Optimizing Patients Management in Lung NETs

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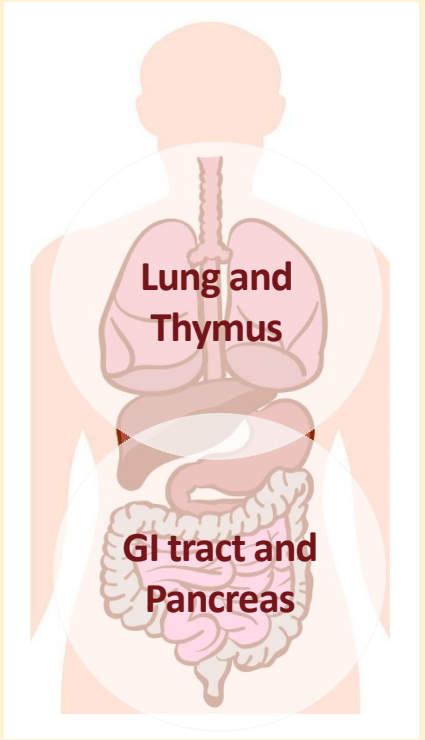
Neuroendocrine Tumors

Neuro**e**ndocrine **t**umors (**NETs**) comprise a heterogeneous group of malignancies that arise from neuroendocrine cells throughout the body.

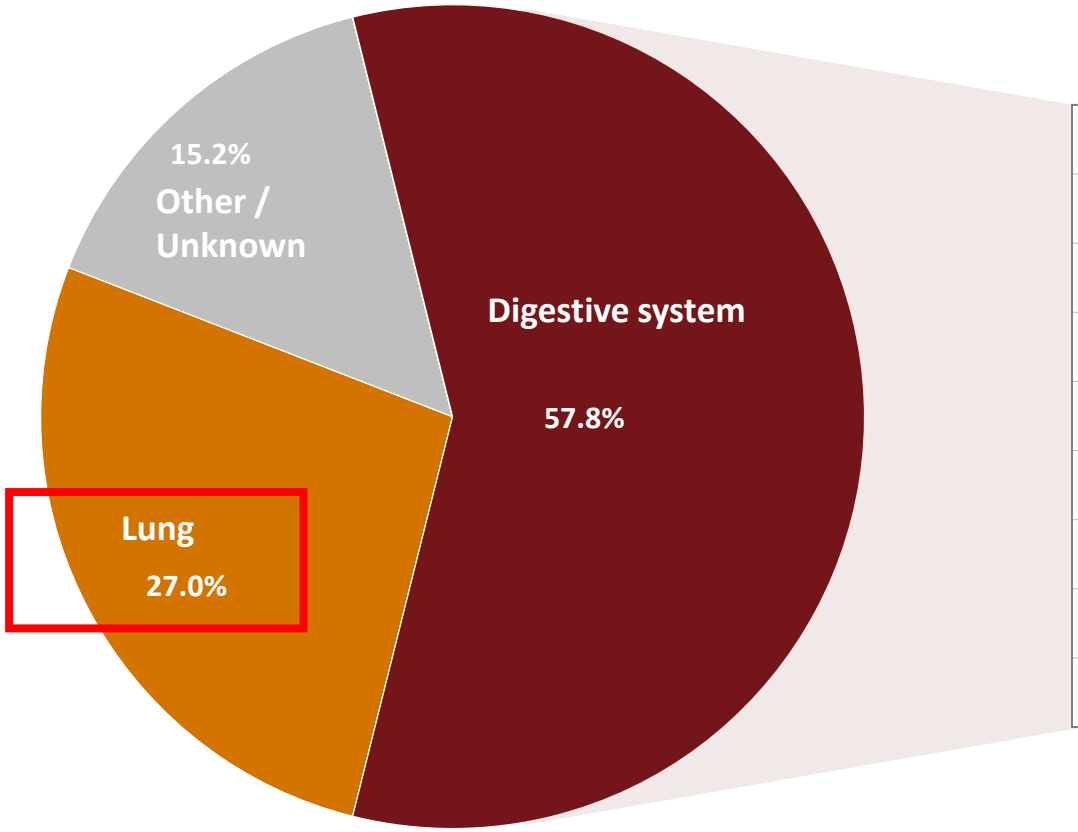
- Most occurs in the **lung**, **thymus**, **gastrointestinal tract** and **pancreas.**
- NETs of gastrointestinal tract and pancreas groups together as **GEP-NETs**, GastroEnteroPancreatic NeuroEndocrine Tumors.
- Like other NET, **pancreatic NET** can also be **nonfunctional tumors** (tumors whose hormones cause no symptoms)



Hendifar AE, et al. Thorac Oncol. 2017;12(3):425-436; 2.Oberg K, et al. Cancer Metastasis Rev. 2011;30:3-7

Incidence of NETs by Location in the US

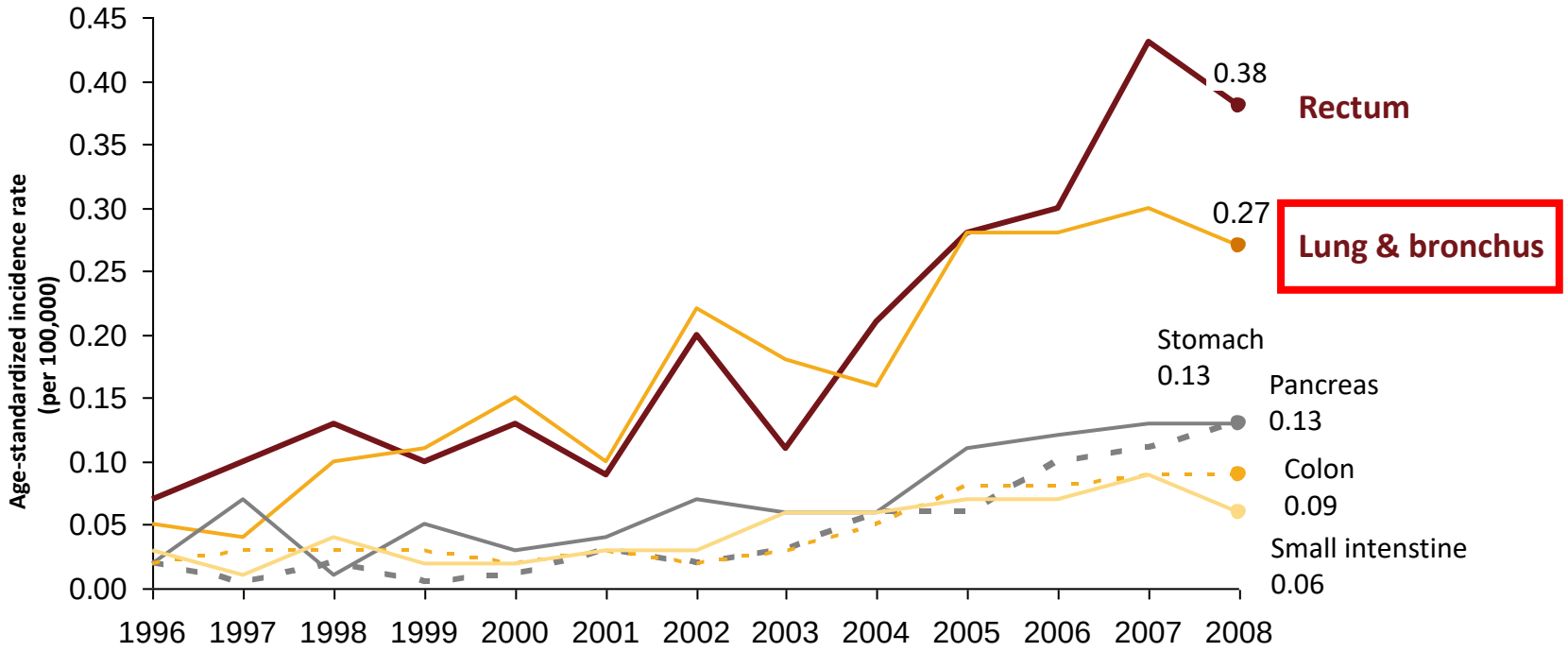
35,618 patients with NETs from 1973 to 2004



Rectum	17.2%
Jejunum/ileum	13.4%
Pancreas	6.4%
Stomach	6.0%
Colon	4.0%
Duodenum	3.8%
Cecum	3.2%
Appendix	3.0%
Liver	0.8%

Yao JC, et al. J Clin Oncol. 2008;26(18):3063-72

The age-standardized incidence rate of neuroendocrine tumors, Taiwan, 1996–2008 (by primary sites)



- The age-standardized annual incidence rate of NETs in Taiwan increased from **0.30** per 100,000 in 1996, to 0.55 per 100,000 in 2000, and to **1.51** per 100,000 in 2008
- The age-standardized incidence rate of NETs increased by **83%** from 1996 to 2000 and by **175%** from 2000 to 2008.

