Supplementary Table.T1. Characteristics of primary resection study population

Characteristic	Institution			
	DF/BWCC	URMC	SCI	Total
Number of subjects	105	74	110	289
Men (n, %)	44(42%)	42(57%)	68(62%)	154(53%)
Age (median, IQR), years	64(58-71)	67(59-72)	69(63-75)	67(59-73)
Race (n, %)				
White	79(75%)	67(91%)	83(75%)	229(79%)
Black	1(1%)	3(4%)	1(1%)	5(2%)
Asian	1(1%)	1(1%)	22(20%)	24(8%)
Other	24(23%)	3(4%)	2(4%)	31(11%)
pT stage (n, %)				
T1-T2	86(82%)	48(65%)	83(75%)	217(75%)
T3-T4	19(18%)	26(35%)	27(25%)	72(25%)
pN stage (n, %)				
N0	31(29%)	17(23%)	37(34%)	85(30%)
N1	44(42%)	27(36%)	37(34%)	108(37%)
N2	30(29%)	30(41%)	36(32%)	96(33%)
Tumor grade (n, %)				
Well/Moderately differentiated	55(52%)	38(51%)	73(66%)	166(57%)
Poorly differentiated / Undifferentiated	48(46%)	35(47%)	34(31%)	117(41%)
Unknown	2(2%)	1(2%)	3(3%)	6(2%)
Lymphovascular invasion (n, %)				
Negative	45(43%)	26(35%)	54(49%)	125(43%)
Positive	51(49%)	46(62%)	37(34%)	134(47%)
Unknown	9(8%)	2(3%)	19(17%)	30(10%)
Resection margin status (n, %)				
R0	40(38%)	40(54%)	63(57%)	143(49%)
R1	63(60%)	34(46%)	44(40%)	141(49%)
R2	2(2%)	0(0)	2(2%)	4(1%)
Rx (not evaluable)	0(0)	0(0)	1(1%)	1(<1%)
Adjuvant systemic chemotherapy (n, %)				
No	29(28%)	20(27%)	34(31%)	83(29%)
Yes	72(68%)	49(66%)	58(53%)	179(62%)
Unknown	4(4%)	5(7%)	18(16%)	27(9%)
Adjuvant radiation therapy (n, %)				
No	44(42%)	43(58%)	61(56%)	148(51%)
Yes	57(54%)	26(35%)	31(28%)	114(40%)
Unknown	4(4%)	5(7%)	18(16%)	27(9%)

Supplementary Table.T1. Characteristics of primary resection cohort population. The primary resection cohort comprised 289 primary resection specimens with full clinicopathologic annotation as detailed in the table. DF/BWCC: Dana-Farber/Brigham and Women's Cancer Centre, URMC: University of Rochester Medical Centre, SCI: Stanford Cancer Institute.

Supplementary Table.T2. Types of adjuvant therapy received by patients in the primary resection cohort.

Adjuvant chemotherapy	**N (%) cases (total N=289)**
No adjuvant chemotherapy	83 (28.7%)
Gemcitabine	153 (52.9%)
Gemcitabine combination	19 (6.5%)
5-FU/LV or capecitabine	2 (0.7%)
FOLFOX	1 (0.4%)
FOLFIRINOX	1 (0.4%)
Unknown	29 (10%)
Other	1 (0.4%)

Supplementary Table.T2. Types of adjuvant therapy received by patients in the primary resection cohort.

Supplementary Table.T3. Characteristics of metastatic biopsy study population

Characteristic	Total
Number of subjects	37
Men (n, %)	16 (43.2%)
Age (median, IQR), years	65 (61-65)
Race (n, %)	
White	35 (94.6%)
Black	0
Asian	0
Other	1 (2.7%)
Unknown	1 (2.7%)
pT stage (n, %)	
T1-T2	7 (18.9%)
T3-T4	8 (21.6%)
Tx	2 (5.4%)
Unknown	20 (54%)
pN stage (n, %)	
N0	6 (16.2%)
N1	7 (18.9%)
N2	1 (2.7%)
Nx	3 (8.1%)
Unknown	20 (54%)
Tumor grade (n, %)	
Well/Moderately differentiated	13 (35.2%)
Moderately differentiated / Poorly differentiated	3 (8.1%)
Poorly differentiated / Undifferentiated	8 (21.6%)
Unknown	13 (35.1%)
Lymphovascular invasion (n, %)	
Negative	12 (32.4%)
Positive	22 (59.5%)
Unknown	3 (8.1%)

