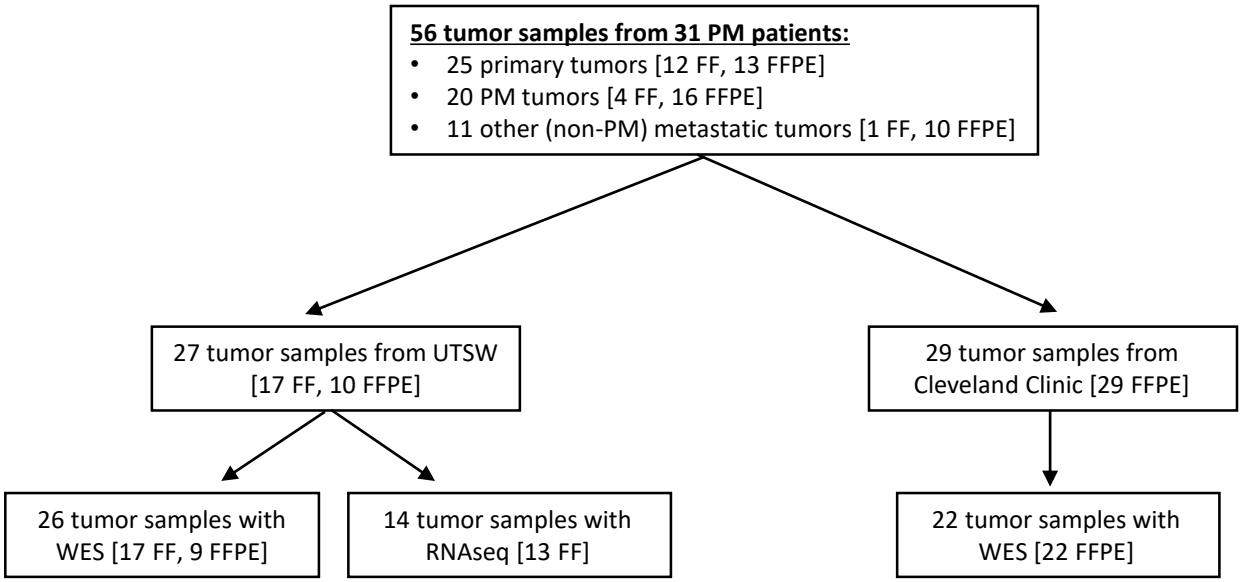
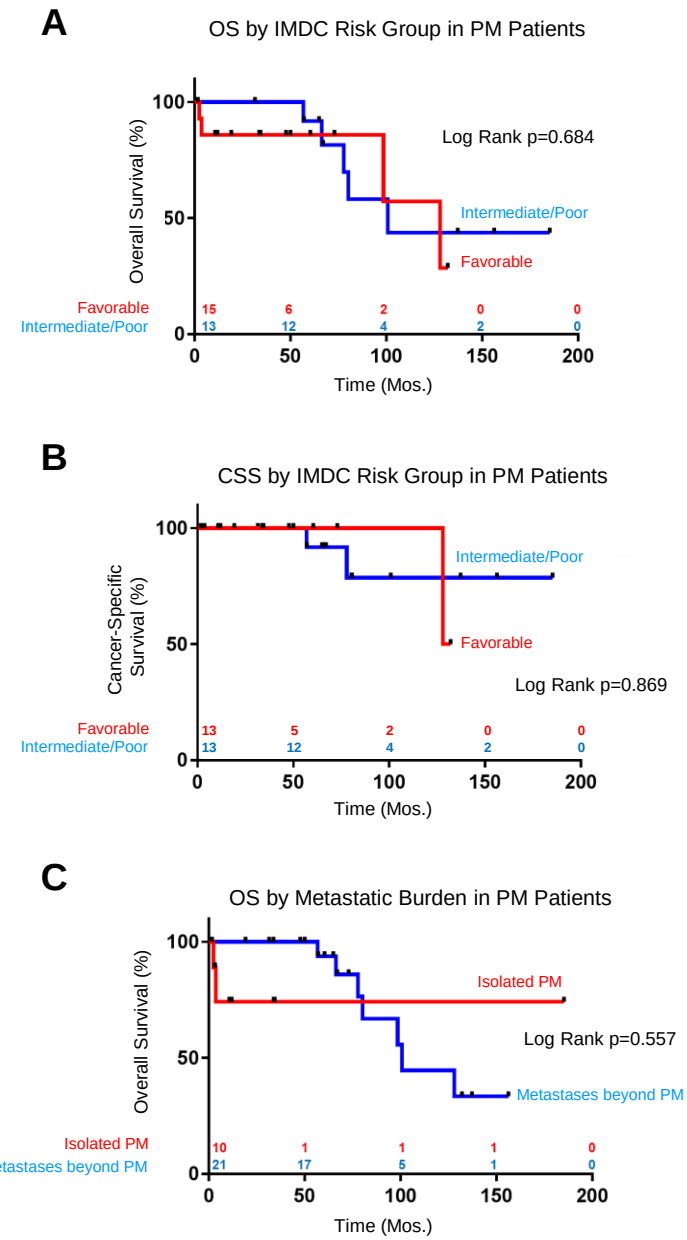