Tsai HJ, et al. PLoS One. 2013;8(4):e62487

Lung NET has Worse Prognosis than Most GI NETs

Median survival (months)
G1/G2 NET diagnosed 1988–2004

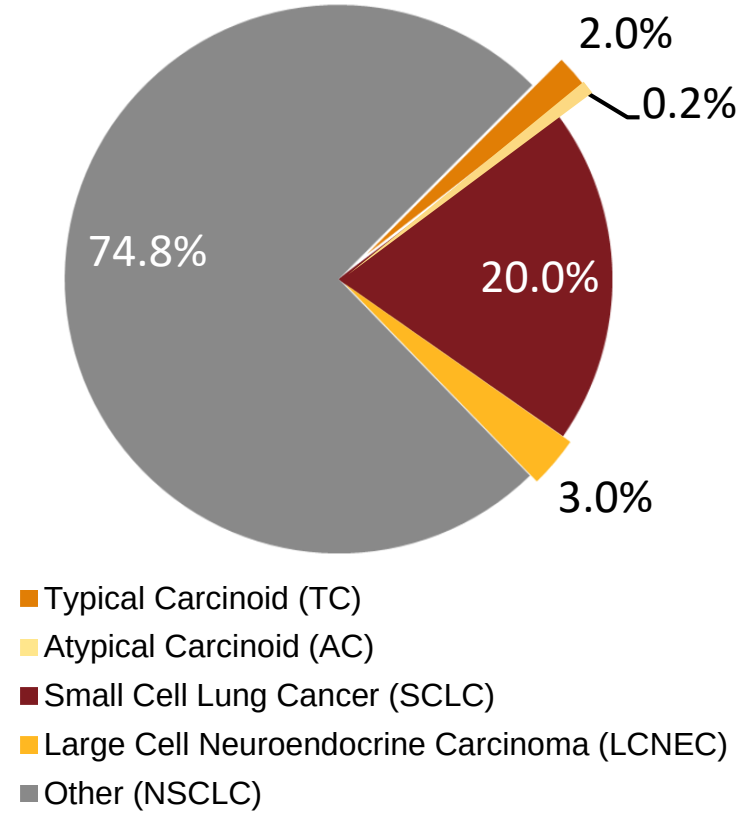
Site	Localized	Regional	Distant
Jejunum/ileum	115	107	65
Duodenum	112	69	57
Caecum	135	107	55
Thymus	92	68	40
Appendix	NR	NR	31
Pancreas	NR	111	27
Rectum	NR	90	26
Lung	**NR**	**151**	**17**
Gastric	163	76	13
Liver	47	14	12
Colon	NR	52	7

Median OS: 75 months
(Any NET diagnosed between 1973-2004)

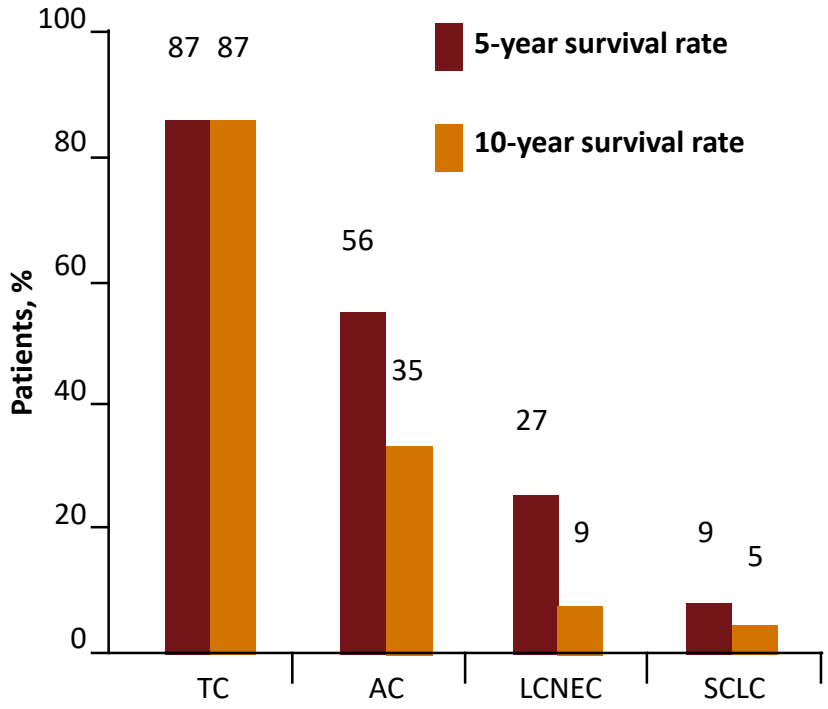
Yao JC, et al. J Clin Oncol. 2008;26(18):3063-72;
Rekhtman N, et al. Arch Pathol Lab Med. 2010;134(11):1628-1638;
Phan AT, et al. Pancreas. 2010;39(6):784-798

Patients with Atypical Carcinoid and Poorly Differentiated Lung NEC Have Worse Prognosis

Prevalence of different classifications of lung NET



Patients with AC and poorly differentiated NEC have worse prognosis vs. TC



Rekhtman N, et al. Arch Pathol Lab Med. 2010;134(11)1628-1638;
Travis WD, et al. Am J Surg Pathol. 1998 Aug;22(8):934-44; 23.
Natasha Rekhtman, et al. Arch Pathol Lab Med 2010;134.

Epidemiology

Bronchial NET epidemiology

- 1% of all lung cancer and ~30% of all NETs

  (Prevalence Rate: 0.2-2 per 100,000)

- 40's to 60's is most common age

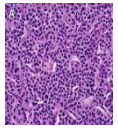
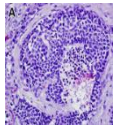
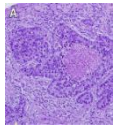
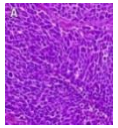
  (45 y/o in TC and 55 y/o in AC)

- TC : AC ≅ 8-10 : 1
  - Smoking related to AC, no other known environmental risk factors

- Inherited risk
  - 95% sporadic and not associated with inherited risk
  - 5% associated with inherited condition MEN1 (TC>AC)

M.E. Caplin et al. Annals of Oncology 2015; 26:1604-1620

2015 WHO Classification of Lung NET/NEC

	TC	AC	LCNEC	SCLC
Tumor grade	Low	Intermediate	High	High
Histology	Well- differentiated NET	Well- differentiated NET	Poorly- differentiated NET	Poorly- differentiated NET
H&E Stain				
Mitoses/10 HPF	<2	2-10	>10 (median=70)	>10 (median=80)
Ki-67 Index	**<2%**	**<20%**	**20-90%**	**60-100%**
Necrosis	None	Present (focal punctate)	Present (extensive)	Present (extensive)
Malignancy	Fairly benign	Considerable malignant potential	Highly malignant	Highly malignant
TTF1 expression	Mostly negative	Mostly negative	Positive 50%	Positive 85%
Combined with non-SCLC component	No	No	Sometimes	Sometimes

Rekhtman N, et al. Arch Pathol Lab Med. 2010;134(11)1628-1638;
Filosso PL, et al. J Thorac Dis. 2015;7(Suppl 2):S163-S171.