Supplementary Table.T3. Characteristics of metastatic biopsy study population. The metastatic biopsy cohort comprised 37 metastatic biopsy specimens. 24 cases had matched fresh frozen metastatic biopsies of which 14 had bulk RNA sequencing and 10 had single-cell RNA sequencing data avaiable. All 37 cases had full clincopathological annotation as detailed in the table.

Supplementary Table.T4. Characteristics of patient derived organoid study population.

Characteristic	Total
Number of subjects	77
Men (n, %)	50 (65%)
Age (median, IQR), years	67 (60-75)
Race (n, %)	
White	66 (85.7%)
Black	0
Asian	5 (6.5%)
Other	1 (1.3%)
Unknown	5 (6.5%)
pT stage (n, %)	
T1-T2	24 (31.2%)
T3-T4	23 (29.8%)
Tx	2 (2.6%)
Unknown	28 (36.4%)
pN stage (n, %)	
N0	19 (24.7%)
N1	20 (26%)
N2	3 (3.9%)
Nx	7 (9%)
Unknown	28 (36.4%)
Tumor grade (n, %)	
Well/Moderately differentiated	25 (32.5%)
Moderately differentiated / Poorly differentiated	8 (10.4%)
Poorly differentiated / Undifferentiated	15 (19.5%)
Unknown	29 (37.7%)
Lymphovascular invasion (n, %)	
Negative	19 (24.7%)
Positive	56 (72.7%)
Unknown	2 (2.6%)
Organoid passage number at assessment (n, %)	
1-5	13 (16.9%)
6-10	18 (23.4%)
11-15	24 (31.2%)
>15	22 (28.5%)
Patient tissue site of origin for organoid culture (n, %)	
Ascites fluid	13 (16.9%)
Liver	31 (40.2%)
Omentum	4 (5.2%)
Pancreas	28 (36.4%)
Retroperitoneal lymph node	1 (1.3%)
Prior systemic treatment before patient tissue collection (n, %)	
Yes	44 (57.1%)
No	33 (42.9%)

Supplementary Table.T4. Characteristics of patient derived organoid study population. The patient derived organoid cohort comprised 77 cases with clinciopathological annotation as detailed.

Supplementary Table.T5. Summary of protein subtype markers

Marker	Subtype classification in protein panel	Summary	Reference
Claudin 18.2 (CLDN18.2)	Classical	Clinical trial for inhibitor IMAB362 in combination with CAPOX for CLDN18.2 positive patients by IHC	Clinical trial: NCT03653507
		CLDN18 immunohistochemstry used as biomarker in Zolbetuximab trial targeting CLDN18.2 positive cells in combination with Gemcitabine	Türeci, Özlem, Mitnacht-kraus, R., Wöll, S. & Yamada, T. Characterization of zolbetuximab in pancreatic cancer models. *Oncoimmunology* **8**, 1–10 (2019)
		CLDN18.2 RNA upregulated in classical subtype	Lomberk, G. *et al.* Distinct epigenetic landscapes underlie the pathobiology of pancreatic cancer subtypes. *Nat. Commun.* **9**, 1978 (2018).
		CLDN18 RNA differentially expressed in pancreatic cancer	Karanjawala, Z. E. *et al.* New markers of pancreatic cancer identified through differential gene expression analyses: claudin 18 and annexin A8. *Afile///C/Users/hlw18/Downloads/nihms105560 (1).pdfmerican J. Surg. Pathol.* **32**, 188–196 (2008)
Trefoil factor 1 (TFF1)	Classical	Upregulated in classical subtypes	Collisson, E. A. *et al.* Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. *Nat. Med.* **17**, 500–503 (2011).
		Identified as top 5 most differentially expressed genes between classical and basal-like cells from tumor samples by scRNA-seq	Zhou, D. C. *et al.* Spatial drivers and pre-cancer populations collaborate with the microenvironment in untreated and chemo-resistant pancreatic cancer. *bioRxiv* 2021.01.13.426413 (2021) doi:10.1101/2021.01.13.426413.
		Included in 50-gene set to determine classical subtype	Moffitt, R. A. *et al.* Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. *Nat. Genet.* **47**, 1168–1178 (2015).
		Increased gene expression in L1 subtype which corresponds with Collisson and Moffitt classical subtype	Zhao, L., Zhao, H. & Yan, H. Gene expression profiling of 1200 pancreatic ductal adenocarcinoma reveals novel subtypes. *BMC Cancer* **18**, 603 (2018).
		Upregulated in progenitor subtype	Bailey, P. *et al.* Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* **531**, 47–52 (2016).
GATA-binding factor 6 (GATA6)	Classical	Distinguishes classical subtype	Kane, G. M. *et al.* GATA6 Expression Distinguishes Classical and Basal-like Subtypes in Advanced Pancreatic Cancer. *Clin. Cancer Res.* **26**, 4901 LP – 4910 (2020).
		Biomarker of response	Clinical trial NCT04472910