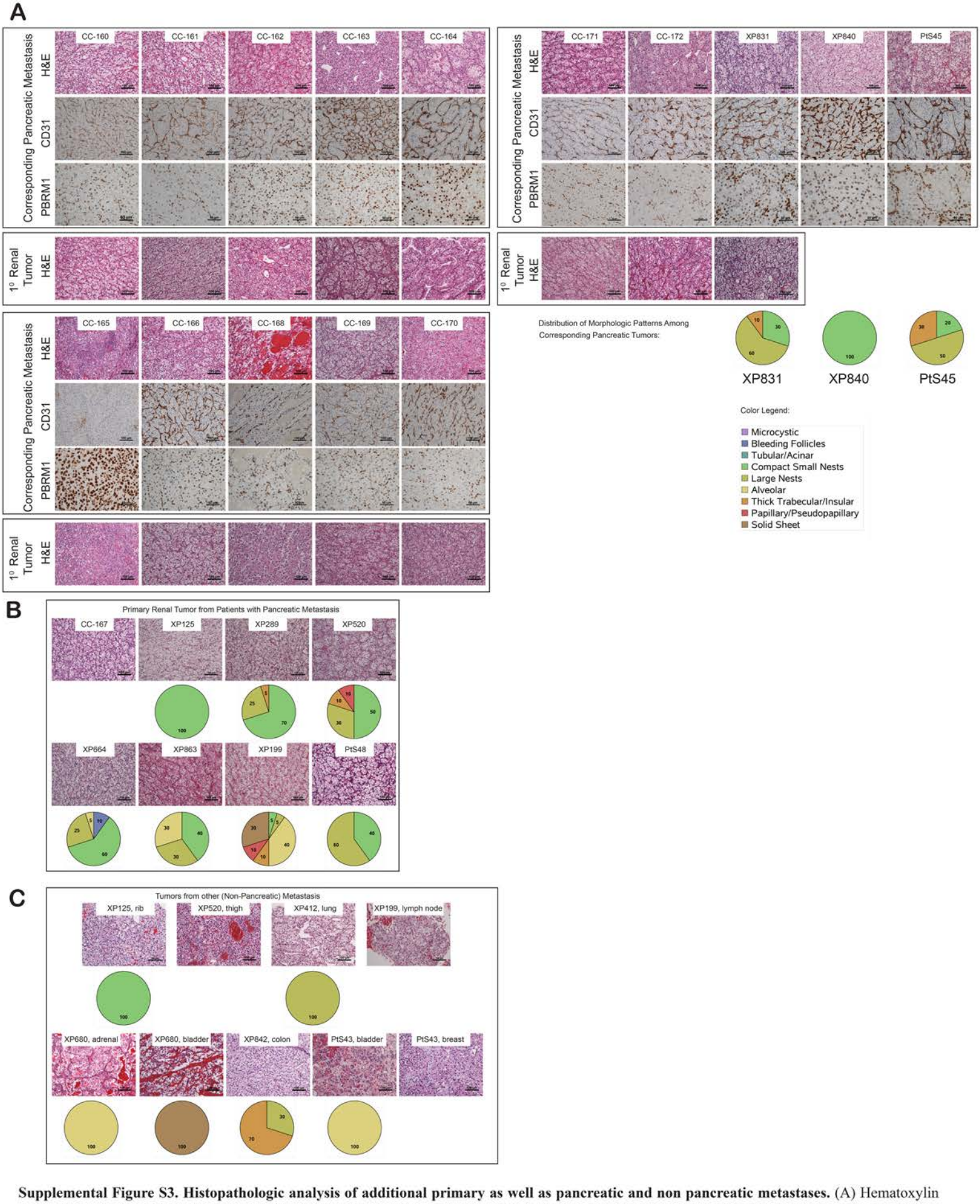