2015 WHO Classification of Lung NETs

Key differentiating characteristics

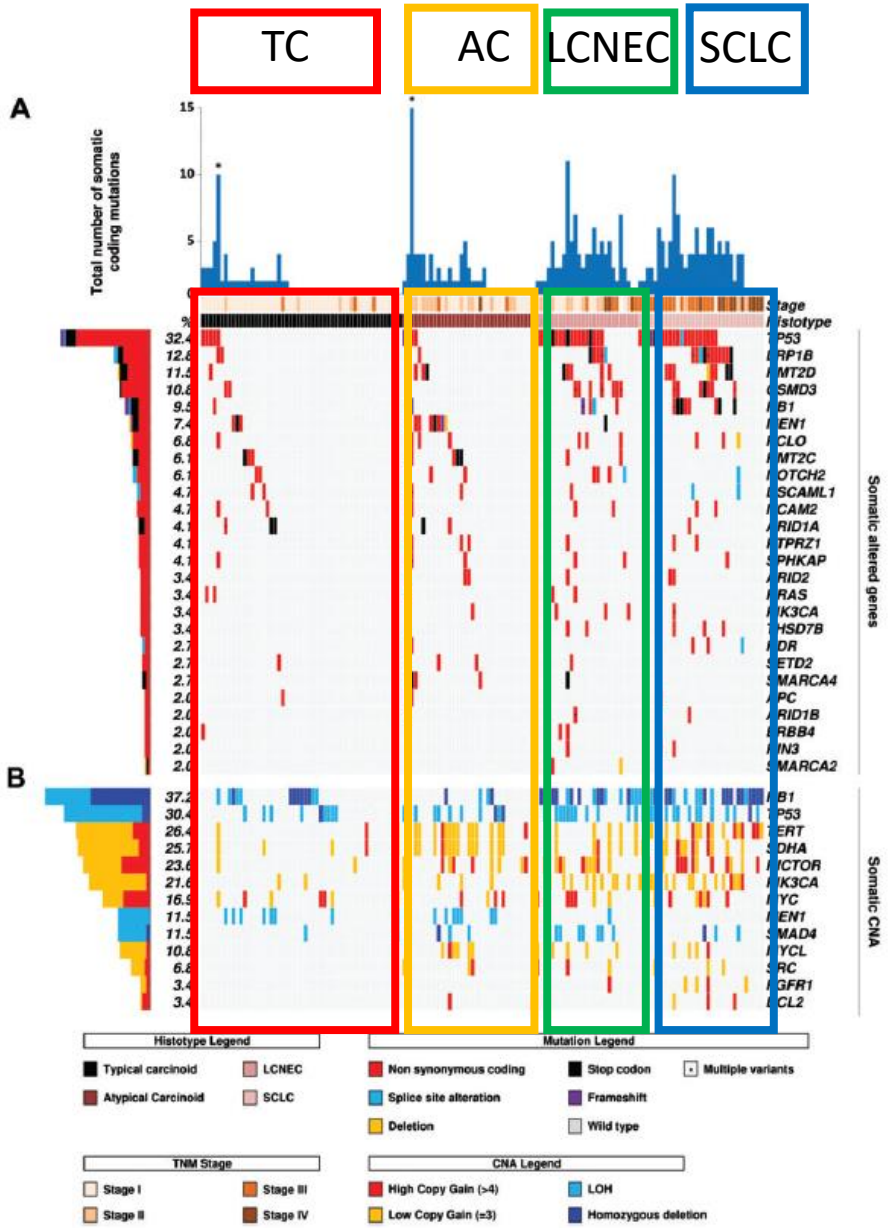
- Presence/absence of necrosis
- Mitoses/2 mm
- Ki-67 outperformed mitotic index as a prognostic factor; useful in distinguishing subtypes of lung NET

Lung carcinoids (TC/AC) are low-intermediate grade tumors, however

- Lymph-node involvement + local recurrence or distant metastases can occur, impacting prognosis
- Metastases seen in patients with both TC (5-20%) and AC (30-70%)
- Significantly longer median OS with localized vs metastatic lung NET (227 vs 16 months)

Yao JC, et al. J Clin Oncol. 2008;26(18):3063-72 ;
Travis WD J, et al. Thorac Oncol. 2015;10(9)1243-1260;
Filosso PL, et al. J Thorac Dis. 2015;7(Suppl 2)S163-S171;
Volante M, et al. Endocrine. 2015; 11. Gustafsson BI, et al. Cancer. 2008;113(1):5-21.

Molecular Landscape



Carcinoid:

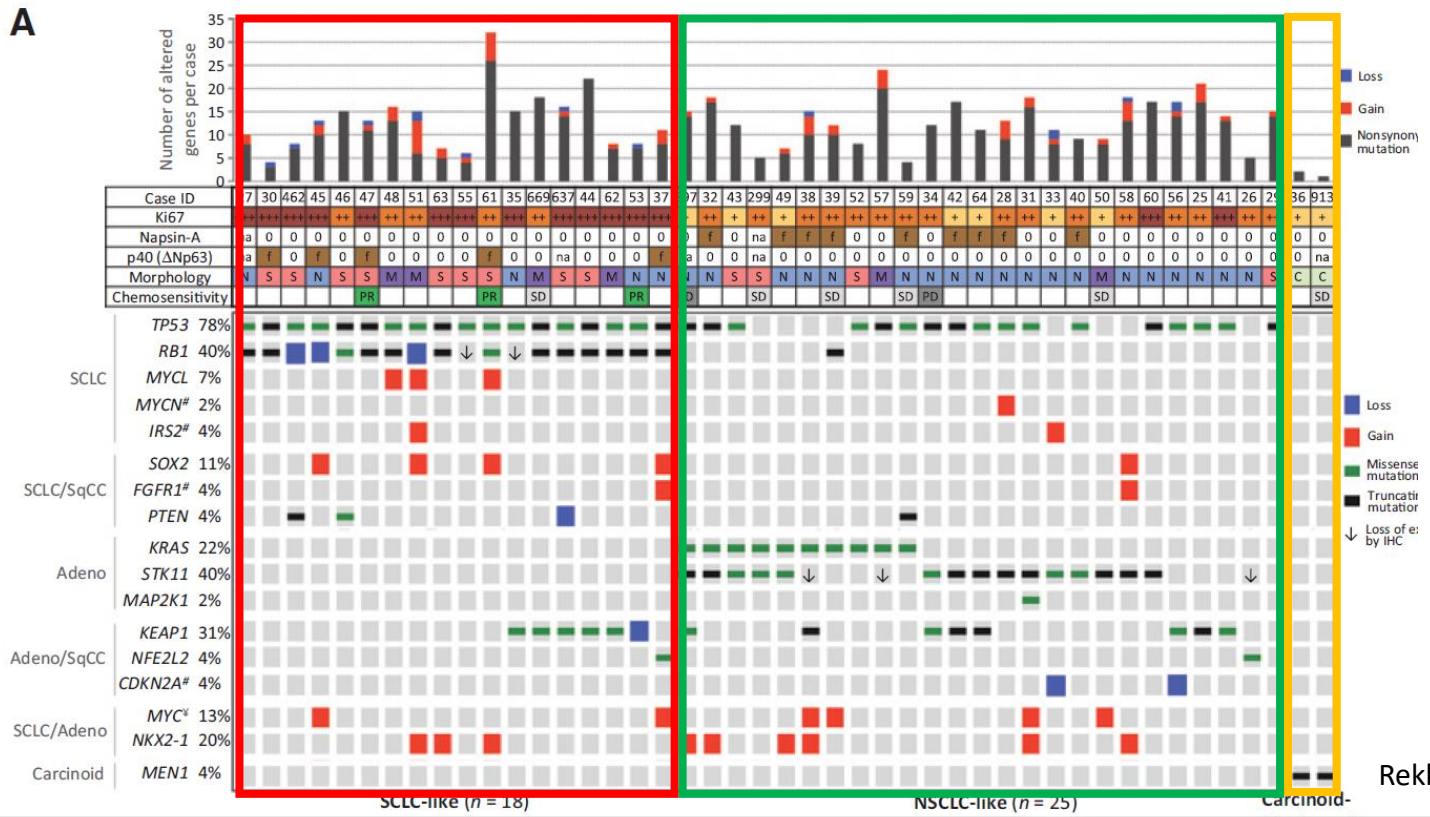
- TC+AC
- MEN1 mutation
- Chromatin-remodeling genes mutations

Carcinomas:

- LCNEC+SCLC
- TP53 mutation
- RB1 mutation
- Cell cycle regulation genes

Simbolo M, et al. Journal of Pathology. 2017;241:485-500 ;

Molecular Landscape (Heterogeneous classification LCNEC)



Rekhtman N, et al. Clin Cancer Res. 2016;22:3618-29.