		Biomarker of response	Clinical trial NCT04469556
		GATA6 highly expressed in classical tumors	Collisson, E. A. *et al.* Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. *Nat. Med.* **17**, 500–503 (2011).
S100 calcium binding protein A2 (S100A2)	Basal	Associated with squamous basal PDAC and hypermethylated in progenitor subtype	Bailey, P. *et al.* Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* **531**, 47–52 (2016).
		Increased expression in basal subtype	Moffitt, R. A. *et al.* Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. *Nat. Genet.* **47**, 1168–1178 (2015).
		Increased expression in quasi-mesenchymal subtype	Collisson, E. A. *et al.* Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. *Nat. Med.* **17**, 500–503 (2011).
Keratin 17 (KRT17)	Basal	Most lethal molecular subtype	Roa-Peña, L. *et al.* Keratin 17 identifies the most lethal molecular subtype of pancreatic cancer. *Sci. Rep.* **9**, 11239 (2019).
		Increased gene expression in L2 subtype which corresponds with Moffitt basal subtype and Collisson quasi-mesenchymal subtype	Zhao, L., Zhao, H. & Yan, H. Gene expression profiling of 1200 pancreatic ductal adenocarcinoma reveals novel subtypes. *BMC Cancer* **18**, 603 (2018).
		KRT17 expressing PDAC correlates with resistance to Gemcitabine and 5-FU	Pan, C.-H. *et al.* An unbiased high-throughput drug screen reveals a potential therapeutic vulnerability in the most lethal molecular subtype of pancreatic cancer. *Mol. Oncol.* **14**, 1800–1816 (2020).
		Correlation of response to chemotherapy and resistance	Clinical trial NCT04469556
Keratin 5 (KRT5)	Basal	KRT5 associated with squamous cell lineage	Somerville, T. D. D. *et al.* TP63-Mediated Enhancer Reprogramming Drives the Squamous Subtype of Pancreatic Ductal Adenocarcinoma. *Cell Rep.* **25**, 1741-1755.e7 (2018).
		GATA6-silenced cells express KRT5	Martinelli, P. *et al.* GATA6 regulates EMT and tumour dissemination, and is a marker of response to adjuvant chemotherapy in pancreatic cancer. *Gut* **66**, 1665 LP – 1676 (2017).

Supplementary Table.T5. **Summary of subtype markers selected for subtype determination.** The subtype markers selected for the multiplex immunofluorescence assay are highlighted in the table and were selected based upon their importance across multiple studies for determining tumor subtypes, biological underpinning of the specific subtypes and relevance as biomarkers in clinical trials.

Supplementary Table.T6. Summary of primary antibodies and Opal fluorophores used in the the multiplex immunofluorescence assay.

