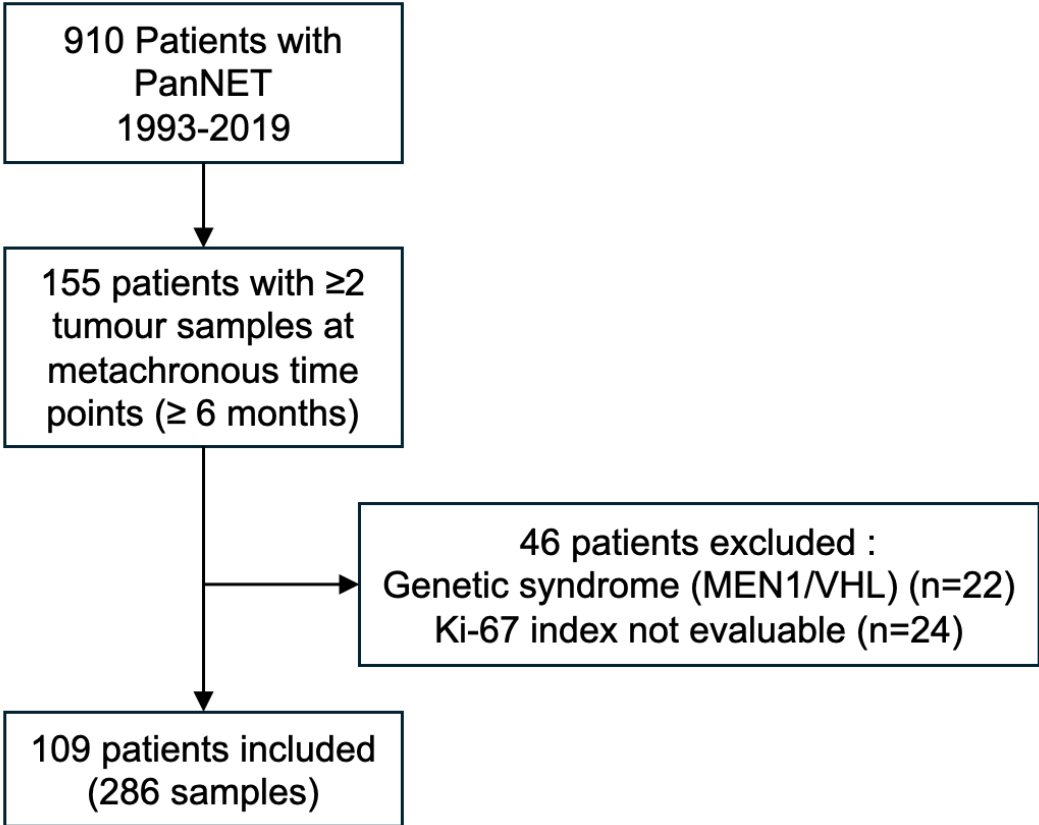


Temporal increase in Ki-67 index in patients with pancreatic neuroendocrine tumours

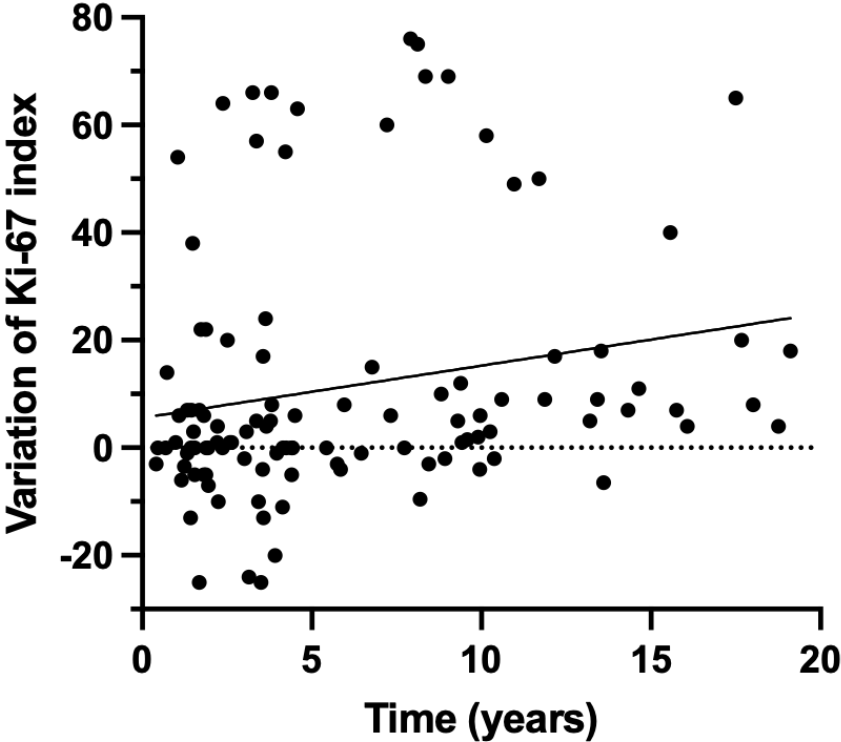
Pauline Bourdeleau¹, Johanna Pokossy-Epée^{1,2}, Olivia Hentic¹, Matthieu Tihy³, Zaima Afzal-Awan², Anne Couvelard^{2,3}, Maxime Ronot^{2,4}, Vinciane Rebours^{1,2}, Philippe Ruszniewski^{1,2}, Jérôme Cros^{2,5}, Louis de Mestier^{1,2}