NSCLS GROUP/LCNEC I

LCNEC Morphology + SCLC/ADK Molecular Features

- ✓ RB1 or TP53: YES
- ✓ STK11 and KRAS: YES
- ✓ MYCL, SOX2:NO
- ✓ FGFR1 :NO
- ✓ MEN1: NO

CARCINOID GROUP

LCNEC Morphology + Carcinoid Molecular Features

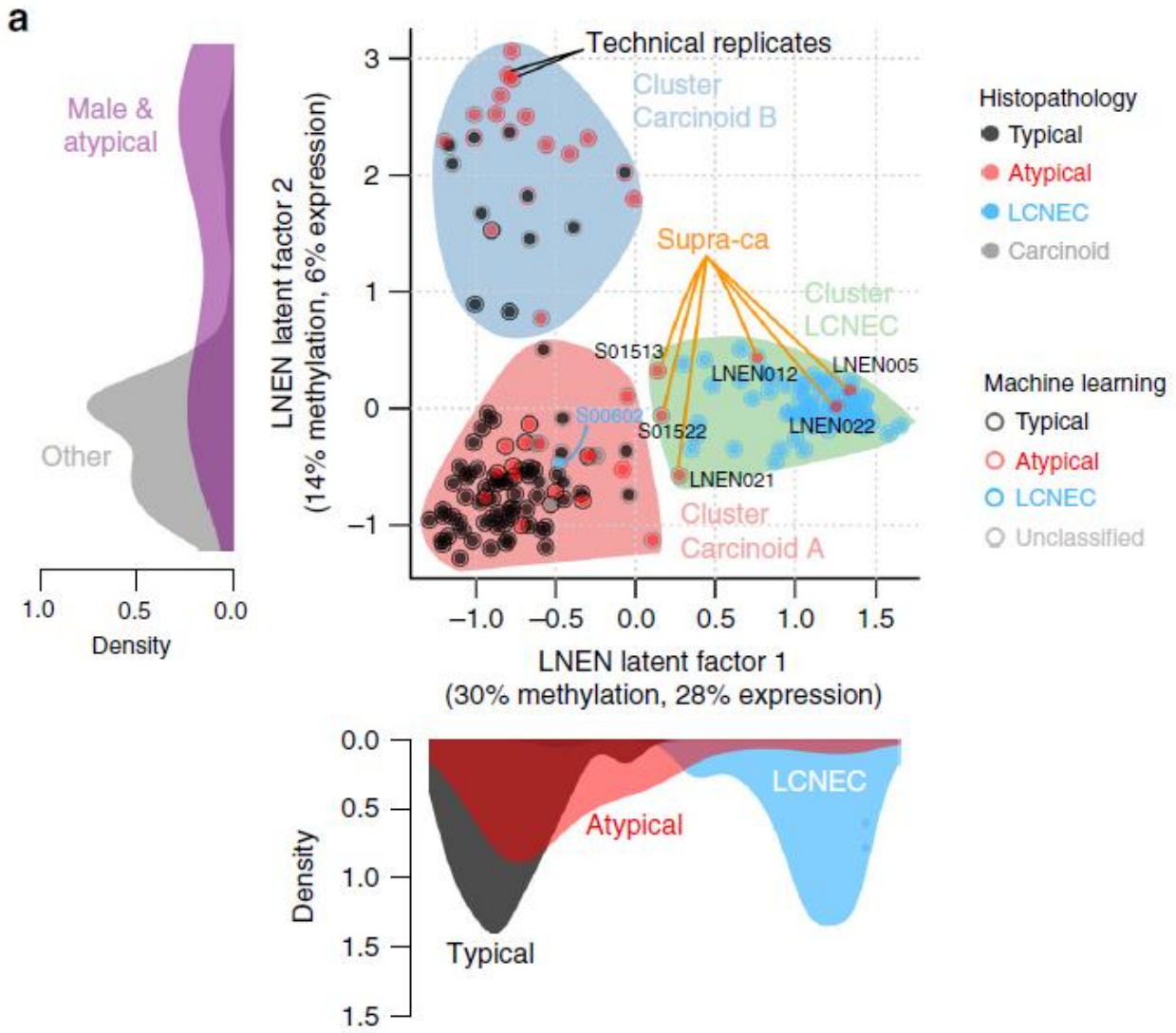
- ✓ RB1 or TP53: NO
- ✓ STK11 and KRAS: NO
- ✓ MYCL, SOX2:NO
- ✓ FGFR1 :NO
- ✓ MEN1: YES

SCLC GROUP/LCNEC II

LCNC Morphology + SCLC Molecular Features

- ✓ RB1+TP53: YES
- ✓ STK11 and KRAS: NO
- ✓ MYCL, SOX2:YES
- ✓ FGFR1:YES
- ✓ MEN1:NO

Molecular Landscape (Heterogeneous classification Supracarcnoid)



- 81 Typical
- 35 Atypical
- 75 LCNEC
- 66 SCLC

- Atypical NETs stratified in to two groups
  - 10yr OS 88%
  - 10yr OS 27%

  - Poorer OS
  - morphologically Atypical NEN
  - molecularly and clinically LCNEC

- "Supra-carcinoid"

Ancala N, et al. NATURE COMMUNICATIONS. 2019;10:3407

Supracarcinoid: 披著羊皮的狼 ??

Treatment Consideration

Disease Factors	Patient, health system
- Histopathology (TC, AC, Ki67?)	- Age
- Genomics (TC, AC, supracarcinoid)	- Comorbidities
- Previous treatment (Radiation)	- Access of therapy (PRRT…..)
- Functional symptoms	
- Pace of disease	
- Tumor burden	

