



Hospices Civils de Lyon
Lyon University Hospital

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TEN HOT TOPICS TO SOLVE IN LUNG NET

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Hospices Civils de Lyon

INSTITUT DE
CANCÉROLOGIE



Conflicts of interest

- Novartis, IPSEN, Keocyt, Amgen, Abvie, Roche



1. Atypical carcinoid but G3

Table 1 WHO classifications of neuroendocrine neoplasms of bronchopulmonary (BP) and gastroenteropancreatic (GEP) neuroendocrine neoplasms (BP-NEN WHO 2015 and GEP-NEN WHO 2019).

Differentiation	BP-NEN				GEP-NEN		
	Terminology	Mitoses per 2 mm ²	Necrosis	Ki67 index ^a	Terminology	Mitoses per 2 mm ²	Ki67 index
Well-differentiated	TC	0–1	No	up to 5%	NET G1	<2	<3%
	AC	2–10	Focal, if any	up to 20%	NET G2	2–20	3–20%
					NET G3	>20	>20%
Poorly differentiated	LCNEC	>10	Yes	40–80%	Large cell type (LCNEC)	>20	>20%
	SCLC	>10	Yes	50–100%	Small cell type (SCNEC)	>20	>20%
Mixed NE and non-NE neoplasms	Combined SCLC / LCNEC ^b				MiNEN ^c		

■ Interest of Ki67 index in lung NET

■ Terminology^(a)

Lung or BP-NET G1-G3 more adapted than TC/AC ?

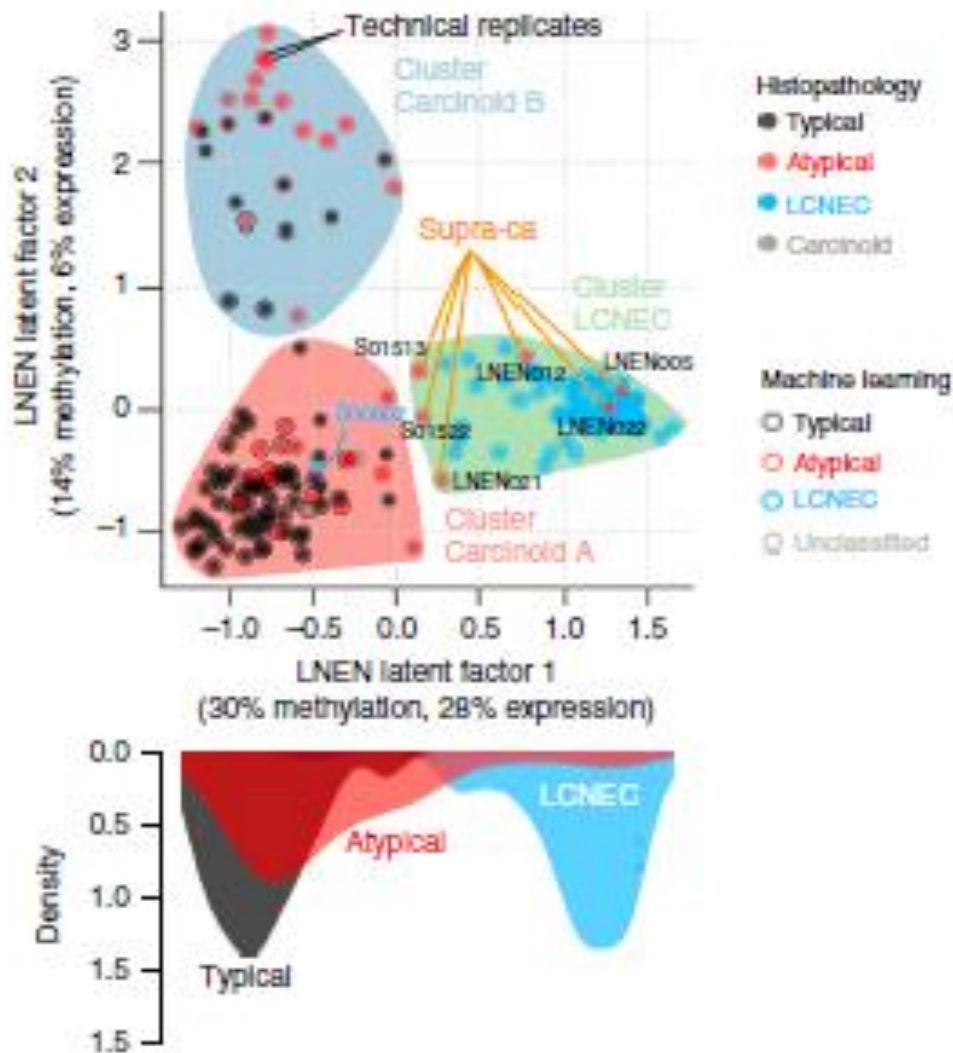
■ There is a black box: 4%^(b), but until 27% at stage IV^(c)

(a) Kasajima A and Kloppel G, ERC 2020; (b) Kasajima, NEN 2019 and Oka NEN 2020;

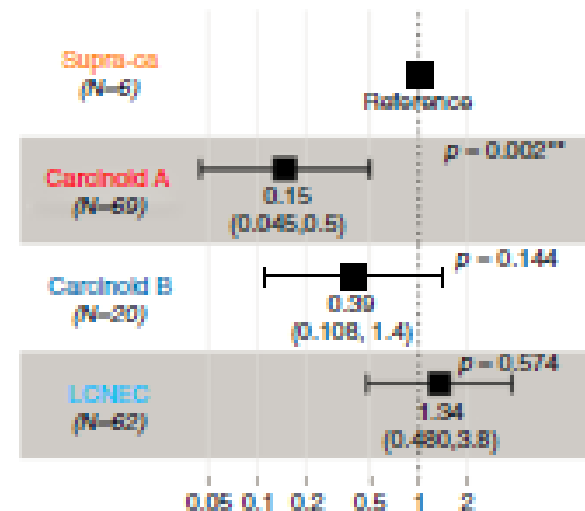
(c) Rekhtman, Modern Pathol 2019



1. Atypical carcinoid but G3



- Help of molecular classification?
- Transcriptome and methylome analyses
- Supra-carcinoid ?