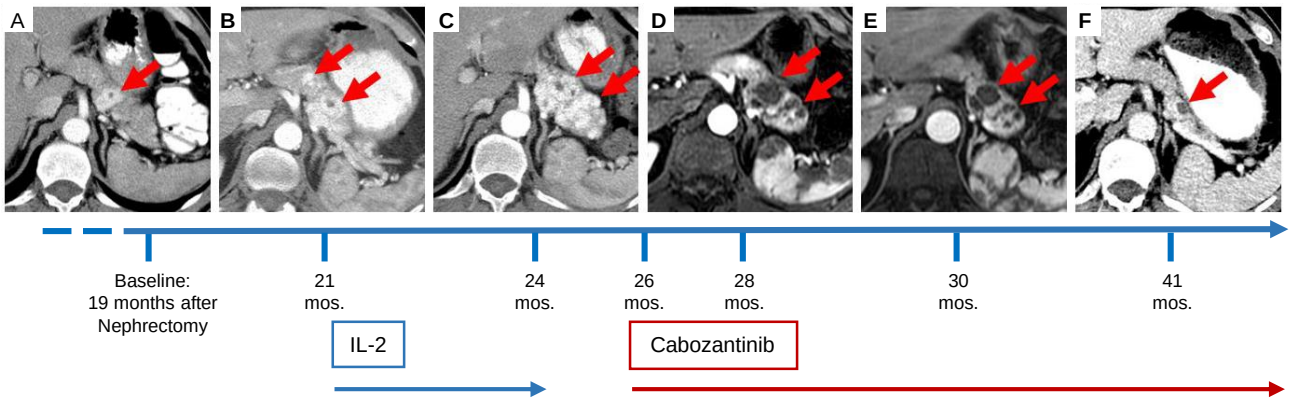
Supplemental Figure S1. Flow diagram of 56 tumor samples from 31 PM patients from UTSW and Cleveland Clinic. FF, fresh frozen. FFPE, formalin-fixed paraffin-embedded.