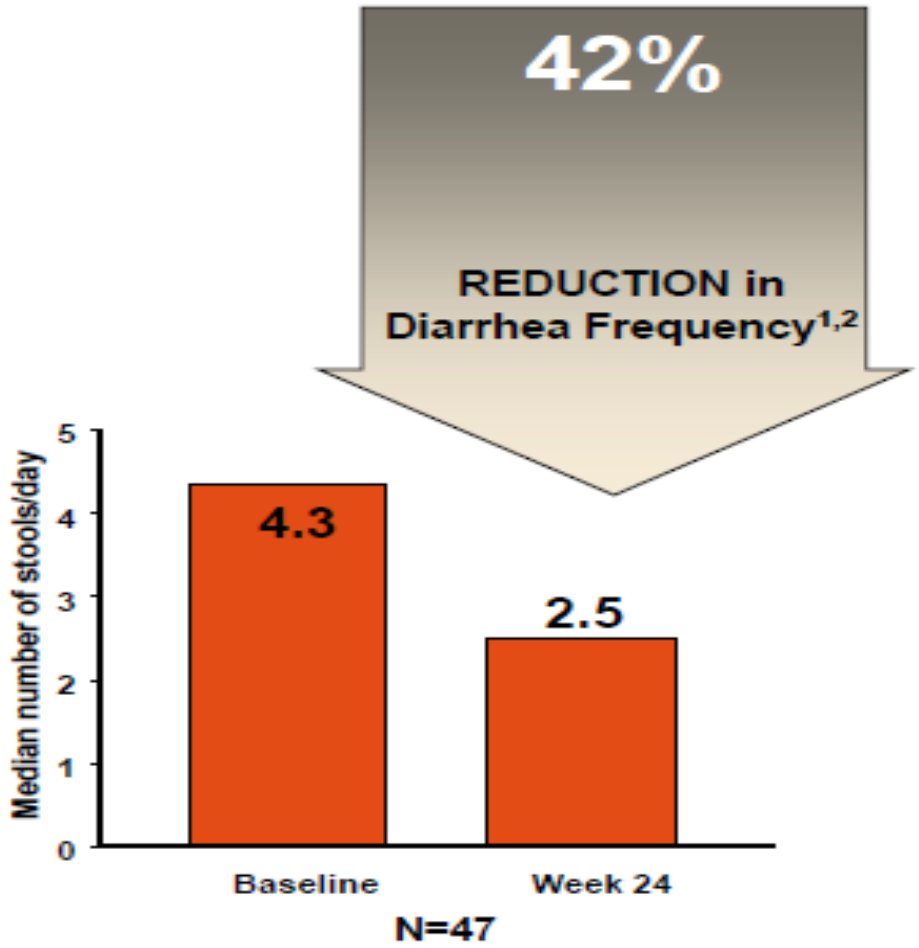
Treatment Choices

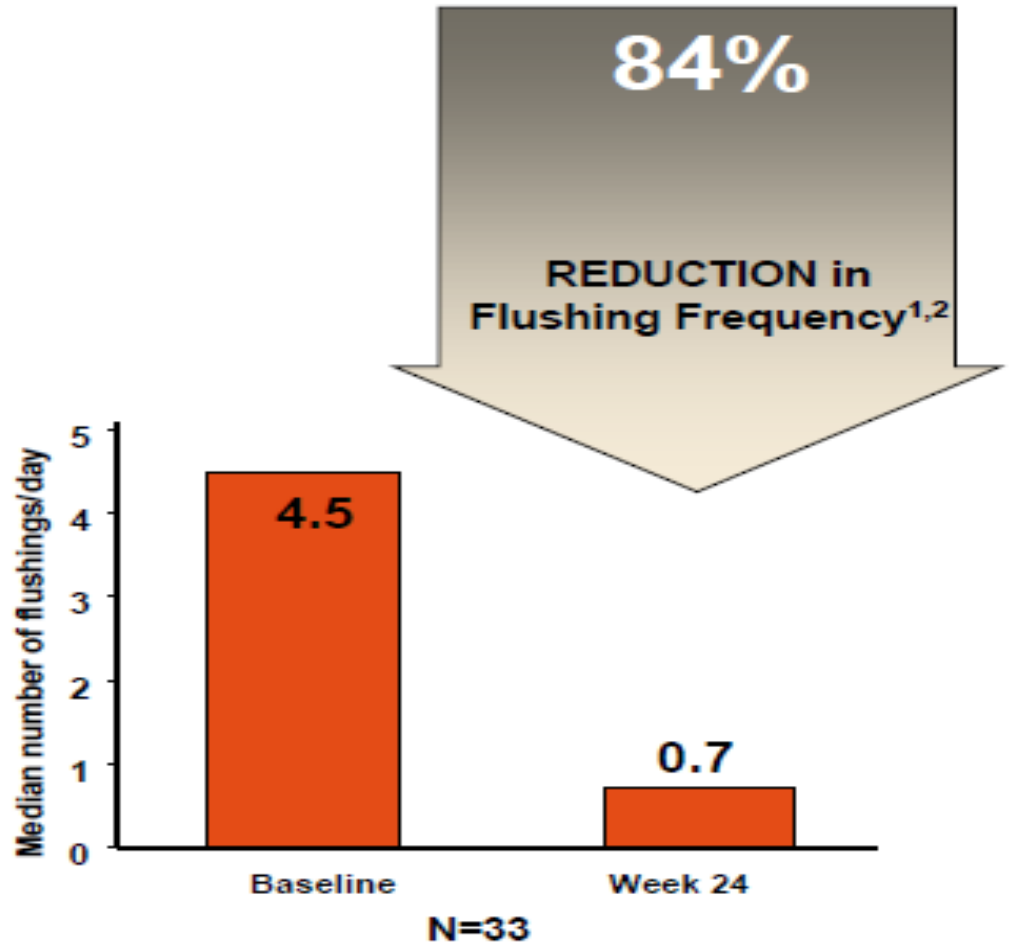
Tools	Evidence level
- SSA (Somatostatin Analog)	
- Everolimus	
- Chemotherapy	
- PRRT	

Somatostatin Receptors

Carcinoid Tumours	**sst2**>sst5>sst1>sst3&4	
Gastrinomas	**sst2**>sst5=sst1>sst3>sst4	
Insulinomas	sst5>sst3>**sst2**>sst4>sst1	benign
Non-functional pancreatic ET	**sst2**>sst3>sst1>sst5>sst4	
Merkel Cell Tumour / Phaeochromocytoma	**sst2**>sst1>sst5=sst4>ssst3	

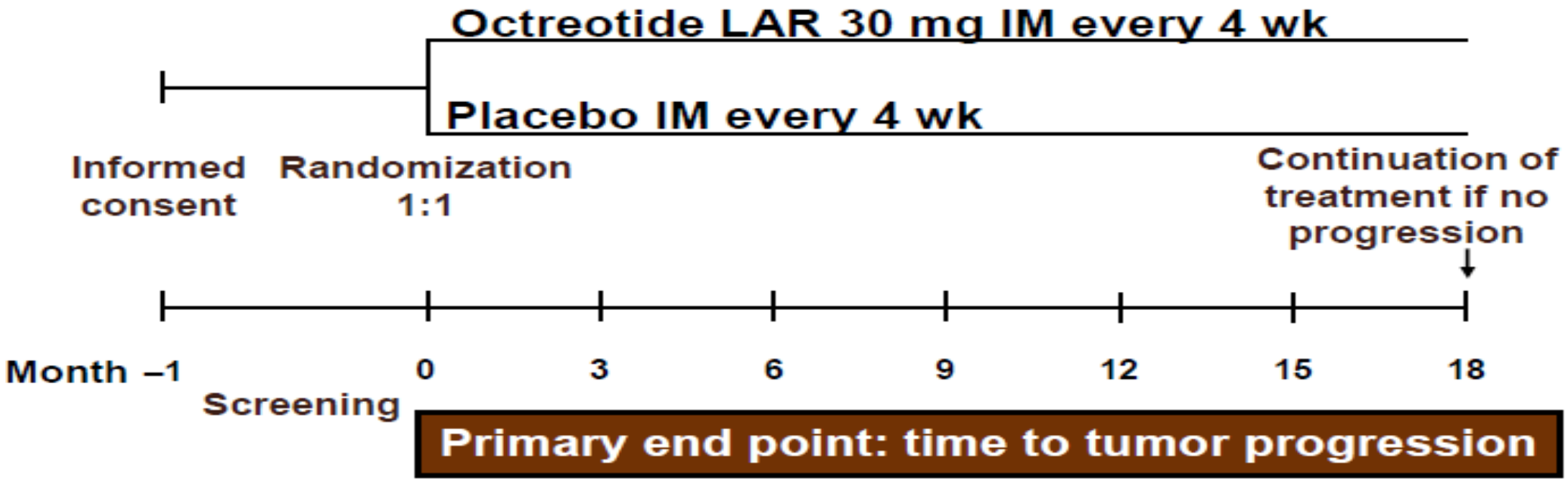
Octreotide LAR Provides Effective Symptom Relief





PROMID Study Design

MidGut + unknown primary!!, **no lung NET**

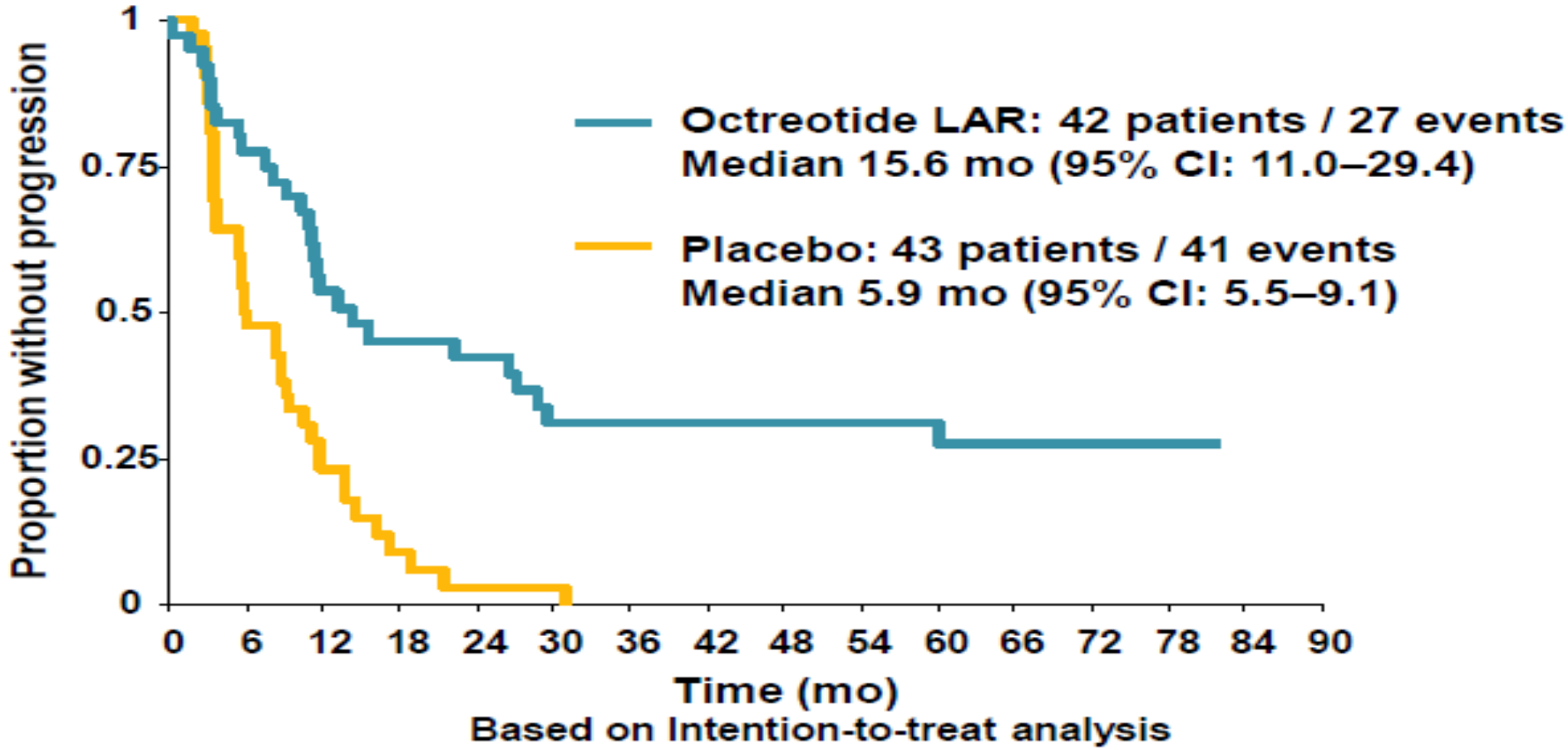


- Treatment was continued until CT or MRI documented tumor progression (WHO)
- Follow-up until death
- CT and/or MRI were evaluated by a blinded central reader

Rinke A, et al. *J Clin Oncol*. 2009;27:4656-4663.