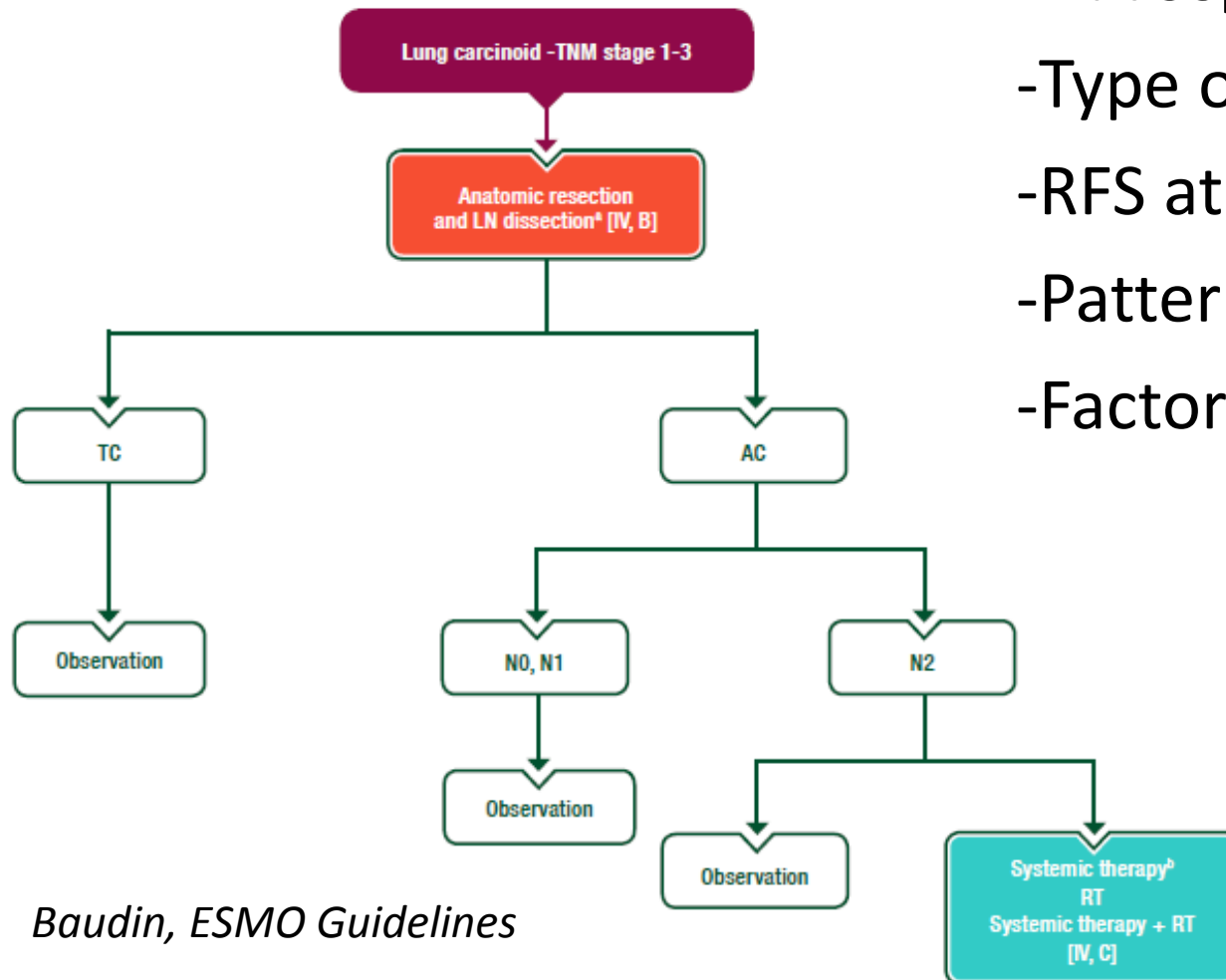
Overall survival

Alcala, Nat Comm 2019

2. Atypical carcinoid N2

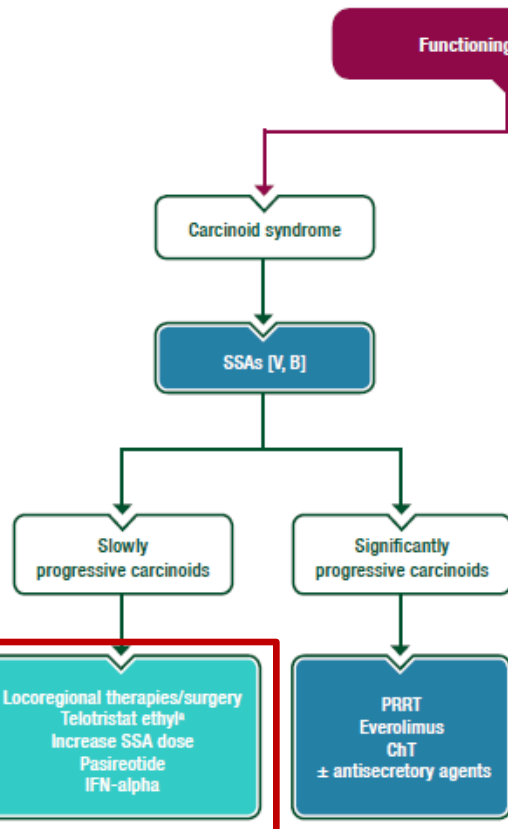
- Adjuvant treatment ?
- Prospective study:
 - Type of surgeries
 - RFS at 5, 10, 15, 20 years
 - Pattern of recurrence (RT?)
 - Factors associated with RFS

- Help of
 - Molecular tissue analysis?
 - NETtest and cfDNA?