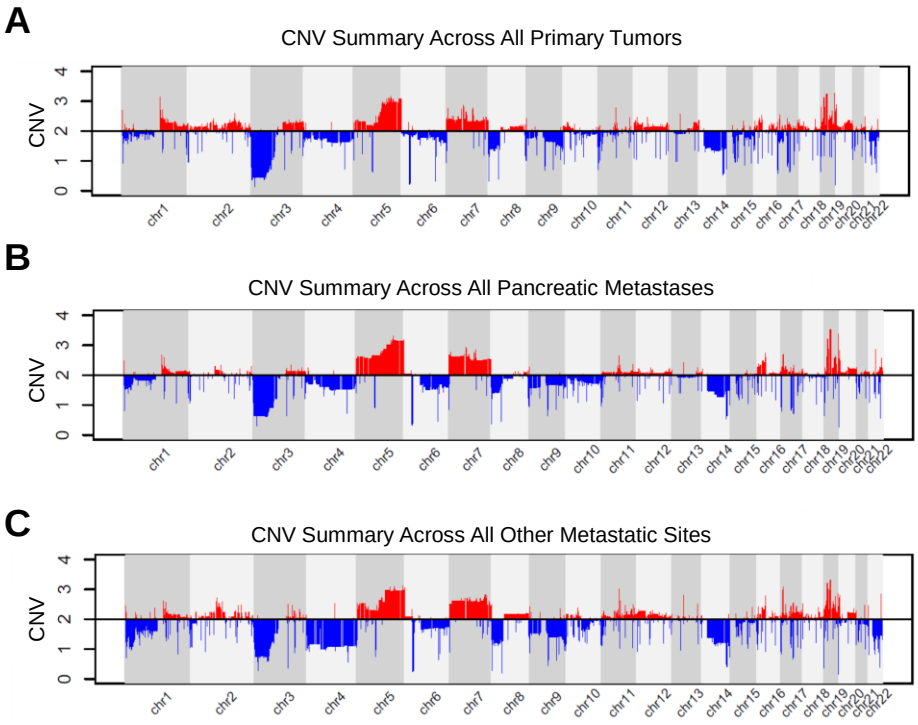
Supplemental Figure S2. IMDC and tumor burden are not prognostic in PM patients. (A) Overall Survival and (B) Cancer-Specific Survival of PM patients by IMDC risk group stratification. (C) Overall Survival analyses of PM patients comparing patients with isolated PM versus those with involvement of additional sites. Time is measured from metastatic diagnosis.