Octreotide LAR 30 mg Significantly Increases Time to Tumor Progression

Octreotide LAR vs placebo *P*=0.000017
HR= 0.33 (95% CI: 0.19–0.55)



Based on Intention-to-treat analysis

1. Rinke A, et al. *J Clin Oncol*. 2009;27:4656-4663;
2. Arnold R, et al. *J Clin Oncol*. 2009;27(suppl):15s; Abstract 4508.

Study aim and design

GEP NET!!, **no lung NET**

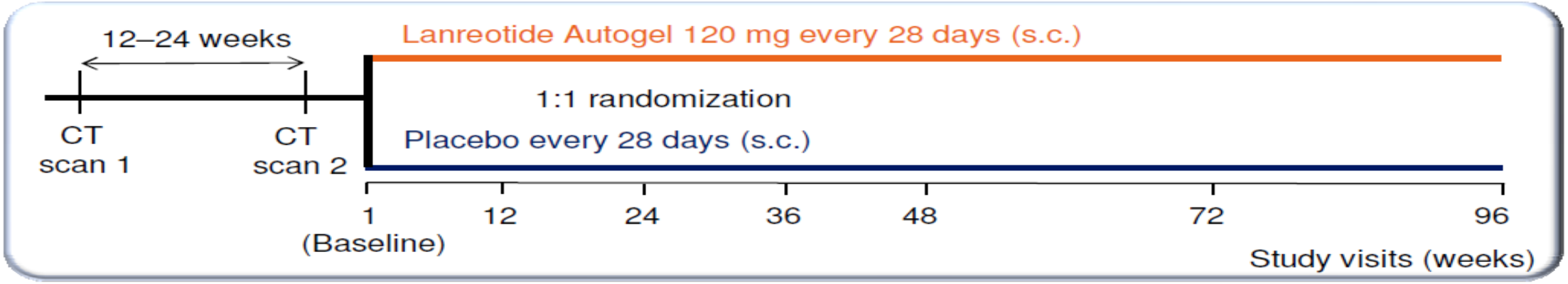
CLARINET
(Controlled study of Lanreotide Antiproliferative Response In NET)

Aim

- To compare effect of lanreotide Autogel 120 mg vs. placebo on PFS in well-/moderately differentiated non-functioning GEP-NETs

Design

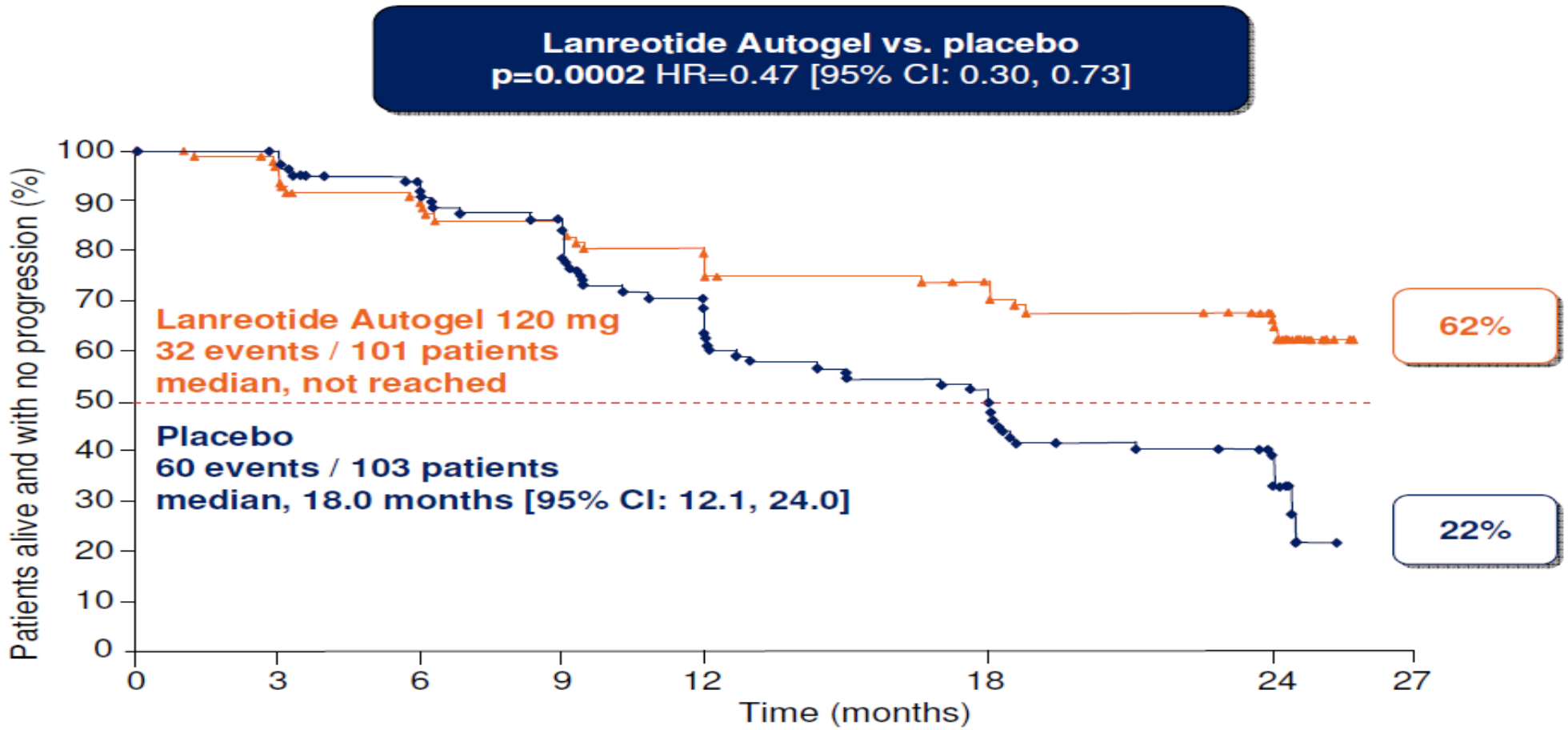
- International multicentre randomized double-blind placebo-controlled phase 3 study



ClinicalTrials.gov NCT00353496; EudraCT 2005-004904-35.

Presentation Presidential Session of the 17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Congress, 28 September 2013, abstract E17-7103 , Amsterdam- EJC, vol 49 (3), 2013

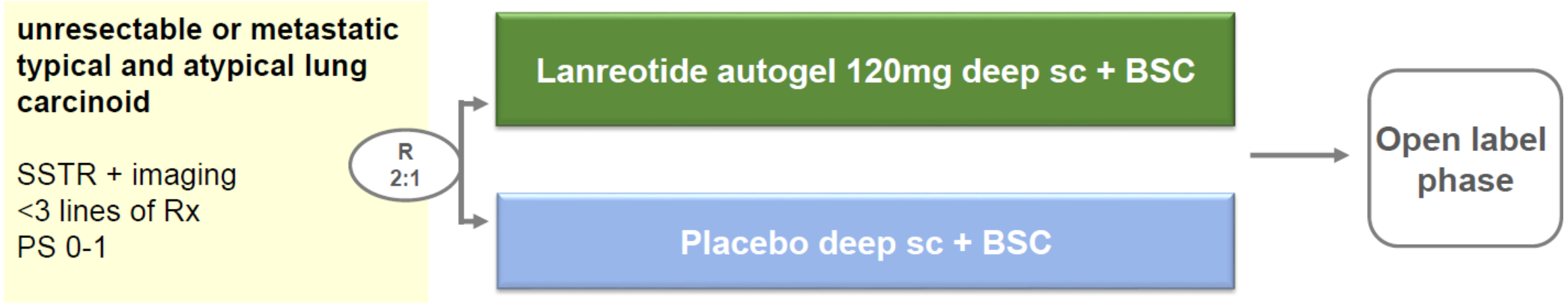
Primary endpoint: PFS (ITT population, N=204)



P-value derived from stratified log-rank test; HR derived from Cox proportional hazard model.
HR, hazard ratio; ITT, intention-to-treat.