Baudin, ESMO Guidelines

3. Secretory syndromes



Total population, n=162
metastatic lung NET

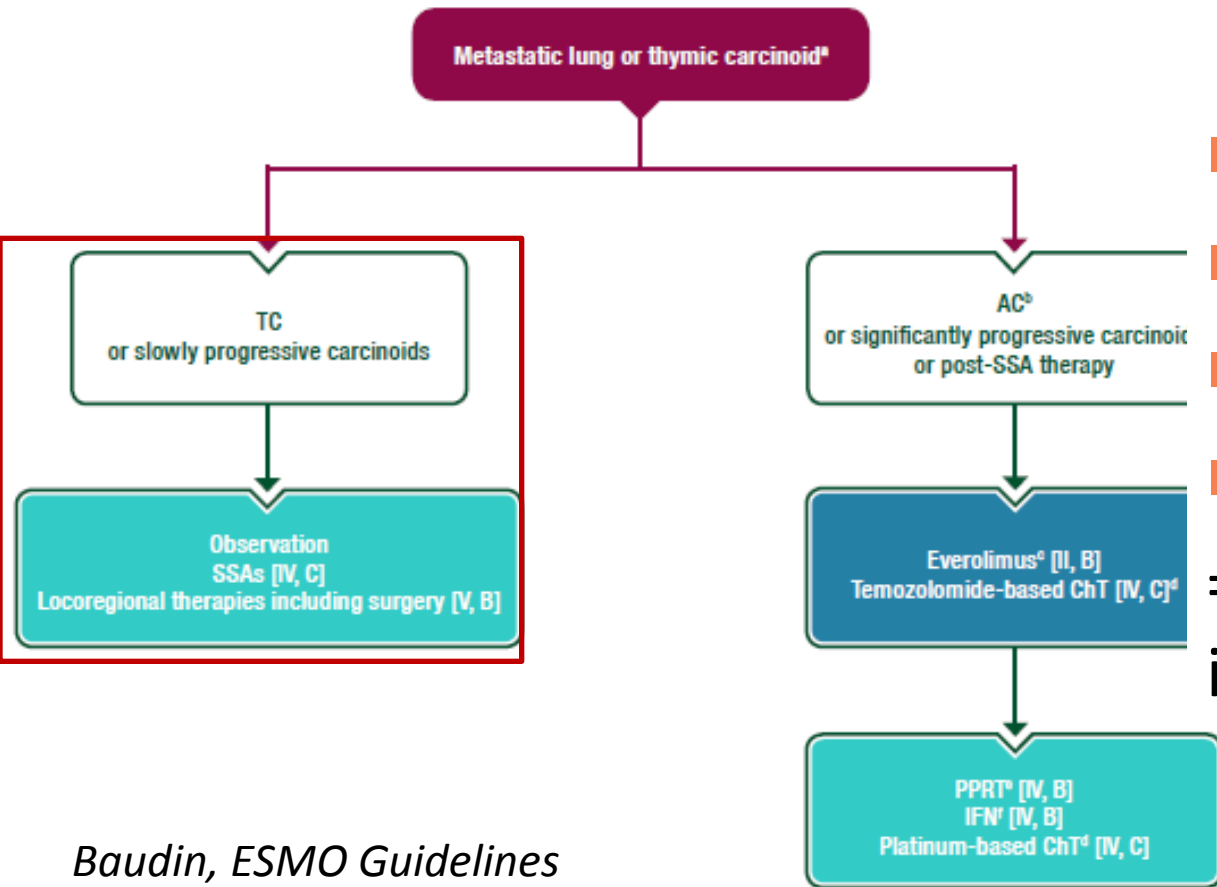
Functioning tumors, n (%)

Nonfunctioning	92 (57%)
Carcinoid syndrome	62 (38%)
Cushing syndrome	4 (2%)
Acromegaly	1 (1%)
PTH-rp	2 (1%)

Robelin P, JTO 2019

- Carcinoid syndrome is not rare
- SSA, pasireotide? Telotristat?
- Risk of CHD? Help of 5HIAA?

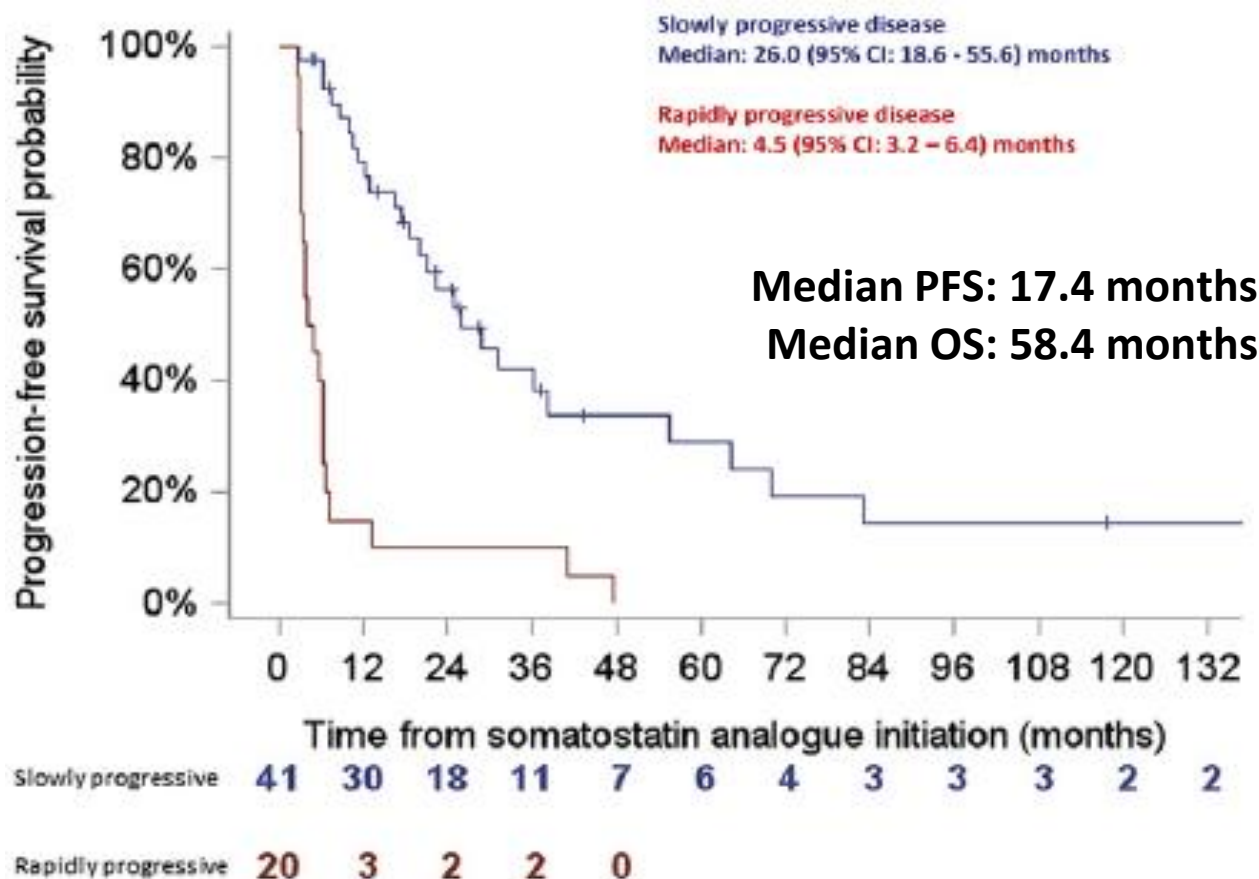
4. SSA for “slowly” advanced lung NET



Baudin, ESMO Guidelines

- Low mitotic index (Ki67?)
 - Low tumour slope
 - Low tumour burden
 - High SSTR2 uptake?
 - Low FDG uptake ?
- => Stabilization
in 30-70% of patients