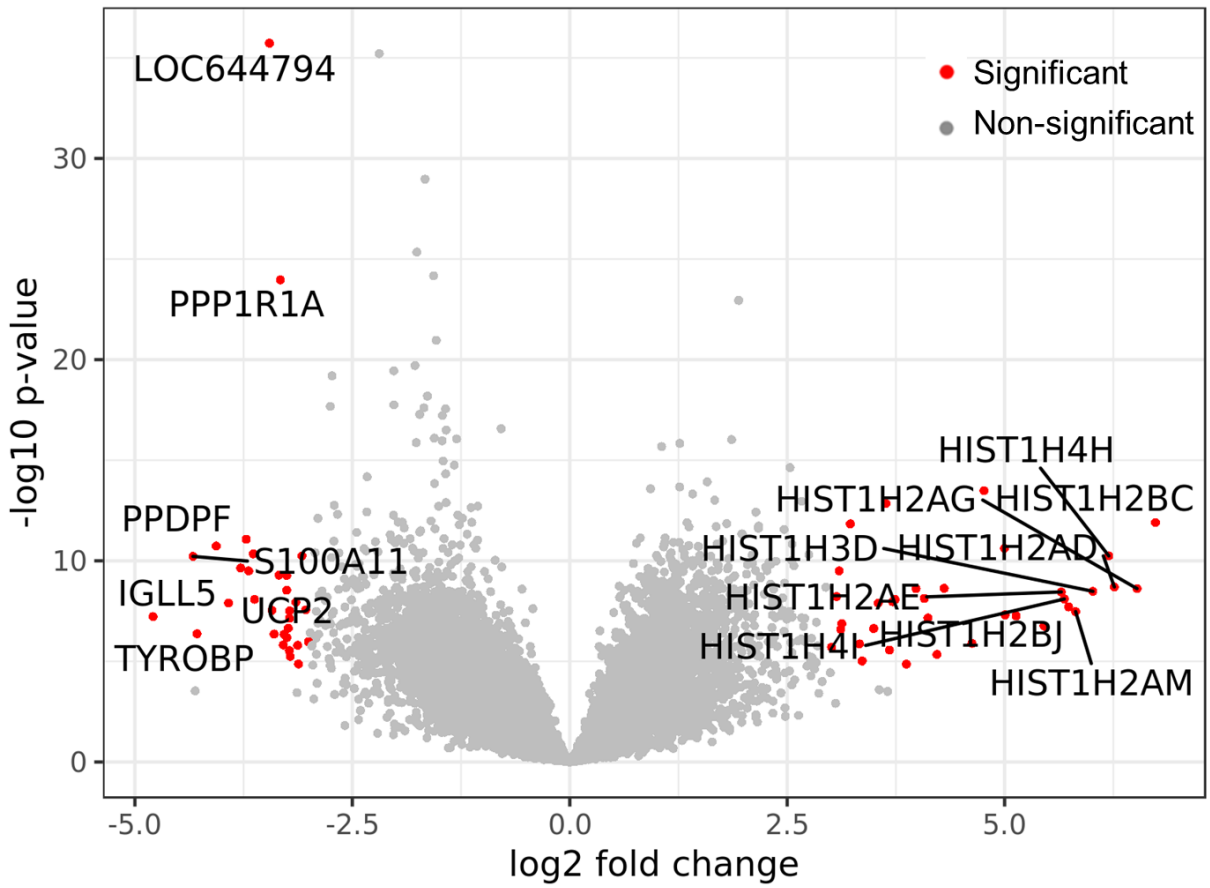
Supplemental Figure S3. Histopathologic analysis of additional primary as well as pancreatic and non pancreatic metastases. (A) Hematoxylin and eosin (H&E) sections, with immunohistochemistry for PBRM1 and CD31 of PM, as well as H&E of corresponding primary tumors with corresponding pie charts illustrating the relative percentage of the different architectures where sufficient sections for analyses were available. (B) H&E sections with corresponding pie charts of additional primary renal tumors of PM patients without available PM samples. (C) H&E sections with corresponding pie charts of non-pancreatic metastatic sites from PM cohort.



