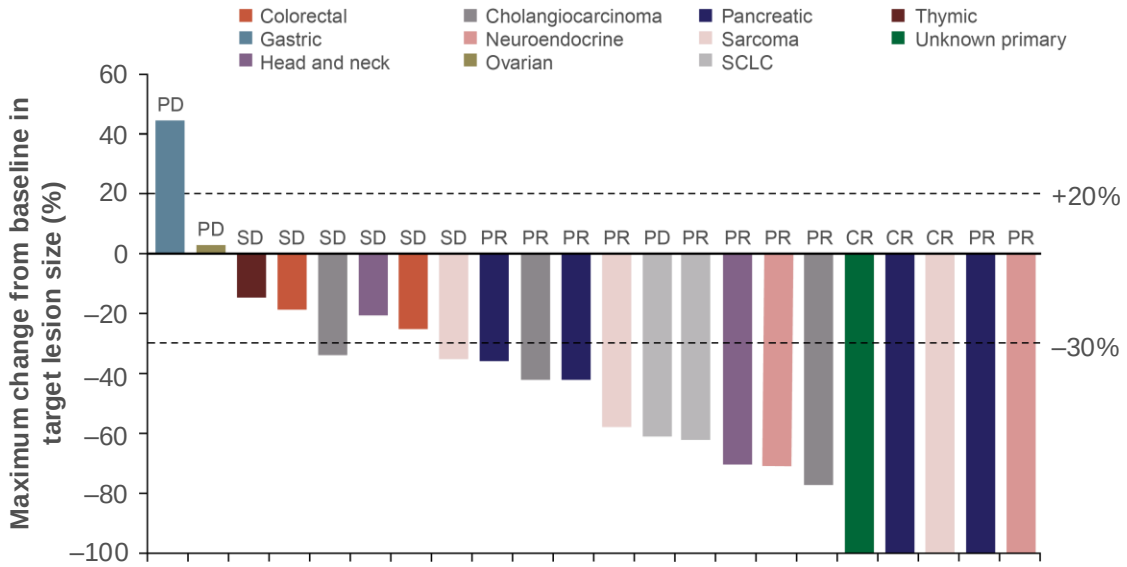
CI, confidence interval; GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; MASC, mammary analogue secretory carcinoma; NSCLC, non-small-cell lung cancer; TRK, tropomyosin receptor kinase

1. Drilon A, et al. N Engl J Med. 2018;378:731-739; 2. Doebele RC, et al. Lancet Oncol. 2020;21:271-282

INITIAL EFFICACY RESULTS OF *RET* INHIBITORS: RESPONSES BY TUMOUR TYPE

ARROW: pralsetinib[1]

Data cut-off: 18 Oct 2021

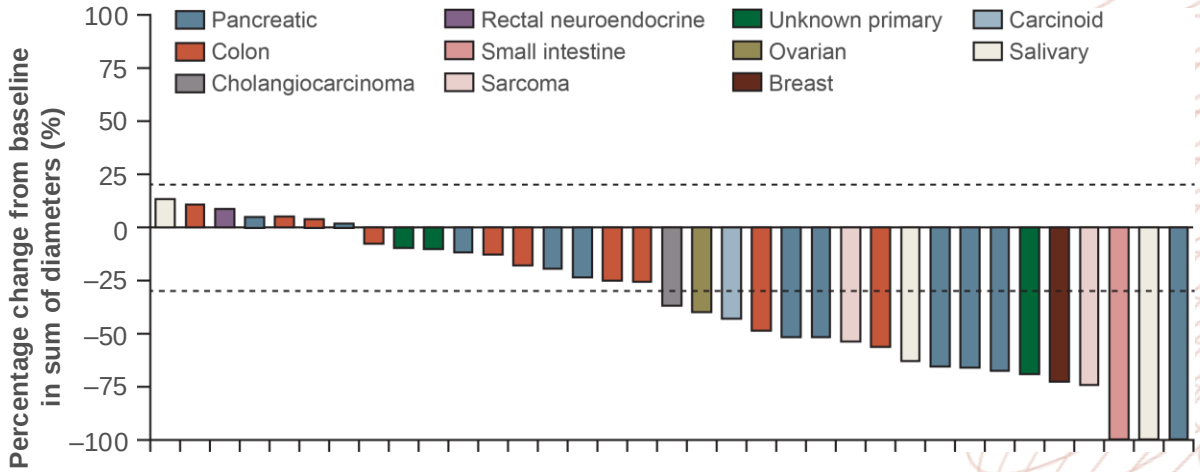


Objective responses with pralsetinib are seen in multiple tumour types

ORR: 57%, 95% CI: 35-77

LIBRETTO-001: selpercatinib[2]