Purpose	Marker	Clone	Manufacturer, catalogue number	Antibody dilution	Fluorophore	Manufacturer, Catalogue number	Fluorophore dilution	Antigen retrieval prior to primary antibody
Classical subtype marker	Cldn18.2	EPR19202-244	Abcam, 241330	1:700	Opal 570	FP1488001KT	1:300	ER1
Classical subtype marker	GATA6	D61E4	CST, 5851	1:400	Opal 540	FP1494001KT	1:300	ER1
Classical subtype marker	TFF1	EPR3972	Abcam, 92377	1:1500	Opal 690	FP1497001KT	1:200	ER1
Basal subtype marker	Keratin-17	E3	ThermoFisher, MA513539	1:75	Opal 520	FP1487001KT	1:300	ER2
Basal subtype marker	Keratin-5	EP1601Y	Abcam, 52635	1:500	Opal 480	FP1500001KT	1:300	ER1
Basal subtype marker	S100a2	EPR5392	Abcam, 109494	1:2500	Opal 650	FP1496001KT	1:1000	ER1
Epithelial marker	CKPAN	AE1/AE3 C11	Dako, M3515; CST, 4545	1:50 1:500	Opal 620	FP1495001KT	1:300	ER1

Supplementary Table.T6. Summary of primary antibodies and Opal fluorophores used in subtyping assay. Details of primary antibody dilutions and Opal fluorophore pairings.

Supplementary Table.T7. List of ancillary reagents used in the multiplex immunofluorescence assay.

Reagent	**Manufacturer, catalogue number**
Xylene	Fisher Scientific, X3P1GAL
Ethanol	Fisher Scientific, HC-800-1GAL
BOND Epitope Retrieval Solution 1	Leica Biosystems, AR9961
BOND Epitope Retrieval Solution 2	Leica Biosystems, AR9640
Antibody diluent/block	Akoya Biosciences, ARD1001EA
Secondary Opal polymer HRP Ms + Rb	Akoya Biosceicnes, ARH1001EA
1x Plus Automation Amplification Diluent	Akoya Biosciences, FP1609
Spectral DAPI	Akoya Biosciences, FP1490
ProLong Gold Antifade Mountant	Fisher Scientific, P36930

Supplementary Table.T7. List of reagents used in the multiplex immunofluorescence assay. Details of all reagents used for multiplex immuofluorescence assay on the Leica BOND RX Research Stainer (Leica Biosystems, Buffalo, IL).

Supplementary Table.T8. Single marker z-scored mean intensity positive thresholds.

Subtype marker	Z-scored fluorescence mean marker intensity threshold for cell positivity (raw mean intensity range)
CLDN18.2	2 (0.4-0.85)
TFF1	1.5 (4.8-6.3)
GATA6	1 (1.2-2.8)
KRT17	0.5 (0.6-1.4)
KRT5	0.5 (0.25-0.89)
S100A2	2 (2-5.8)

Supplementary Table.T8. Single marker immunofluorescence gating parameters. Raw mean intensities for each marker were normalized per TMA to account for potential variability in staining performance based upon tissue institute of origin. Following normalization, z-scored fluorescence marker intensity 'gates' were determined to classify cells as positive or negative for each single marker.

Supplementary Table.T9. Cell subtype marker combinations and subtypes

	Cell subtype													
Marker	Basal							Classical						All marker negative
KRT17	■	■	■		■									
KRT5	■		■	■		■								
S100A2	■	■		■			■							
CLDN18.2								■			■		■	■
GATA6									■		■	■		■
TFF1										■		■	■	■

	Cell subtype
Marker	Co-expressor
KRT17	
KRT5	
S100A2	
CLDN18.2	
GATA6	
TFF1	

Supplementary Table.T9. Cell subtype marker combinations and subtypes. A combinatorial approach to cell subtype determination was devised. Each cell was assessed for expression of each of the 6 markers in the subtyping mIF panel. Basal cell subtype was determined by expression of any of the 3 basal markers (KRT17, KRT5, S100A2), classical by any of the 3 classical markers (GATA6, CLDN18.2, TFF1) and co-expressor subtype by any combination of both basal and classical marker expression within a cell.