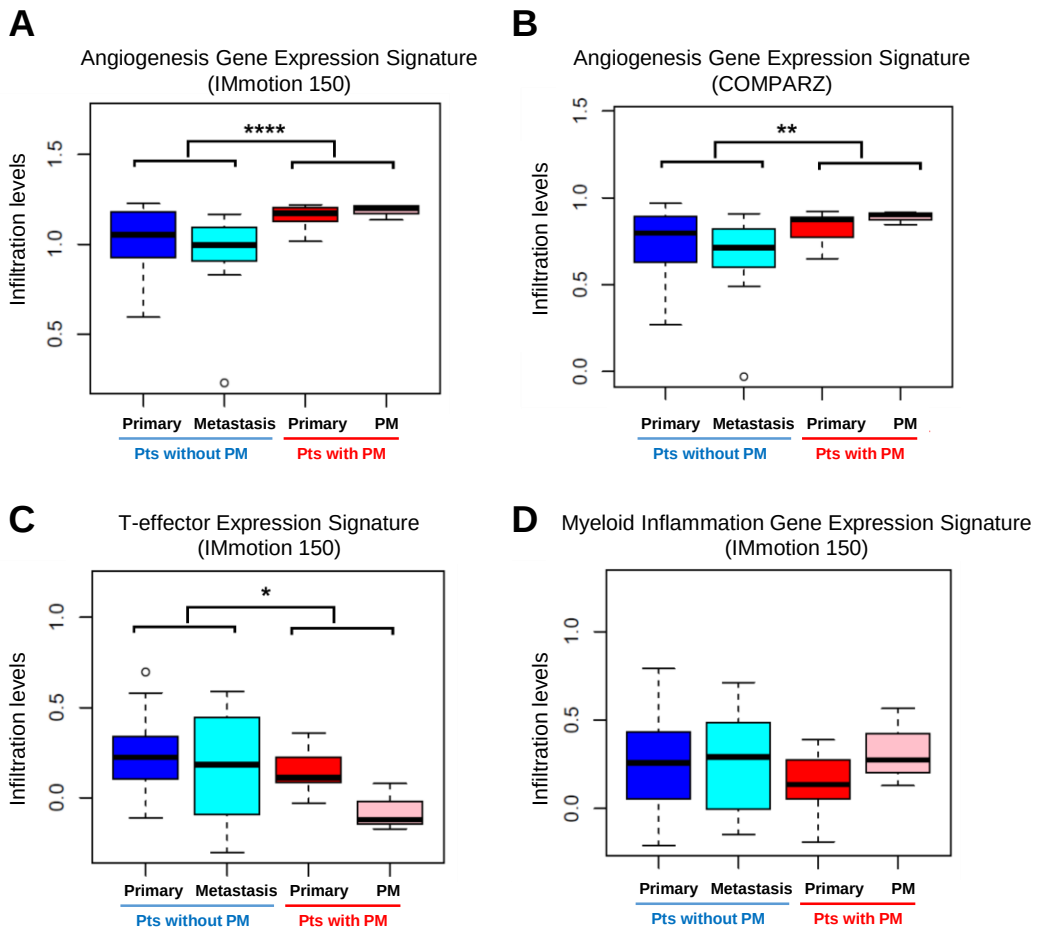
Supplemental Figure S4. Devascularization of pancreatic metastases and tumor growth inhibition with cabozantinib but not IL2. Axial contrast-enhanced CT (A, B, C, F) and MR (D, E) images of the upper abdomen acquired during the arterial phase in a patient with PM. PM that progressed through IL-2 immunotherapy (red arrows in B and C) became progressively devascularized and regressed with cabozantinib, an anti-angiogenic agent (D-F).