4. SSA for “slowly” advanced lung NET



Sullivan, ERC 2017

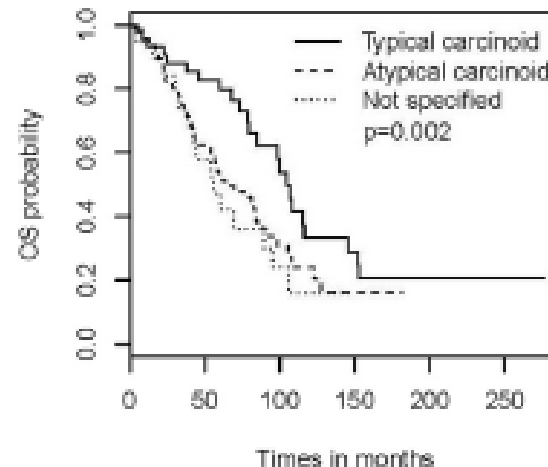
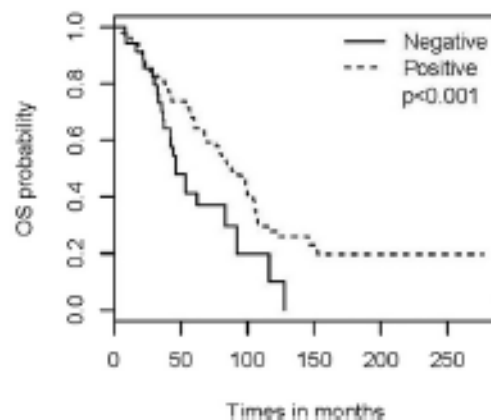
Prognostic factors at metastatic stage

Characteristics	Total Population N= 162
WHO classification, n (%)	
Typical carcinoid	46 (28%)
Atypical carcinoid	97 (60%)
Not otherwise specified carcinoid (only metastatic sample available)	19 (12%)
Uptake on SRS, n (% of patients with SRS)	108/143 (76%)
Uptake on FDG-PET, n (% of patients with FDG-PET)	72/80 (90%)

- Grading
- Tumor volume (CgA)
- High SSTR2 uptake
- PS 0-1 vs 2-3

=> We need to better stratify the prognosis of each patient (molecular help?)

E Somatostatin receptor scintigraphy



4. SSA for “slowly” advanced lung NET

216 subjects:

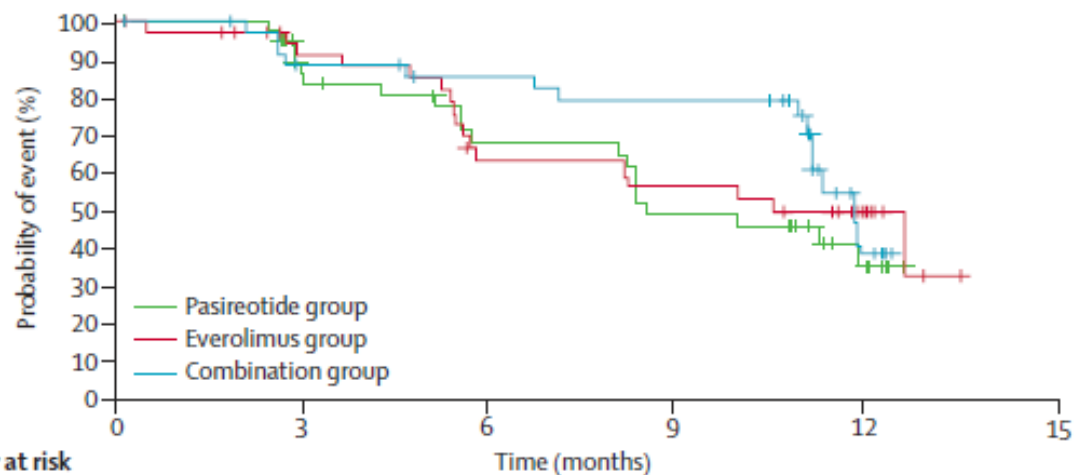
- Metastatic/unresectable
 - Typical
 - Atypical
- SRS + (Krenning grade 2+)

RANDOMIZATION (2:1)

Lanreotide
120mg/28days
(144 subjects)

Placebo
(72 subjects)

■ SPINET study



■ Luna study with pasireotide

■ OR: 2.4% in each arm

Ferolla, Lancet Oncol 2017



5. Everolimus for “aggressive” advanced lung NET

- Everolimus, the only approved drug
- Everolimus (Radiant-4)
- PFS, HR=0.48, 3.9 to 11.0 months
- ORR=2%

Metastatic lung or thymic carcinoid*

TC
or slowly progressive carcinoids

Observation

SSAs [IV, C]

Locoregional therapies including surgery [V, B]

