Supplementary Table S1: Patient outcomes by tumor type across all cohorts

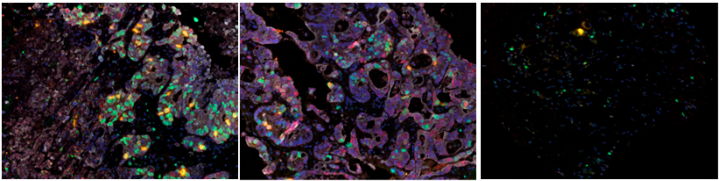| Tumor Type	Number of Patients	Median Weeks on Treatment (Range)	Best response by RECIST Number (Percent)				Reason for Study Discontinuation Number (Percent)				
			Partial Response	Stable Disease	Progressive Disease	Not Evaluable	Progression	Clinical Progression	Toxicity	Unrelated Medical Comorbidities	Patient Choice
Pancreatic Adenocarcinoma	14	9.2 (4-47)	0/14 (0%)	5/14 (36%)	3/14 (21%)	6/14 (43%)	7/14 (50%)	3/14 (21%)	2/14 (14%)	1/14 (7%)	1/14 (7%)
Breast Adenocarcinoma ER+/HER2-	7	8.9 (2-14.9)	1/7 (14%)	3/7 (43%)	2/7 (29%)	1/7 (14%)	3/7 (43%)	1/7 (14%)	3/7 (43%)	0/7 (0%)	0/7 (0%)
Breast Adenocarcinoma TNBC	2	5.3 (3.6-7)	0/2 (0%)	0/2 (0%)	1/2 (50%)	1/2 (50%)	1/2 (50%)	1/2 (50%)	0/2 (0%)	0/2 (0%)	0/2 (0%)
Colorectal Adenocarcinoma	4	9.4 (4.9-12.7)	0/4 (0%)	0/4 (0%)	4/4 (100%)	0/4 (0%)	4/4 (100%)	0/4 (0%)	0/4 (0%)	0/4 (0%)	0/4 (0%)
Ovarian Serous Carcinoma	2	12.1 (11.1-13)	0/2 (0%)	2/2 (100%)	0/2 (0%)	0/2 (0%)	2/2 (100%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)
Renal Cell Carcinoma	1	1.1 (N/A)	0/1 (0%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
Uterine Serous Carcinoma	1	10 (N/A)	0/1 (0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)

Supplementary Table S2: Treatment-related adverse events attributed to one or both drugs occurring in at least 10% of patients across treatment groups

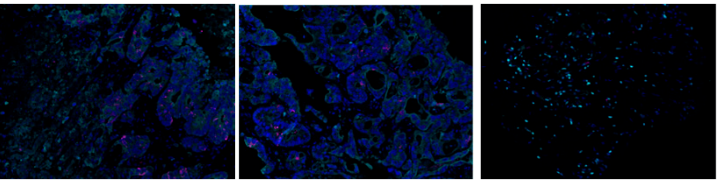| Number (percent)	Alisertib Lead-In N=10 Patients A-1 through A-10		Sapanisertib Lead-In N=10 Patients S-1 through S-10		Pancreatic Cancer Expansion N=11 Patients P-1 through P-11		All Treatment Groups N=31		
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Total
Fatigue	2	1	4	0	6	0	12 (39%)	1 (3%)	13 (42%)
Mucositis	3	2	2	0	1	1	6 (19%)	3 (10%)	9 (29%)
Hyperglycemia	2	1	2	0	3	0	7 (23%)	1 (3%)	8 (26%)
Nausea	2	0	1	0	4	0	7 (23%)	0	7 (23%)
Neutropenia	0	1	1	0	0	3	1 (3%)	4 (13%)	5 (16%)
Thrombocytopenia	2	0	1	0	1	1	4 (13%)	1 (3%)	5 (16%)
Diarrhea	1	0	1	0	2	0	4 (13%)	0	4 (13%)
Cognitive disturbance	0	0	1	0	2	0	3 (10%)	0	3 (10%)
Vomiting	1	0	0	0	2	0	3 (10%)	0	3 (10%)
Anorexia	1	0	0	0	2	0	3 (10%)	0	3 (10%)
Alopecia	3	0	0	0	0	0	3 (10%)	0	3 (10%)

Supplementary Figure S1
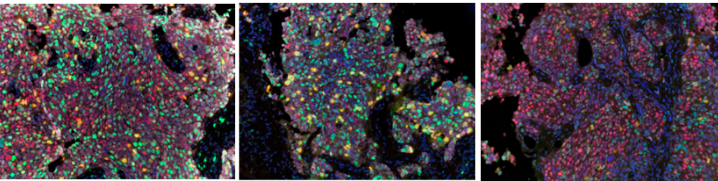
Patient A-4

Baseline C1D7 C2D7

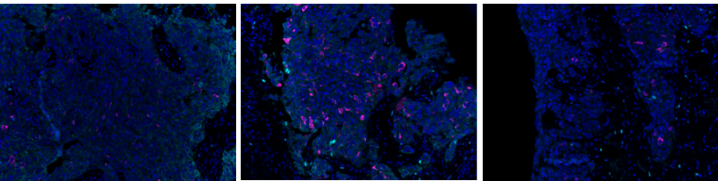CK=White, pHH3=Yellow, Ki67=Green, p53=Red