Supplemental Figure S5. Pancreatic metastases exhibit a copy number alteration profile most similar to primary tumors. Average copy number alterations according to tumor site, including (A) primary (n=21), (B) pancreatic (n=17), and (C) other (non-pancreatic; n=10) metastatic sites from patients with PM.



Supplemental Figure S6. Volcano plot of differentially expressed genes in primary and metastatic tumors from patients with PM compared to non-PM metastatic ccRCC patients. Log_2 fold-changes in gene expression (PM:non-PM) were calculated, and genes with fold-changes >3 or <-3 with p<0.0001 are shown with red dots.



Supplemental Figure S7. Pancreatic metastasis tumors are characterized by high angiogenesis and low inflammation based on IMmotion and COMPARZ signatures. High angiogenesis and low inflammation in PM tumors according to IMmotion150 and COMPARZ gene signatures. Box-and-whisker plots comparing median relative gene expression levels and interquartile ranges (IQR) of the angiogenesis gene signatures used in the (A) IMmotion150 and (B) COMPARZ trials. Relative gene expression levels of the (C) T-effector and (D) myeloid signatures from the IMmotion150 trial are also shown. Open circles, most extreme data points (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001).

Sample ID	Institution	Tumor Source	Fresh frozen (FF) vs. FFPE	IHC	WES	RNAseq	Consented to release of genomic data
XP96T	UTSW	Kidney	FF	Yes	1620A-MK-312	1620A-MK-340	no
XP125T1	UTSW	Kidney	FF	Yes	1620A-MK-314	1620A-MK-341	no
XP133T1	UTSW	Kidney	FF	Yes	1620A-MK-316	1620A-MK-342	yes
XP133M1	UTSW	Adrenal	FFPE	Yes	1620R_MK801	No	yes
XP133M2	UTSW	Pancreas	FFPE	Yes	1620R_MK802	No	yes
XP199T	UTSW	Kidney	FF	Yes	1620A-MK-318	1620A-MK-343	no
XP203T	UTSW	Kidney	FF	Yes	1620A-MK-320	1620A-MK-344	no
XP203M1	UTSW	Pancreas	FF	Yes	1620A-MK-321	1620A-MK-345	no
XP289T	UTSW	Kidney	FF	Yes	SAM19944213	SAM19944337	no
XP412M2	UTSW	Pancreas	FFPE	Yes	SAM19944218_37475	No	yes
XP412M1	UTSW	Lung	FFPE	Yes	1620A-MK-303	No	yes
XP520T3	UTSW	Kidney	FF	Yes	1620A-MK-323	1620A-MK-346	yes
XP664T2	UTSW	Kidney	FF	Yes	1620A-MK-325	1620A-MK-347	yes
XP664M	UTSW	Pancreas	FFPE	Yes	No	No	yes
XP680M	UTSW	Lung	FFPE	Yes	1620A-MK-328	No	no
XP680M2	UTSW	Bladder	FFPE	Yes	1620A-MK-329	No	no
XP680M1	UTSW	Adrenal	FFPE	Yes	1620A-MK-327	No	no
XP831M	UTSW	Pancreas	FF	Yes	1620A-MK-331	1620A-MK-349	yes
XP840M	UTSW	Pancreas	FF	Yes	1620A-MK-333	1620A-MK-351	yes
XP842M	UTSW	Colon	FF	Yes	1620A-MK-335	1620A-MK-352	yes
XP863T	UTSW	Kidney	FF	Yes	1620A-MK-337	1620A-MK-353	yes
PtS43M	UTSW	Bladder	FFPE	Yes	1620A-MK-339	No	no
PtS45M	UTSW	Pancreas	FFPE	Yes	1620R-MK804	No	no
PtS47M1	UTSW	Pancreas	FF	Yes	1620R-MK810	No	no
PtS47T	UTSW	Kidney	FF	Yes	1620D-MK808	No	no
PtS47Th	UTSW	Thrombus	FF	Yes	1620D-MK809	No	no
PtS48T	UTSW	Kidney	FF	Yes	1620D-MK812	No	no
CC-UT-160M1	CC	Pancreas	FFPE	Yes	CC-UT-160C_AACTCACC_BCC8T8ANXX_L007_001	No	no
CC-UT-160T	CC	Kidney	FFPE	Yes	No	No	no
CC-UT-161M1	CC	Lymph node	FFPE	No	CC-UT-181C_GCCAAGAC-_ACCL7KANXX_L004_001	No	no
CC-UT-161M	CC	Pancreas	FFPE	Yes	CC-UT-161C_GCTAACGA_BCC8T8ANXX_L008_001	No	no
CC-UT-161T	CC	Kidney	FFPE	Yes	CC-UT-161A_ATCATTCC_BCC8T8ANXX_L003_001	No	no
CC-UT-162T	CC	Kidney	FFPE	Yes	No	No	no
CC-UT-162M	CC	Pancreas	FFPE	Yes	No	No	no
CC-UT-163T	CC	Kidney	FFPE	Yes	No	No	no
CC-UT-163M	CC	Pancreas	FFPE	Yes	No	No	no
CC-UT-163M1	CC	Adrenal	FFPE	No	No	No	no
CC-UT-164T	CC	Kidney	FFPE	Yes	No	No	no
CC-UT-164M1	CC	Pancreas	FFPE	Yes	CC-UT-164C_CTGTAGCC_BCC8T8ANXX_L001_001	No	no
CC-UT-165M1	CC	Lymph node	FFPE	No	CC-UT-183C_GACTAGTA-_ACCL7KANXX_L004_001	No	no
CC-UT-165M	CC	Pancreas	FFPE	Yes	CC-UT-165C_GCTCGGTA_BCC8T8ANXX_L004_001	No	no
CC-UT-165T	CC	Kidney	FFPE	Yes	CC-UT-165A_GCCACATA_BCC8T8ANXX_L006_001	No	no
CC-UT-166M	CC	Pancreas	FFPE	Yes	CC-UT-166C_ACACGACC_BCC8T8ANXX_L005_001	No	no
CC-UT-166T	CC	Kidney	FFPE	Yes	CC-UT-166A_ACCACTGT_BCC8T8ANXX_L005_001	No	no
CC-UT-167T	CC	Kidney	FFPE	Yes	CC-UT-167A_CTGGCATA_BCC8T8ANXX_L001_001	No	no
CC-UT-168T	CC	Kidney	FFPE	Yes	CC-UT-168A_ACCTCCAA_BCC8T8ANXX_L002_001	No	no
CC-UT-168M	CC	Pancreas	FFPE	Yes	CC-UT-168C_AGTCACTA_BCC8T8ANXX_L005_001	No	no
CC-UT-169T	CC	Kidney	FFPE	Yes	CC-UT-169A_GCGAGTAA_BCC8T8ANXX_L004_001	No	no
CC-UT-169M	CC	Pancreas	FFPE	Yes	CC-UT-169C_AACGCTTA_BCC8T8ANXX_L004_001	No	no
CC-UT-170M1	CC	Pancreas	FFPE	Yes	CC-UT-170C_GGAGAACA_BCC8T8ANXX_L007_001	No	no
CC-UT-170T	CC	Kidney	FFPE	Yes	CC-UT-170A_CACTTCGA-_ACCL7KANXX_L001_001	No	no
CC-UT-171M1	CC	Adrenal	FFPE	No	CC-UT-182C_CGCTGATC_BCC8T8ANXX_L007_001	No	no
CC-UT-171M	CC	Pancreas	FFPE	Yes	CC-UT-171C_CATCAAGT_BCC8T8ANXX_L007_001	No	no
CC-UT-171T	CC	Kidney	FFPE	Yes	CC-UT-171A_ACTATGCA_BCC8T8ANXX_L006_001	No	no
CC-UT-172T	CC	Kidney	FFPE	Yes	CC-UT-172A_CGGATTGC_BCC8T8ANXX_L003_001	No	no
CC-UT-172M1	CC	Pancreas	FFPE	Yes	CC-UT-172C_AAGGTACA_BCC8T8ANXX_L007_001	No	no