AC^b
or significantly progressive carcinoids
or post-SSA therapy

Everolimus^a [II, B]
Temozolomide-based ChT [IV, C]^d

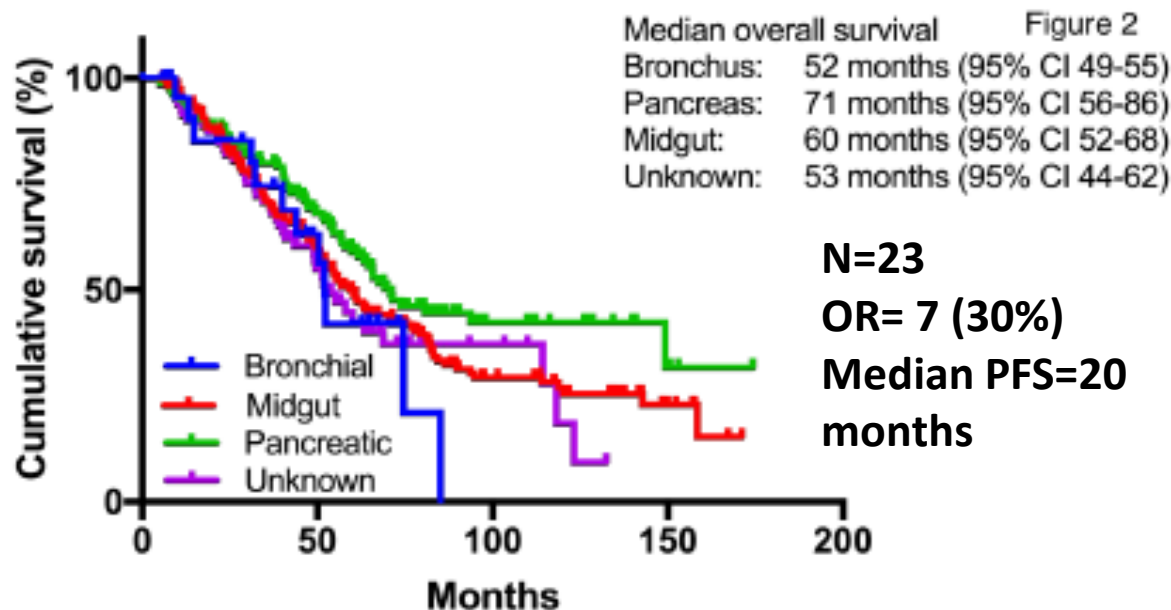
PPRT^a [IV, B]
IFN^a [IV, B]
Platinum-based ChT^d [IV, C]

Baudin, ESMO Guidelines

5. PRRT for advanced lung NET

- Series of 22-124 patients
- Median PFS of 10-28 months, mOS=31-59 months
- We need it! => access programm, clinical trials (PRRT vs everolimus)