Cyclin B1= Magenta, p21=Cyan
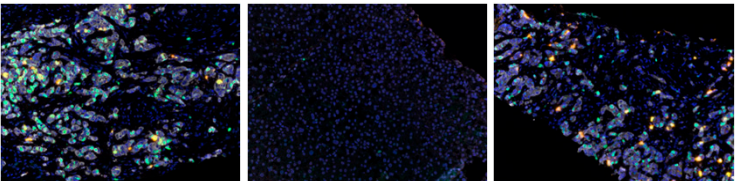
Patient A-9

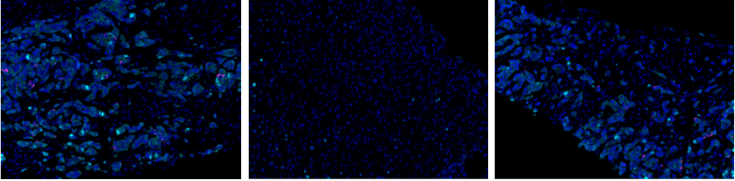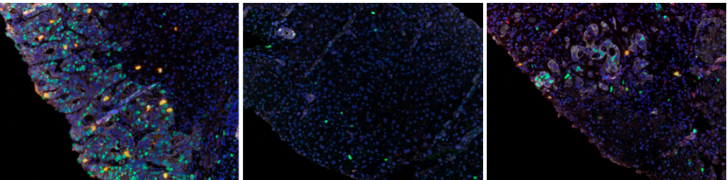Baseline C1D7 C2D7

CK=White, pHH3=Yellow, Ki67=Green, p53=Red

Cyclin B1= Magenta, p21=Cyan

Patient A-2

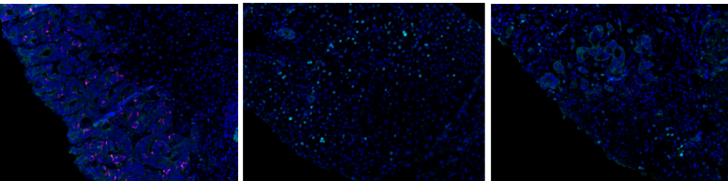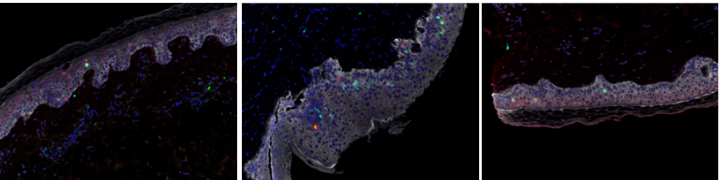Baseline C1D7 C2D7

CK=White, pHH3=Yellow, Ki67=Green, p53=Red

Cyclin B1= Magenta, p21=Cyan

Patient S-2

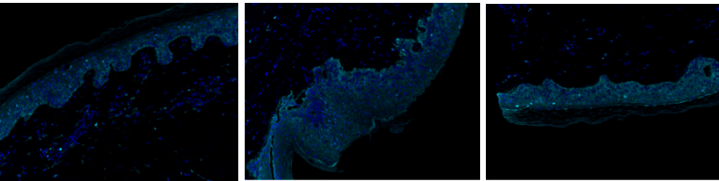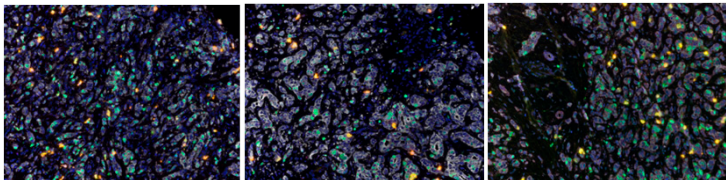Baseline C1D7 C2D7

CK=White, pHH3=Yellow, Ki67=Green, p53=Red

Cyclin B1= Magenta, p21=Cyan

Patient S-5

Baseline C1D7 C2D7

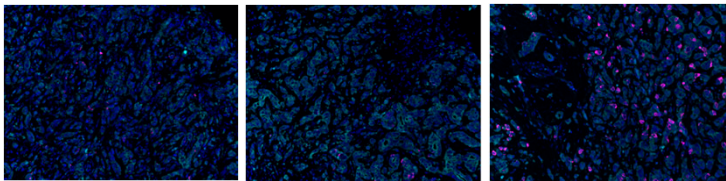CK=White, pHH3=Yellow, Ki67=Green, p53=Red

Cyclin B1= Magenta, p21=Cyan

Patient S-4

Baseline C1D7 C2D7

CK=White, pHH3=Yellow, Ki67=Green, p53=Red

Cyclin B1= Magenta, p21=Cyan

Supplementary Figure S2