Supplemental Table S1. List of samples analyzed.

Variable	PM patients	Historic control*
OS	31	268
PFS (frontline angiogenic inhibitor)	12	177
PFS (mTOR inhibitor)	6	117
PFS (nivolumab)	9	66
PBRM1 IHC**	30	105
BAP1 IHC**	30	117

**Historic control consists of patients with metastatic ccRCC without PM treated at UTSW*
***Includes only patients with interpretable and unequivocal IHC without heterogeneity between matched sites, where available*

Supplemental Table S2. Patients used in clinical analyses, including overall survival (OS), progression-free survival (PFS), and IHC comparisons for PBRM1 and BAP1.

	CNV	Patients (%)	Total Samples (%)	Primary Tumors (%)	PM (%)	Other Metastatic Site (%)
	Total	29	48	21	17	10
Most common CNVs	**3p losses**	27 (93%)	43 (90%)	19 (90%)	15 (88%)	9 (90%)
	5q gains	21 (72%)	31 (65%)	12 (57%)	13 (76%)	6 (60%)
	7 gains	12 (41%)	18 (38%)	4 (19%)	9 (53%)	5 (50%)
CNVs associated with aggressive phenotype	**9p losses**	10 (34%)	13 (27%)	3 (14%)	5 (29%)	5 (50%)
	14q losses	15 (52%)	23 (48%)	9 (43%)	8 (47%)	6 (60%)
	4q losses	11 (38%)	18 (38%)	6 (29%)	6 (35%)	6 (60%)
	8q gains	8 (28%)	9 (19%)	4 (19%)	3 (18%)	2 (20%)

Supplemental Table S3A. Frequencies of CNVs for the most common alterations in patients with PM and for those associated with more aggressive phenotypes in ccRCC (22,31,33,34-36). Presented both on a per-patient level and per-sample level with sample origin.

CNV: Per-patient analyses	**Primary Tumor Samples**		**Metastatic-Only Cohort[22]**		
	TRACERx Renal cohort (n=101)[33]	**Sato et al. cohort (n=240)[32]**	**TRACERx Renal: "TRACERx cohort" (n=38)[22]**	**TRACERx Renal: "HUC cohort" (n=26)[22]**	**TRACERx Renal: "MSK cohort" (n=34)[22]**
3p losses	96%	94%	97%	96%	97%
5q gains	73%	65%	74%	77%	65%
7 gains	56%	41%	76%	69%	71%
9p losses	59%	25%	87%	85%	82%
14q losses	65%	27%	76%	81%	88%
4q losses	40%	-	53%	54%	56%
8q gains	37%	-	47%	46%	44%

Supplemental Table S3B. Frequencies of selected CNVs in ccRCC patients from published cohorts, including analyses on primary tumor samples (32,33) and across matched samples in purely metastatic cohorts (22). Analyses were conducted on a per-patient level.