Supplementary material

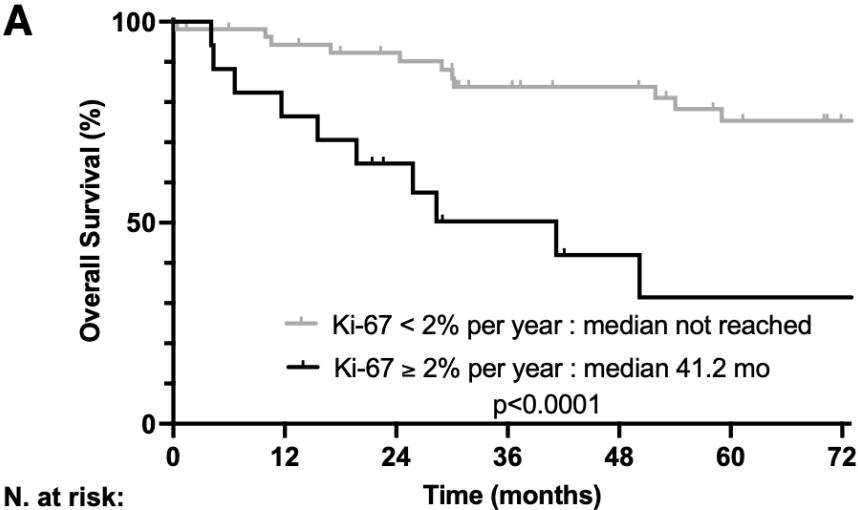
Suppl. Figure 1. Flowchart of the study



Suppl. Figure 2. Variation of Ki-67 index depending on the time elapsed between the initial (S0) and last (Smax) samples.

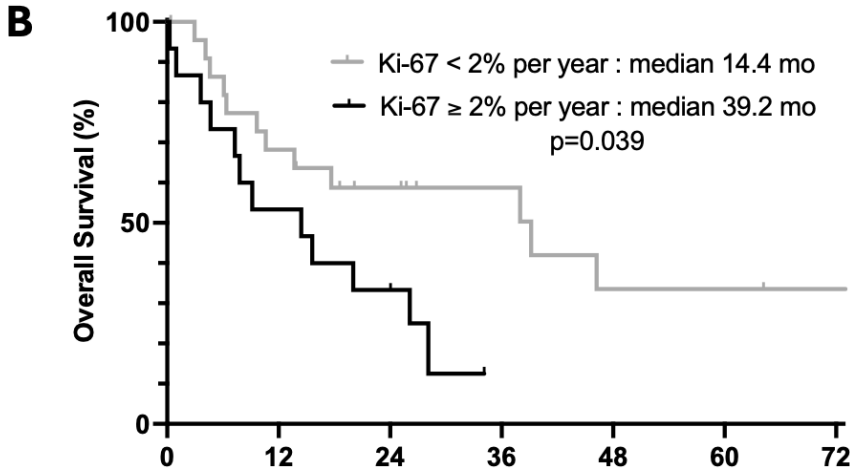


Suppl. Figure 3. Overall Survival depending on the variation of Ki-67 over time depending on the context of the last sample (Smax). A. Patients for whom Smax was a surgical specimen. B. Patients for whom Smax was a metastasis biopsy for clinical progression



N. at risk:

	0	12	24	36	48	60	72
<2%/year:	54	48	44	35	32	26	22
≥2%/year:	17	13	9	6	4	3	3



N. at risk:

	0	12	24	36	48	60	72
<2%/year:	23	16	10	7	4	4	3
≥2%/year:	15	8	5	0	0	0	0

Suppl. Table S1. Univariable Cox proportional hazard analyses of factors associated with the risk of death.