Presentation Presidential Session of the 17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Congress, 28 September 2013, abstract E17-7103 , Amsterdam- EJC, vol 49 (3), 2013

Efficacy and Safety of Lanreotide Autogel/ Depot 120 mg vs. Placebo in Subjects With Lung Neuroendocrine Tumors (SPINET)



-Ipsen sponsored; Austria, Canada, Denmark, France, Germany, Italy, Netherlands, Poland, Spain, UK, USA

-Opened Feb 2016; planned for **216** patients; Recruitment stopped at **77** pts

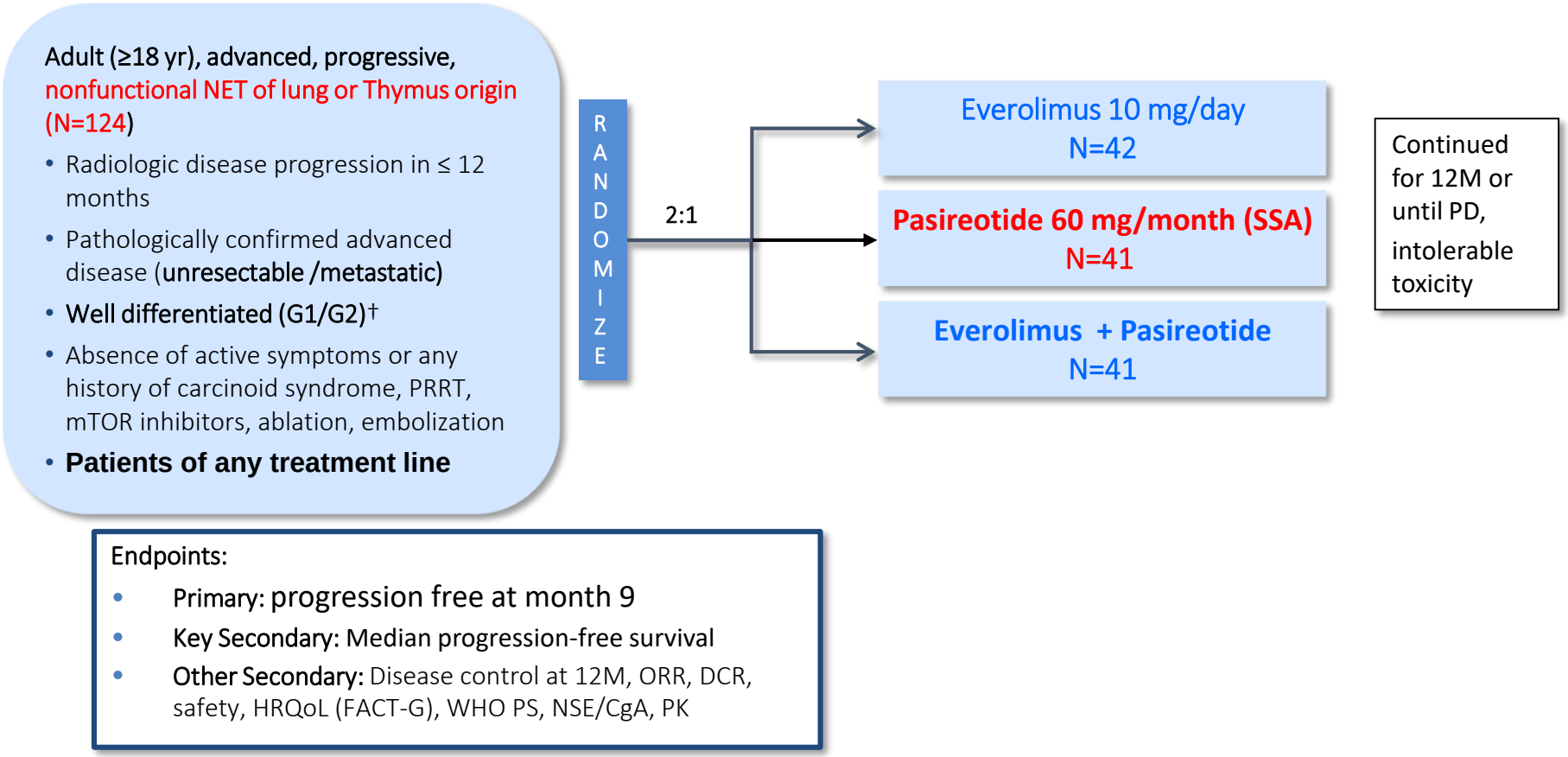
-Primary EP: PFS (RECIST 1.1); 2ndary: RR, OS, TTF, biochem

-final data Feb 2020

https://clinicaltrials.gov/show/NCT02683941

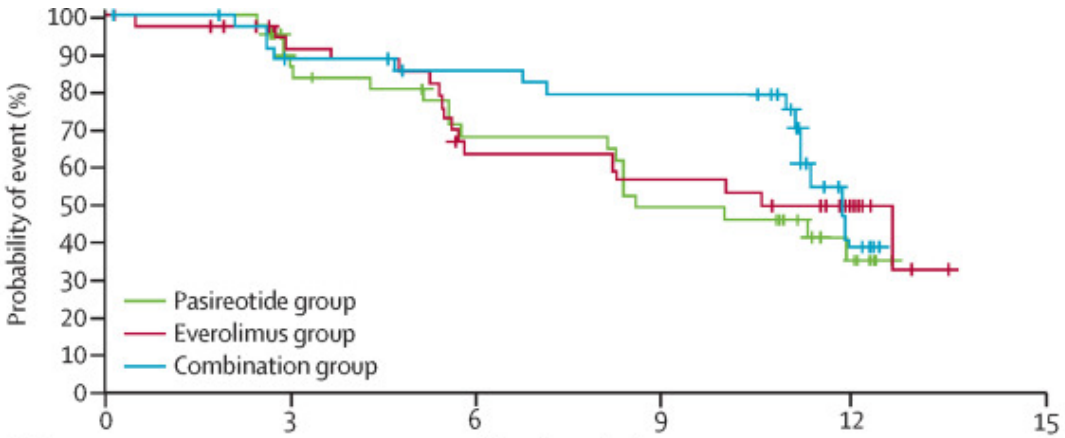
LUNA Design

Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus: an open-label, multicentre, randomised, phase 2 trial



1. Ferolla P et al.Lancet Oncol 2017; 18: 1652–64

PFS by investigator assessment



Number at risk (number censored)						
Pasireotide group	41 (0)	29 (6)	22 (8)	16 (8)	5 (16)	0 (21)
Everolimus group	42 (0)	30 (9)	19 (11)	17 (11)	7 (19)	0 (25)
Combination group	41 (0)	30 (7)	27 (9)	25 (9)	4 (23)	0 (27)

	Pasireotide group (n=41)	Everolimus group (n=42)	Combination group (n=41)
Overall lesion response at month 9			
Complete response	0 (0%, 0·0–8·6)	0 (0%, 0·0–8·4)	0 (0%, 0·0–8·6)
Partial response	1 (2·4%, 0·1–12·9)	1 (2·4%, 0·1–12·6)	1 (2·4%, 0·1–12·9)
Stable disease	14 (34·1%, 20·1–50·6)	13 (31·0%,17·6–47·1)	20 (48·8%, 32·9–64·9)
Progressive disease	7 (17·1%)	1 (2·4%)	0
Unknown	1 (2·4%)	2 (4·8%)	3 (7·3%)
Not assessed	18 (43·9%)	25 (59·5%)	17 (41·5%)
Discontinued before month 9	20 (48·8%)	24 (57·1%)	16 (39·0%)

Ferolla P, et al. Lancet Oncol 2017; 18: 1652–64

Treatment Choices

Tools	Evidence level
- SSA	SPINET (early terminated), LUNA (Can extrapolate to other SSA?)
- Everolimus	
- Chemotherapy	
- PRRT	

RADIANT-4, the Phase III Study of Afinitor® in Treating Advanced Neuroendocrine Tumors

Adult patients with **advanced, non-functional, well-differentiated (G1/G2) NET of lung or GI origin** (N = 302)

- Pathologically confirmed advanced disease
- Absence of active or any history of carcinoid syndrome
- Enrolled within 6 months from radiologic progression

2:1 randomization was stratified by:

- Tumor origin
- WHO PS
- Prior somatostatin analogue treatment

Everolimus 10 mg/day
N = 205

Treated until PD, start of new cancer therapy, intolerable AE, or consent withdrawal

Placebo
N = 97

Primary Endpoints:

- **PFS (central)**

Key Secondary Endpoints:

- **OS**

Secondary Endpoints:

ORR, DCR, HRQoL, WHO PS, PK, changes in chromogranin A and neuron-specific enolase levels and safety

RADIANT-4: The RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial; **PFS:** progress free survival; **OS:** overall survival; **ORR:** objective response rate; **DCR:** Disease control rate; **HRQoL:** health-related quality of life; **WHO PS:** WHO performance status; **PK:** pharmacokinetics

17.Yao JC, et al Lancet. 2016 Mar 5;387(10022):968-977.