Data cut-off: 24 Sep 2021



Objective responses with selpercatinib are seen in multiple tumour types

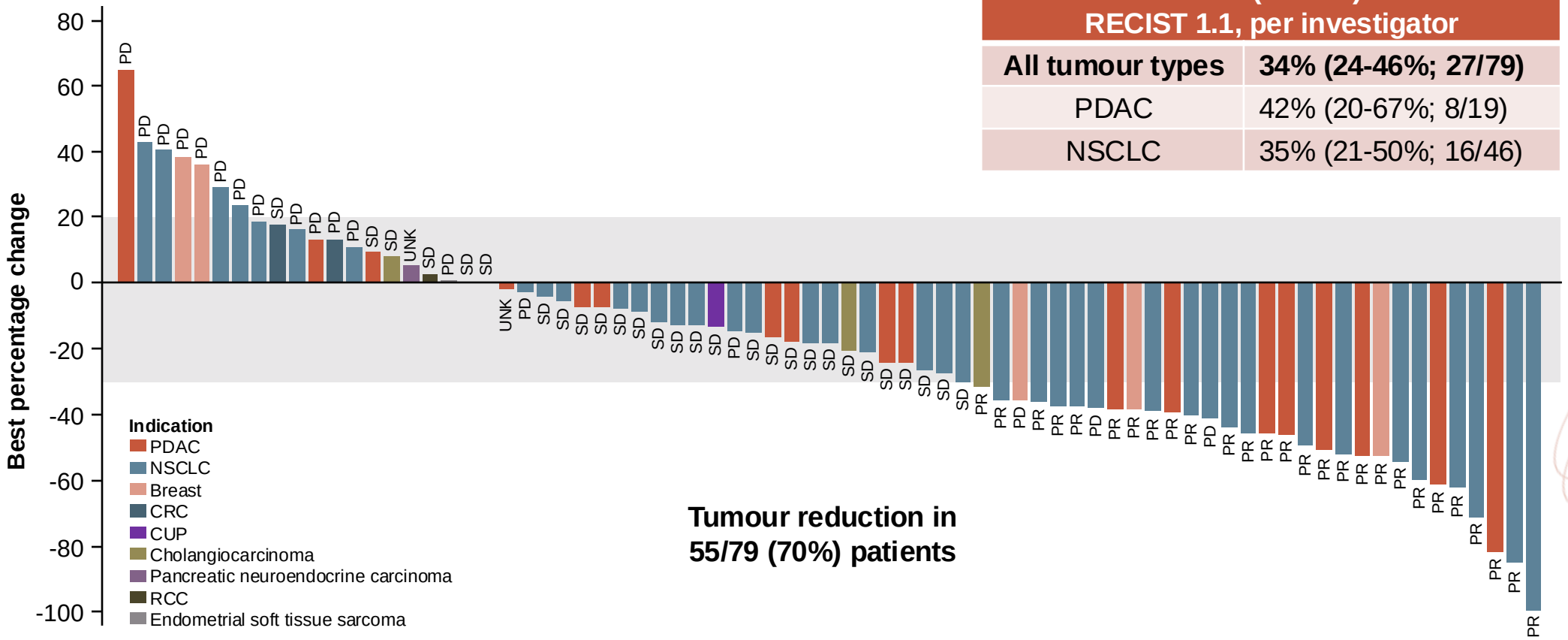
ORR: 43.9%, 95% CI: 28.5-60.3

CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; RET, rearranged during transfection; SCLC, small-cell lung cancer; SD, stable disease

1. Subbiah V, et al. Nat Med. 2022;28:1640-1645; 2. Subbiah V, et al. Lancet Oncol. 2022;23:1261-1273

INITIAL EFFICACY RESULTS OF NRG1 INHIBITOR ZENOCUTUZUMAB: RESPONSES BY TUMOUR TYPE

ORR (95% CI) RECIST 1.1, per investigator	
All tumour types	**34% (24-46%; 27/79)**
PDAC	42% (20-67%; 8/19)
NSCLC	35% (21-50%; 16/46)