	n	HR	95% CI	p-value
Age (each + 1 year)	109	1.02	0.99 – 1.04	0.21
Female sex	109	0.56	0.31 – 0.99	0.051
Hormonal syndrome	109	0.54	0.27 – 1.01	0.067
Obtention of Smax on a biopsy	109	4.67	2.55 – 8.64	<0.001
Worsening of PS between S0 and Smax	107	6.18	3.32 – 11.39	<0.001
Metastatic sites > 2 at Smax	109	4.57	2.36 – 8.49	<0.001
Liver involvement > 25% at Smax	98	4.34	2.33 – 8.36	<0.001
Treatment with SST analogues	104	1.48	0.81 – 2.73	0.20
Treatment with alkylating chemotherapy	108	2.08	1.14 – 4.02	0.022
Liver-directed treatment	109	2.38	1.30 – 4.31	0.004
Ki-67 index on Smax (q)	109	1.03	1.02 – 1.04	<0.001
Variation of Ki-67 (each +1%)	109	1.03	1.02 – 1.04	<0.001
Variation of Ki-67 > +7%	109	3.86	2.17 – 6.96	<0.001
Variation of Ki-67/year (each +1%/year)	109	1.08	1.04 – 1.11	<0.001
Variation of Ki-67 ≥ 2%/an	109	3.62	2.02 – 6.50	<0.001
Grade on Smax	109			
Grade 1		1		
Grade 2		2.65	1.12 – 7.35	0.039
Grade 3		7.83	3.16 – 22.67	<0.001
Increase in tumour grade	109	2.15	1.22 – 3.79	0.008
ATRX/DAXX lost on Smax	76	0.96	0.49 – 1.94	0.92
MEN1 lost on Smax	42	0.73	0.22 – 2.78	0.61
PDX1/ARX signature on Smax	56			
Beta-like (PDX1+/ARX-)		1		
Alpha-like (PDX1-/ARX+)		0.67	0.21 – 2.17	0.49
No alpha-like, no beta-like		0.49	0.16 – 1.51	0.20

Suppl. Table S2. Occurrence of Ki-67 increase \geq 2%/year stratified by previous therapies performed

	Ki-67 increase \geq 2%/year	p-value
Pretreated	29/90 (32.2%)	0.18
Not pretreated	3/19 (15.8%)	
Pretreated by SSAs	16/53 (30.2%)	0.85
Not pretreated by SSAs	16/56 (28.6%)	
Pretreated by alkylating agents	24/62 (38.7%)	0.01
Not pretreated by alkylating agents	8/47 (17%)	
Pretreated by other chemotherapy	3/14 (21.4%)	0.75
Not pretreated by other chemotherapy	29/95 (30.5%)	
Pretreated by oral targeted therapy	7/19 (36.8%)	0.79
Not pretreated by oral targeted therapy	25/90 (27.8%)	
Pretreated by PRRT	2/8 (25%)	0.99
Not pretreated by PRRT	30/101 (29.7%)	
Pretreated by liver-directed therapy	9/34 (26.5%)	0.66
Not pretreated by liver-directed therapy	23/75 (30.7%)	

Suppl. Table S3. Univariable logistic regression analyses of factors associated with Ki-67 increase \geq 2%/year between S0 and Smax

	n	OR	95% CI	p-value
Age (each additional 1 year)	109	1.01	0.97 – 1.05	0.69
Female sex	109	0.70	0.30 – 1.61	0.83
Hormonal syndrome	109	1.23	0.50 – 2.93	0.46
Obtention of Smax on a biopsy	109	2.21	0.94 – 5.21	0.069
Worsening of PS between S0 and Smax	107	2.46	0.92 – 6.48	0.067
Delta Metastatic sites > 1	109	1.27	0.46 – 3.30	0.63
Metastatic stage at S0	109	3.09	1.14 – 9.90	0.037
Liver involvement > 25% at S0	96	2.02	0.79 – 5.13	0.137
Increase in liver involvement	96	2.44	1.00 – 6.12	0.051
Treatment with SST analogues	104	1.14	0.49 – 2.70	0.76
Tumour control with SST analogues	104	0.42	0.15-1.07	0.079
Treatment with alkylating chemotherapy	108	3.52	1.41 – 9.72	0.0097
Liver-directed treatment	107	0.83	0.32 – 2.04	0.70
Treatments received \geq 2	109	1.77	0.76 – 4.27	0.193
Ki-67 index on S0 (each additional 1%)	109	0.99	0.94 – 1.05	0.82
Grade on S0	109			
Grade 1		1		
Grade 2		1.41	0.54 – 4.00	0.49
Grade 3		0.86	0.11 – 4.65	0.87
ATRX/DAXX lost on S0	61	0.68	0.22 – 2.09	0.49
ATRX/DAXX lost on Smax	76	0.56	0.20 – 1.57	0.26
MEN1 lost on S0	42	0.22	0.04 – 0.99	0.057
MEN1 lost on Smax	42	0.47	0.10 – 2.26	0.33
PDX1/ARX signature on S0	55			
Beta-like (PDX1+/ARX-)		1		
Alpha-like (PDX1-/ARX+)		2.12	0.42 – 16.04	0.40
No alpha-like, no beta-like		2.08	0.37 – 16.44	0.43
PDX1/ARX signature on Smax	55			
Beta-like (PDX1+/ARX-)		1		
Alpha-like (PDX1-/ARX+)		0.91	0.17 – 4.81	0.91
No alpha-like, no beta-like		1.11	0.27 – 5.02	0.89