Marienello, EANM 016
Brabander, CCR 2017
Robelin P, JTO 2019



N=23
OR= 7 (30%)
Median PFS=20 months

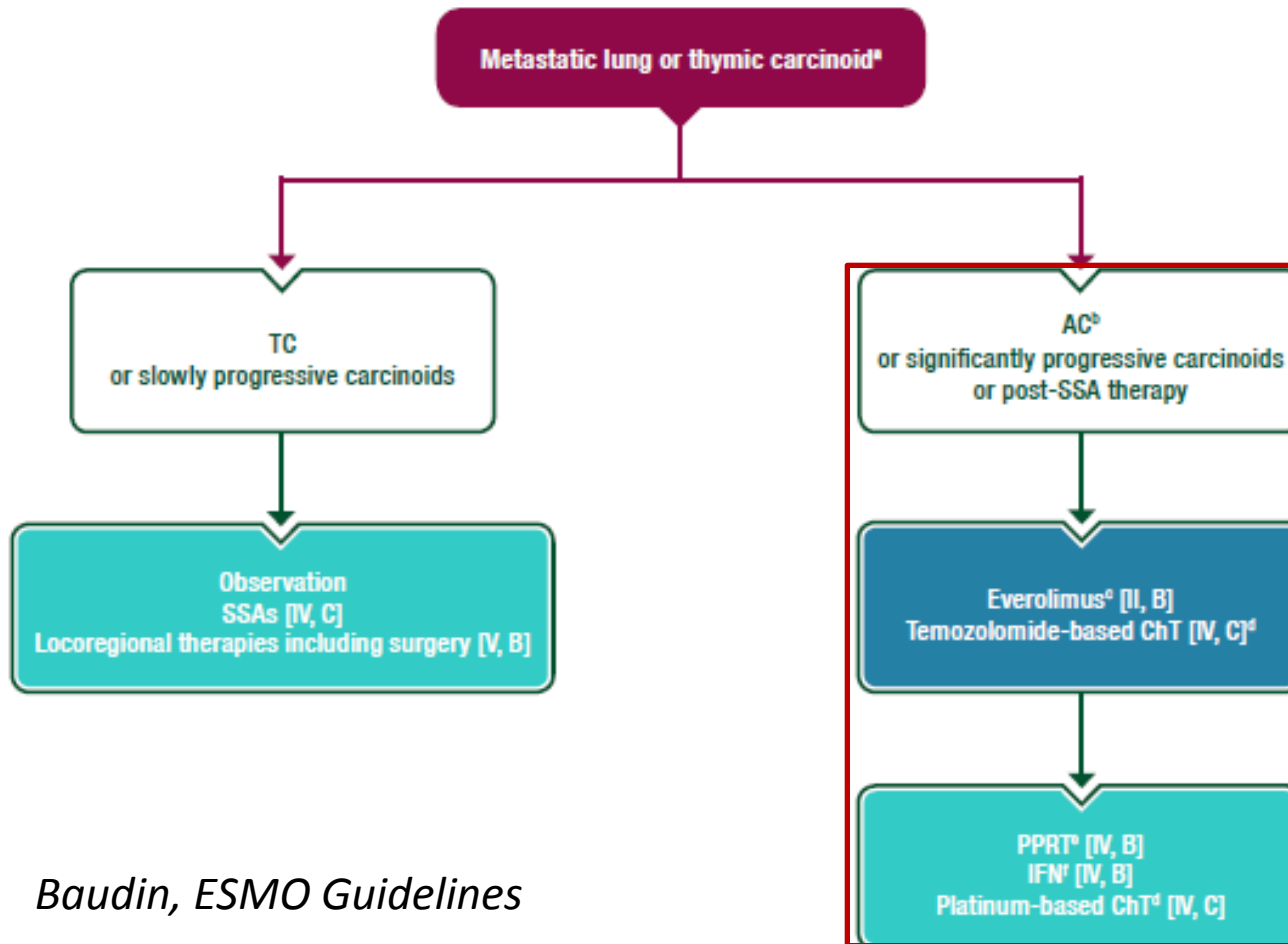
No at risk

Bronchus	23	10	0	0
Midgut	181	92	28	7
Pancreas	133	71	17	4

Brabander, CCR 2017



6. CT for “aggressive” advanced lung NET

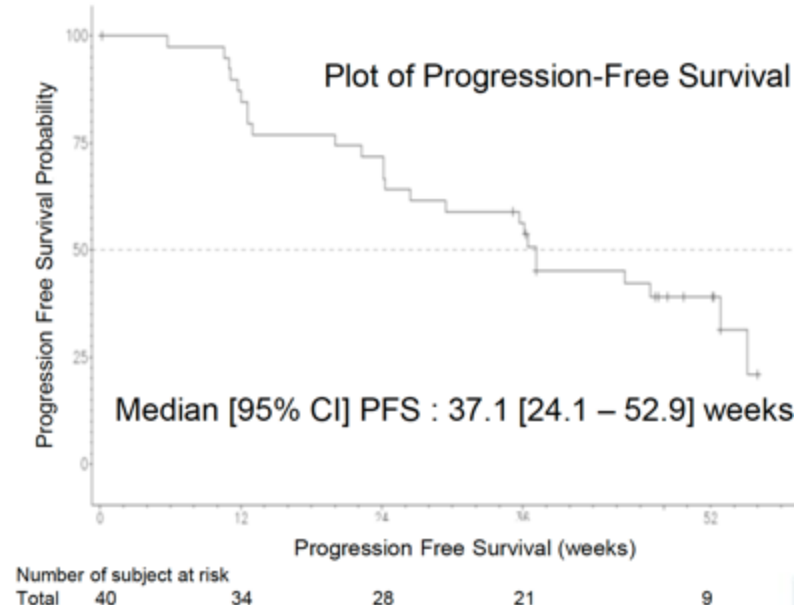
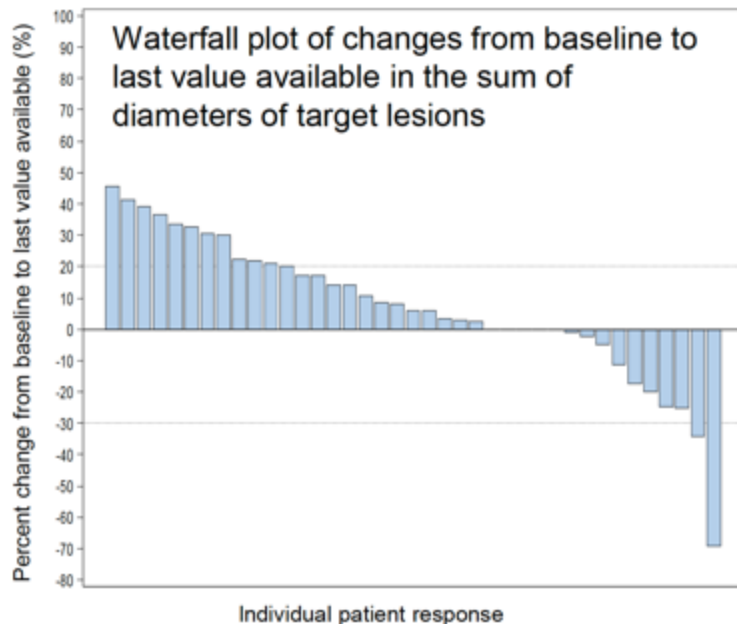


Baudin, ESMO Guidelines

- Chemotherapy for high grade and/or rapidly progressive NET
- Response rate is inversely related to Ki67 index

6. CT for “aggressive” advanced lung NET

- Too few data; Tem-based in guidelines
- ATLANT: Lanreotide + temozolomide in progressive lung/thymic NET, n=40
- ORR: 7.5%, median PFS < 9 months



6. CT for “aggressive” advanced lung NET

- Toxicity is considerable with cisplatin (OR≈)
- Tem-based per os or Dacarcabazine-based IV CT

	Platin/ Etoposide, n= 24	Oxaliplatin- Based, n= 84	Tem-Based, n= 58	Dacar-Based, n= 27	Strept-Based, n= 29
Median time between metastatic diagnosis and treatment start, months (range)	2 (0.1-38.5)	18.8 (0.2-122.7)	28.5 (0.3-144.6)	15.8 (0.9-117.9)	19.8 (2.0-63.6)
Number of prior systemic lines					
0	18 (75)	22 (26)	1 (2)	4 (15)	4 (14)
1	5 (21)	27 (32)	16 (28)	3 (11)	12 (41)
2	0 (0)	14 (17)	20 (34)	12 (44)	7 (24)
≥3	1 (4)	21 (25)	21 (36)	8 (30)	6 (21)
Median time under treatment, months (range)	2 (0.1-5.2)	3.2 (0.2-29.9)	3 (0.1-12.7)	3.6 (0.1-10.6)	3.9 (0.1-15.2)
Median number of cycles (range)	4 (1-6)	8 (1-24)	3 (1-14)	5 (1-9)	4 (1-14)
Reason for discontinuation					
Progressive disease and death	8 (33)	24 (29)	38 (66)	9 (33)	10 (34)
Scheduled	10 (42)	35 (42)	6 (16)	10 (37)	11 (38)
Toxicity	4 (17)	22 (26)	5 (9)	5 (19)	7 (24)
Unknown	2 (8)	1 (1)	1 (2)	2 (7)	1 (3)
Best response					
Objective response	2 (8)	15 (18)	6 (10)	6 (22)	3 (10)
Stable disease	13 (54)	52 (62)	22 (38)	14 (52)	15 (52)
Progressive disease	7 (29)	13 (15)	23 (40)	3 (11)	8 (28)
Unknown	2 (8)	4 (5)	7 (12)	4 (15)	3 (10)
Median PFS, months (95% CI)	7.1 (3.9-10.8)	9.3 (7.2-12.7)	4.6 (3.0-5.7)	5.8 (4.6-12.0)	8.0 (6.0-18.2)
Median overall survival, months [95% CI]	44.0 (33.2-NR)	37.8 (29.6-45.2)	25.0 (14.8-40.2)	26.2 (17.4-67.7)	49.2 (35.5-80.9)



6. CT for “agressive” advanced lung NET

	MGMT « deficient » (Kulke, Clin Can Res 2009)	MGMT « deficient » (Dussol, Cancer 2015)
Pancreas NET	19/37 (51%)	7/13 (54%)
Midgut NET	0/20 (0%)	2/16 (12%)
Lung NET	0/40 (0%)	1/8 (12%)

- One explanation of less response in lung NET with alkylating agent
- This must be confirmed
- Other option in proficient MGMT?

Kulke, Clin Can Res 2009
Dussol, Cancer 2015

6. CT for “aggressive” advanced lung NET

■ Oxaliplatin-based chemotherapy?