Supplementary Table.T10. Univariate and multivariable-adjusted Cox regression models for overall survival and disease-free survival according to tumor expression subtype by multiplex immunofluroscence

Tumor subtype	Overall Survival						Disease-Free Survival					
	No. of patients	Median survival (mo)	Univariate HR (95% CI)	P	Multivariable HR (95% CI)[a]	P	No. of patients	Median survival (mo)	Univariate HR (95% CI)	P	Multivariable HR (95% CI)[a]	P
Tumor subtype (2-class)												
Classical	177	25.9	1.00 (reference)		1.00 (reference)		175	14.3	1.00 (reference)		1.00 (reference)	
Basal	112	16.7	1.62(1.24-2.13)	**0.001**	1.40(1.04-1.87)	**0.02**	110	9.9	1.55(1.16-2.07)	**0.003**	1.52(1.13-2.05)	**0.006**
Tumor subtype (3-class)												
Classical predominant	120	29.5	1.00 (reference)		1.00 (reference)		119	17.6	1.00 (reference)		1.00 (reference)	
Mixed	130	18.4	1.65(1.24-2.21)	**0.001**	1.50(1.11-2.03)	**0.009**	128	10.7	1.91(1.40-2.59)	**<0.001**	1.93(1.40-2.65)	**<0.001**
Basal predominant	39	15.7	1.94(1.27-2.96)	**0.002**	1.27(0.79-2.05)	0.30	38	8.8	1.82(1.14-2.91)	**0.01**	1.60(0.99-2.60)	**0.06**

Supplementary Table.T10. Univariate and multivariable-adjusted Cox regression models for overall survival and disease-free survival according to tumor expression subtype by multiplex immunofluorescence. Cox proportional hazards regression models were applied to two-group and three-group classified tumor subtypes. Using the two-group classification, basal tumors were associated with worse overall survival (OS) and disease-free survival (DFS), compared with classical tumors. Using the three-group classification, mixed tumors were associated with intermediate outcomes with OS between basal-predominant and classical-predominant tumors. [a]Cox proportional hazards regression model adjusted for age, sex, pathologic N stage (N0, N1, N2), tumor grade (well/moderately-/poorly-differentiated, unknown), lymphovascular invasion (negative, positive, unknown), receipt of perioperative treatment and resection margin status (R0, R1, R2, unknown). Disease-free survival: n=285; overall survival: n=289.

Supplementary Table.T11. Univariate and multivariable-adjusted cox-regression models for overall survival and disease-free survival according to basal-classical axis score.

Subtype fraction	Overall survival					Disease-free survival				
	No. of patients	Median, IQR (%)	Median survival (mo)	Univariate HR (95% CI)	Multivariable HR (95% CI)[b]	No. of patients	Median, IQR (%)	Median survival (mo)	Univariate HR (95% CI)	Multivariable HR (95% CI)[b]
Basal-classical axis[a]										
Quartile 1	71	0.3 (0-1.4)	31.5	1.00 (reference)	1.00 (reference)	70	0.3 (0-1.4)	16.9	1.00 (reference)	1.00 (reference)
Quartile 2	73	7.3 (3.8-11.1)	23.9	1.55 (1.06-2.29)	1.49 (0.99-2.23)	72	7.2 (3.7-10.9)	14.1	1.26 (0.84-1.89)	1.24 (0.81-1.89)
Quartile 3	74	33.0 (25.0-47.3)	16.9	1.87 (1.27-2.75)	1.57 (1.05-2.36)	74	33.0 (25.0-47.3)	10.5	1.83 (1.24-2.71)	1.85 (1.22-2.81)
Quartile 4	71	91.3 (75.9-99.2)	16.7	2.03 (1.38-3.00)	1.60 (1.05-2.44)	69	91.3 (75.9-99.2)	9.8	1.73 (1.14-2.61)	1.70 (1.11-2.60)
P_{trend}[c]				**0.002**	**0.028**				**0.010**	**0.018**