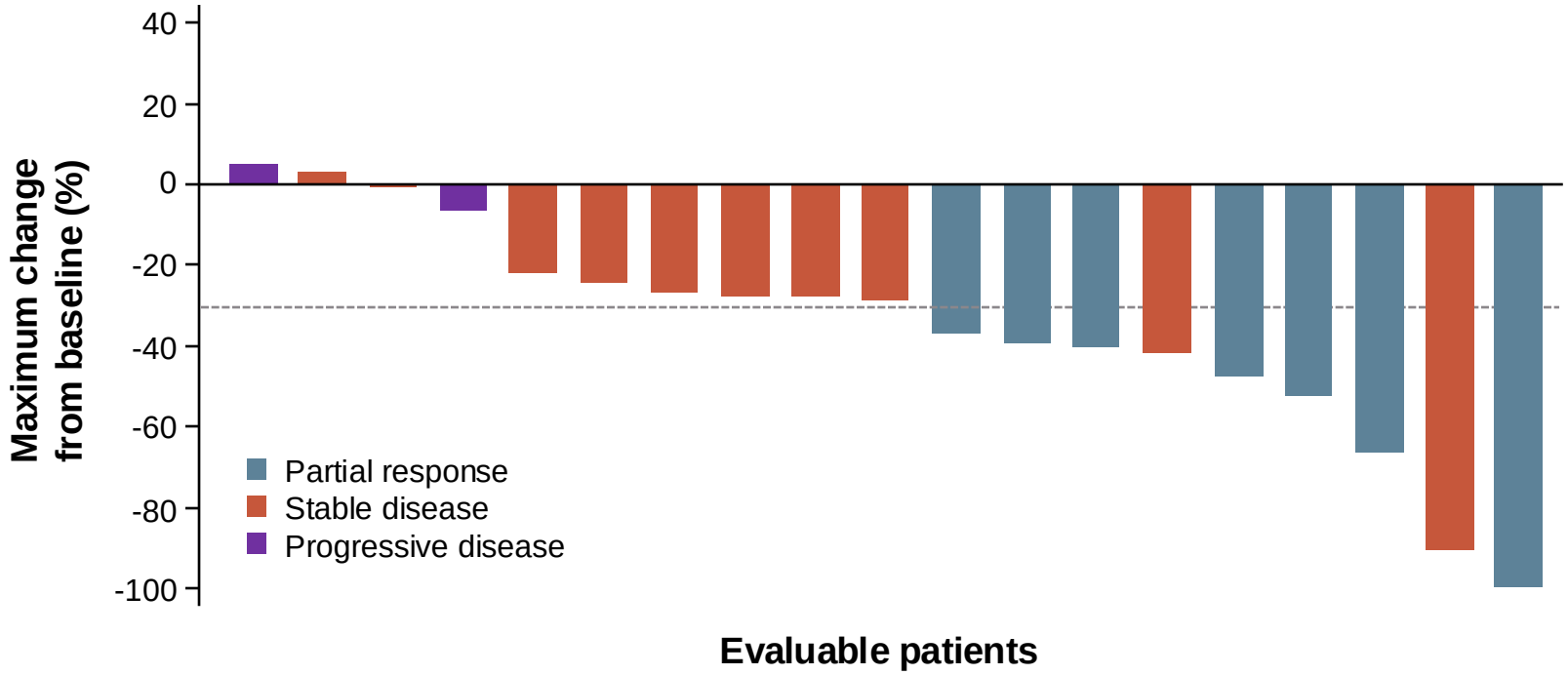


CI, confidence interval; CRC, colorectal cancer; CUP, cancer of unknown primary; PD, progressive disease; NRG1, Neuregulin 1; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; UNK, unknown

Schram A, et al. J. Clin Oncol 2022; 40 (16_suppl): 105 (oral presentation ASCO 2022)

INITIAL EFFICACY RESULTS OF *KRAS* G12C INHIBITOR ADAGRASIB

MAXIMUM PERCENTAGE TUMOUR CHANGE FROM BASELINE IN PATIENTS WITH PDAC



PDAC, pancreatic ductal adenocarcinoma

Bekaii-Saab T, et al. J Clin Oncol 2023; 41: 4097-4106

SUMMARY

- Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with poor prognosis and rising incidence and accounts for the majority of pancreatic neoplasms
- Pancreatic cancer is difficult to diagnose early due to the lack of early symptoms and 80-90% of patients are diagnosed at late stages with unresectable tumours
- Symptoms are generally non-specific with abdominal pain being the most frequently reported clinical symptom
- All patients with metastatic pancreatic cancer should undergo germline and somatic next-generation sequencing to identify possible actionable variants
- Cytotoxic chemotherapy is the cornerstone of systemic therapy for advanced or metastatic pancreatic cancer
- Maintenance therapy after a period of chemotherapy is an option for patients with *BRCA* alterations
- Choice of treatment depends on several factors, including patients' performance status, co-morbidities and molecular targets

BRCA, BReast CAncer gene; PALB2, partner and localiser of BRCA2

COR2ED
THE HEART OF MEDICAL EDUCATION

For more information visit

GI connect
POWERED BY COR2ED

Connect on
LinkedIn @GI CONNECT

Watch on
YouTube @COR2ED

Email
info@cor2ed.com

Visit us at
https://cor2ed.com/

Follow us on
Twitter @giconnectinfo

Heading to the heart of Independent Medical Education since 2012