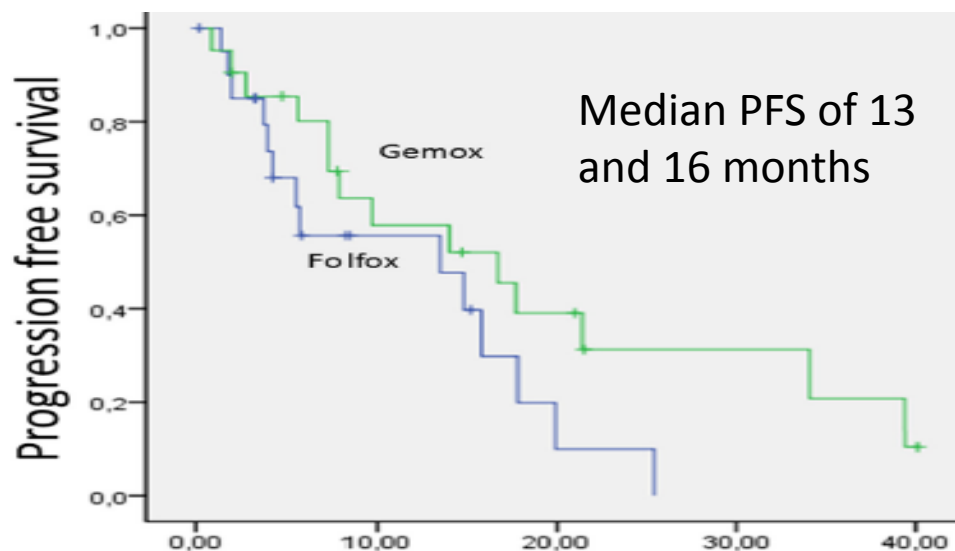
	Pancreas	Gastrointestinal Tract	Lung
Patients, No.	37	33	23
Objective response, No. (%)	14 (38)	1 (3)	6 (26)
Stable disease, No. (%)	16 (43)	25 (76)	15 (65)
Progressive disease, No. (%)	7 (19)	7 (21)	2 (9)
Progression-free survival, median (95% CI), mo	7.3 (5.0-9.6)	6.9 (3.2-10.6)	10.7 (2.1-19.3)
Overall survival, median	25.7 (15.9-35.5)	32.8 (28.2-37.4)	41.4 (25.4-57.4)



6. CT for “agressive” advanced lung NET

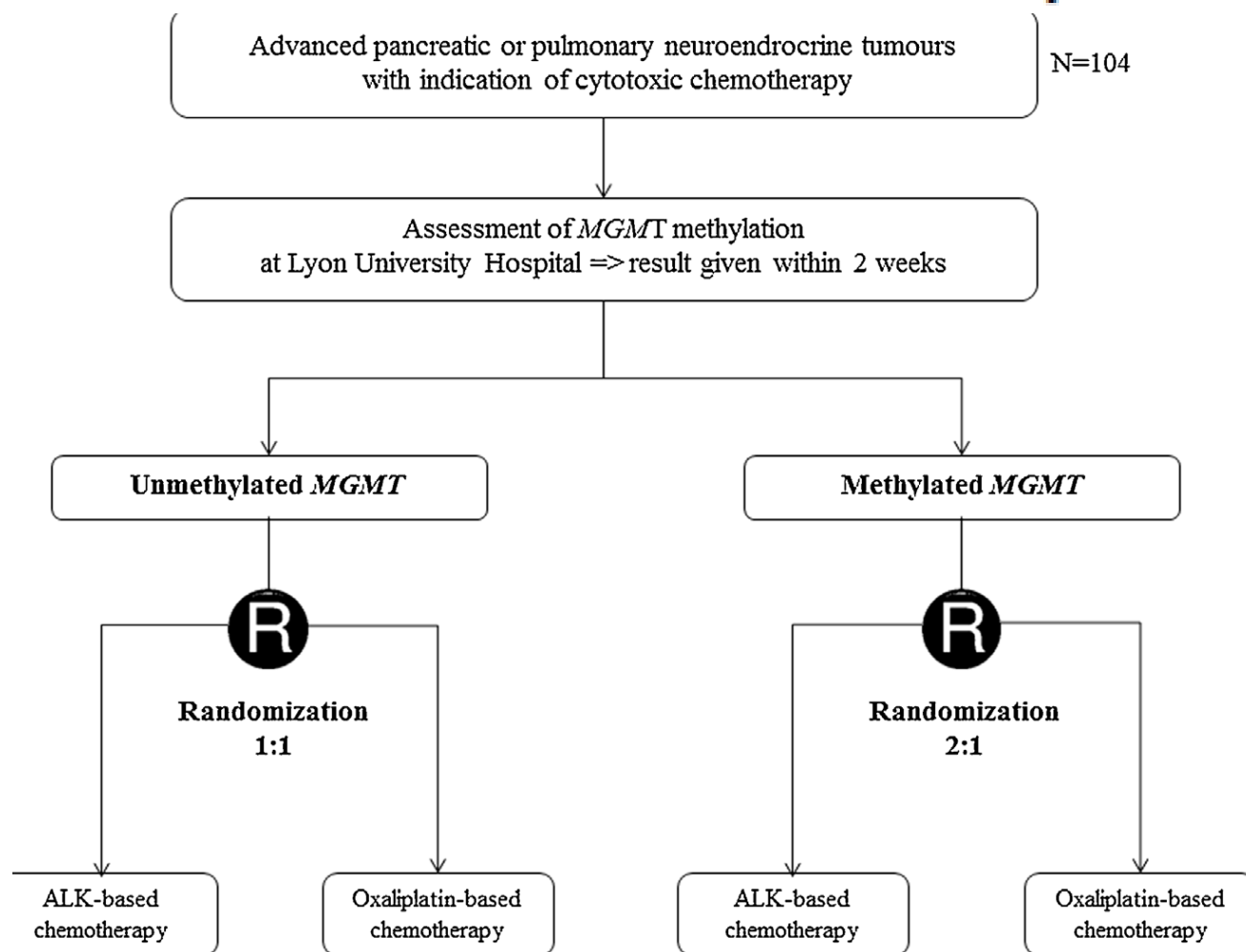
■ Oxaliplatin-based chemotherapy?