Supplementary Table.T11. Univariate and multivariable-adjusted Cox regression models for overall survival and disease-free survival according to basal-classical axis score. For survival analyses, basal-classical axis score was split into quartiles with the lowest quartile as the referent and Cox proportional hazards regression models were applied. Increasing basal-classical axis score was associated with worse overall survival and disease-free survival. [a] Basal-classical axis score was derived from basal fraction taken as a percentage of total basal and classical cells per tumor. A higher score indicates a greater basal cell fraction while a lower score indicates a greater classical cell fraction within a tumor. Disease-free survival: n=285; overall survival: n=289. [b] Cox proportional hazards regression model adjusted for age, sex, pathologic N stage (N0, N1, N2), tumor grade (well/moderately-/poorly-differentiated, unknown), lymphovascular invasion (negative, positive, unknown), and resection margin status (R0, R1, R2, unknown). [c] P_{trend} calculated by the Wald $\chi 2$ test.

Supplementary Table.T12. Univariate and multivariable-adjusted Cox regression models for overall survival and disease-free survival according to co-expressor cell fraction.

	Overall survival					Disease-free survival				
Co-expressor cell fraction[a]	**No. of patients**	**Median, IQR (%)**	**Median survival (mo)**	**Univariate HR (95% CI)**	**Multivariable HR (95% CI)[b]**	**No. of patients**	**Median, IQR (%)**	**Median survival (mo)**	**Univariate HR (95% CI)**	**Multivariable HR (95% CI)[b]**
Q1	71	0.2 (0-0.7)	25.8	1.00 (reference)	1.00 (reference)	70	0.2 (0-0.7)	14.4	1.00 (reference)	1.00 (reference)
Q2	73	3.1 (1.9-4.2)	16.7	1.39 (0.96-2.02)	1.31 (0.87-1.96)	72	3.1 (1.9-4.2)	13.3	1.09 (0.73-1.62)	0.86 (0.55-1.33)
Q3	74	10.9 (8.1-14.6)	24.2	1.09 (0.75-1.60)	1.11 (0.73-1.68)	72	10.9 (8.0-14.6)	14.1	1.05 (0.71-1.54)	0.99 (0.65-1.52)
Q4	71	32.1 (24.1-47.7)	21.5	1.37 (0.94-2.00)	1.28 (0.84-1.93)	71	32.1 (24.1-47.7)	13.7	1.14 (0.77-1.69)	1.09 (0.70-1.69)
P_{trend}				0.278	0.485				0.581	0.406

Supplementary Table.T12. Univariate and multivariable-adjusted Cox regression models for overall survival and disease-free survival according to co-expressor cell fraction. For survival analyses using Cox regression, tumors were divided into quartiles based on co-expressor fraction, with the lowest quartile as the referent**.** [a] Co-expressor cell fraction calculated by dividing the number of co-expressor cells by the sum of basal, classical, and co-expressor cells within a tumor. [b] Cox proportional hazards regression model adjusted for age, sex, pathologic N stage (N0, N1,N2), tumor grade (well/moderately-/poorly-differentiated, unknown), lymphovascular invasion (negative, positive, unknown), receipt of perioperative treatment, resection margin status (R0, R1, R2, unknown) and basal-classical axis score. [c] P_{trend} calculated by the Wald $\chi 2$ test.

Supplementary Table.T13. Tumor subtype and associations with clinicopathological features

Characteristic	Tumor subtype			
	Classical-predominant (N=120)	Mixed (N=130)	Basal-predominant (N=39)	*P*[a]
Gender				0.13
Men	58(48%)	70(54%)	26(67%)	
Women	62(52%)	60(46%)	13(33%)	
Age (median, IQR), years	68(61-73)	66(59-71)	66(58-72)	0.46
Race				0.31
White	102(85%)	95(73%)	32(82%)	
Black	2(2%)	3(2%)	0(0)	
Asian	6(5%)	13(10%)	5(13%)	
Other	10(8%)	19(15%)	2(5%)	
pT stage (n, %)				0.08
T1-T2	98(82%)	95(73%)	24(62%)	
T3-T4	22(18%)	35(27%)	15(38%)	
pN stage (n, %)				0.26
N0	40(33%)	32(25%)	13(33%)	
N1	48(40%)	48(37%)	12(31%)	
N2	32(27%)	50(38%)	14(36%)	
Tumor grade$^{\Delta}$ (n, %)				0.10
Well/Moderately differentiated	76(65%)	74(58%)	16(41%)	
Poorly differentiated / Undifferentiated	41(35%)	53(42%)	23(59%)	
Lymphovascular invasion$^{\Omega}$ (n, %)				0.13
Negative	60(50%)	49(38%)	16(41%)	
Positive	45(38%)	68(52%)	21(54%)	
Resection margin status (n, %)				0.82
R0	62(52%)	63(48%)	18(46%)	
R1	56(46%)	65(50%)	20(51%)	
R2	1(1%)	2(2%)	1(3%)	
Rx (not evaluable)	1(1%)	0(0)	0(0)	