	Folfox	Gemox	All
Number of patients	21	24	45
Median time in months (range) between metastatic diagnosis and treatment start	23 (3–90)	17 (0–74)	22 (0–90)
Number of prior systemic treatments, n (%)			
-0	0 (0)	9 (37)	9 (20)
-1	10 (48)	5 (21)	15 (33)
-2	5 (24)	5 (21)	10 (22)
-≥3	6 (28)	5 (21)	11 (25)
Progressive disease before chemotherapy, n (%)	16 (80)	18 (78)	34 (79)
Not Available, n	1	2	4
Median number of cycles (range)	8 (1–12)	8 (4–11)	8 (1–12)
Best response, n (%)			
Objective response, n (%)	3 (14)	6 (25)	9 (20)



6. CT for “agressive” advanced lung NET

O6-methylguanine-DNA methyltransferase (MGMT) status in neuroendocrine tumors: a randomized phase II study (MGMT-NET)



Lemelin, DigLivDis 2019



7. TKI for advanced lung NET

- Lung carcinoids as a subgroup of NET patients

Phase III RCT	Surufatinib	placebo
n	129	69
N (%) of Lung NET	12 (9%)	11 (16%)
Prior everolimus	7.8%	11.6%
ORR (%)	10%	0%
Median PFS	9.2 months	3.8 months
	HR=0.33, p<0.0001	



7. TKI for advanced lung NET

- Lung carcinoids as a subgroup of NET patients

Phase III RCT	Surufatinib	placebo	
n	129	69	
Primary tumoursite			
C	32/57	20/31	0.47 (0.26-0.84)
B	45/72	31/38	0.33 (0.20-0.53)
Gastrointestinal	36/61	30/32	0.48 (0.29-0.79)
Others	41/68	21/37	0.46 (0.26-0.80)
ORR (%)	10%	0%	
Median PFS	9.2 months	3.8 months	
	HR=0.33, p<0.0001		

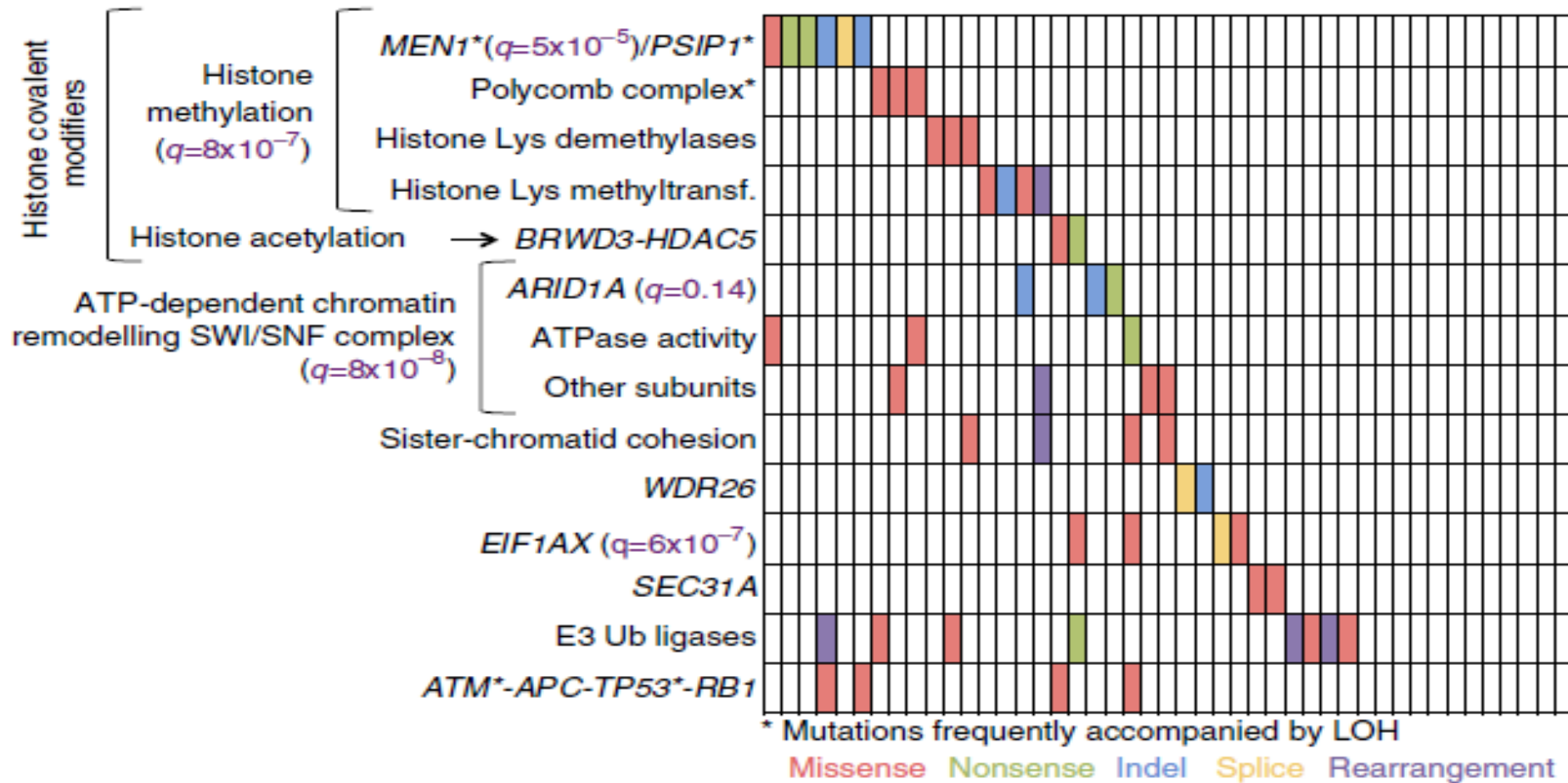
- Phase III ongoing (CABINET, AXITINIB)

8. Immunotherapy for advanced lung NET

Study, reference	PDR001, Yao ESMO 2018	Dune, Capdevilla ESMO 2020
Drug	Spartalizumab	Durvalumab- Tremelimumab
Number of patients	30	27/123
PR, n (%)	6 (20%)	0 (0%)
SD, n (%)	16 (53%)	DFS at 9mo:7.4%

- Not in monotherapy
- But what about combinations? With TKI ? PRRT ?

9. To find new targets



■ Lung carcinoids : how to target epigenetics ?

■ DNA demethylating agent

■ HDAC inhibitors

Fernandez-Cuesta, Nat Comm 2014

Hollebecque, Can Res 2020, phase 1₂₃



10. Surgery of the primary tumour in metastatic lung NET

- « among the 80 patients with synchronous metastases, 21 (26%) did so »
- ⇒ Retrospective study of the GTE (propension score)
- Population: probably very selected with good prognostic factors (vs without surgery)
- Type of procedures, morbidity, survival ?
- Symptomatic benefit on respiratory/carcinoid symptoms ?





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