Supplementary Table.T13. Tumor expression subtype and associations with clinicopathological features. Associations between tumor subtype and clinicopathological features were explored using Fisher's exact test (categorical variables) and Wilcoxon rank-sum test (age). [a]*P* value for Fisher's exact test (categorical variables) and Wilcoxon rank-sum test (age). [Δ]6 cases with unknown tumor grade were removed from analysis. [Ω]30 cases with unknown lymphovascular invasion were removed from this analysis.

Supplementary Table.T14. Tumor expression subtype and association with tumor molecular characteristics

[a]Molecular characteristic	Tumor subtype			[b]*P*
	Classical-predominant (N=120) N (%)	Mixed (N=130) N (%)	Basal-predominant (N=39) N (%)	
KRAS				0.09
Wildtype	12 (11%)	5 (4%)	1 (3%)	
Mutant	101 (89%)	121 (96%)	38 (97%)	
CDKN2A				068
Intact	42 (37%)	40 (32%)	13 (33%)	
Loss	71 (63%)	86 (68%)	26 (67%)	
SMAD4				0.95
Intact	55 (49%)	64 (51%)	20 (51%)	
Loss	58 (51%)	62 (49%)	19 (49%)	
P53				0.16
Wildtype	45 (40%)	42 (33%)	9 (23%)	
Altered	68 (60%)	84 (67%)	30 (77%)	
KRAS Copy number				0.003
Gain	9 (8%)	9 (8%)	10 (28%)	
Normal copy	100 (92%)	101 (92%)	25 (72%)	

Supplementary Table.T14. Tumor expression subtype and association with tumor molecular characteristics. Molecular annotation for the primary resection cohort was performed for KRAS, CDKN2A, SMAD4 and TP53, the four main driver genes altered in pancreatic ductal adenocarcinoma. [a]*KRAS* status was determined by next generation sequencing (or pyrosequencing if predefined NGS coverage metrics were not met) and classified as mutant or wild-type. CDKN2A and SMAD4 status was determined by immunohistochemistry and classified as intact or lost. *TP53* status was determined by combining IHC and sequencing data to make an integrated call as wild-type or altered. Immunohistochemistry and sequencing methodologies were described in detail in [5]. [b]*P* value for Fisher's exact test.

Supplementary Table.T15. Comparison of subtype fractions between primary and metastatic PDAC

	Cohort		[a]*P*
	Primary (N=289)	Metastatic (N=37)	
Subtype fraction			**<0.001**
Basal %, median (IQR)	12.9(2.1-45.2)	16.0(2.8-60.9)	<0.001
Classical %, median (IQR)	68.9(27.9-92.1)	57.9(6.2-85.3)	<0.001
Co-expressor %, median (IQR)	5.7(1.2-18.1)	11.3(2.1-26.0)	<0.001
Tumor subtype			**0.0010**
Classical-predominant, N (%)	85 (29%)	7 (19%)	<0.001
Mixed, N (%)	164 (57%)	18 (49%)	<0.001
Basal-predominant, N (%)	40 (14%)	12 (32%)	<0.0001

Supplementary Table.T15. Comparison of subtype fractions between primary and metastatic PDAC. Comparisons were made between primary and metastatic PDAC for subtype fraction and tumor subtype. Significant differences were observed for both. [a]*P* value for Chi^2 test and Post-hoc Chi^2 test.