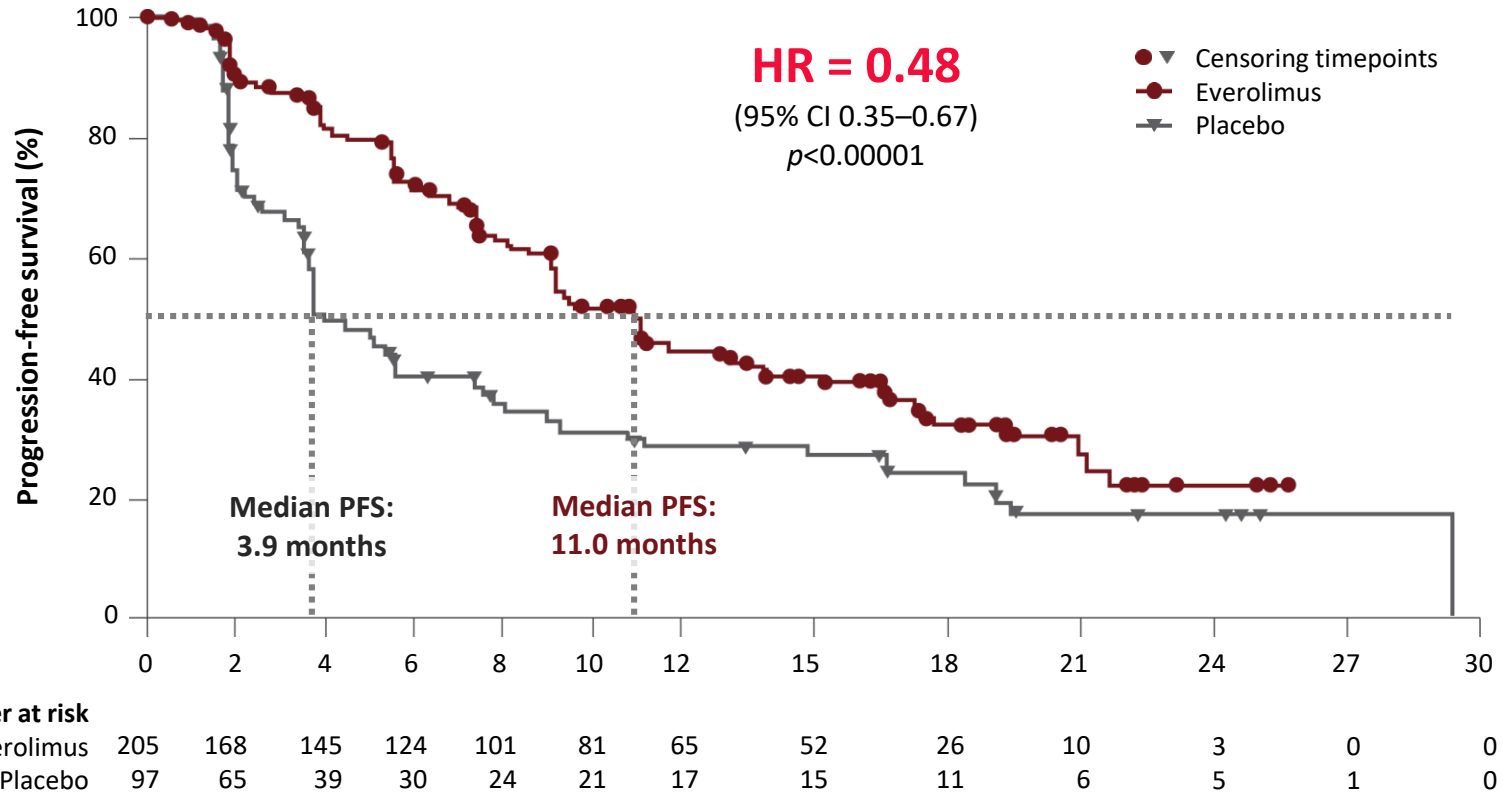
Baseline and Disease Characteristics

		Everolimus (n=205)	Placebo (n=97)
Age, years		65 (22-86)	60 (24-83)
Sex	Men	89 (43%)	53 (55%)
	Women	116 (57%)	44 (45%)
WHO performance status	0	149 (73%)	73 (75%)
	1	55 (27%)	24 (25%)
Primary tumor site	**Lung**	**63 (31%)**	**27 (28%)**
	Ileum	47 (23%)	24 (25%)
	Rectum	25 (12%)	15 (16%)
	Neuroendocrine tumor of unknown primary origin	23 (11%)	13 (13%)
	Jejunum	16 (8%)	6 (6%)
	Stomach	7 (3%)	4 (4%)
	Duodenum	8 (4%)	2 (2%)
	Colon	5 (2%)	3 (3%)
	Other	6 (3%)	2 (2%)
	Caecum	4 (2%)	1 (1%)
	Appendix	1 (1%)	0
Tumor grades	Grade 1	129 (63%)	65 (67%)
	Grade 2	75 (37%)	32 (33%)

17.Yao JC, et al Lancet. 2016 Mar 5;387(10022):968-977.

Progression Free Survival by Central Review

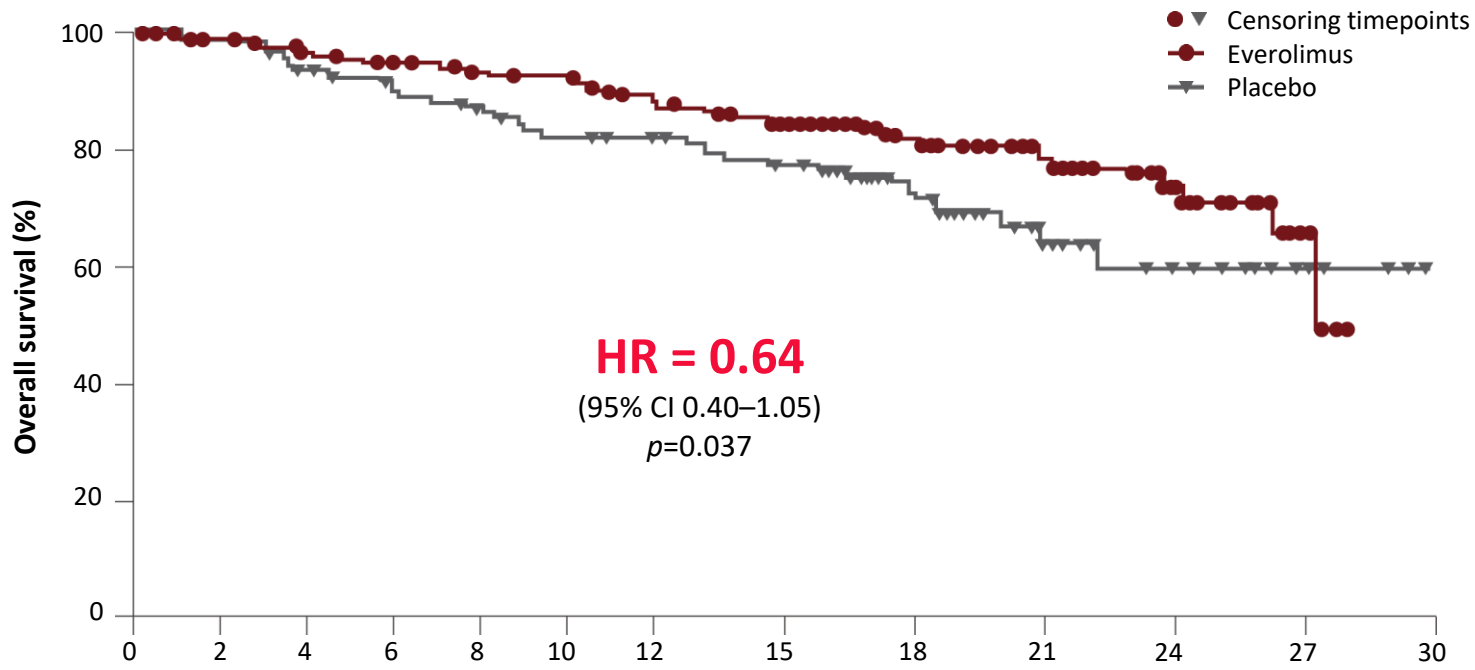
Afinitor reduced the relative risk of progression or death by 52%



17.Yao JC, et al Lancet. 2016 Mar 5;387(10022):968-977.

Overall Survival by Central View

Afinitor reduced the estimated risk of death by 36%



Number at risk													
Everolimus	205	195	184	179	172	170	158	143	100	59	31	5	0
Placebo	97	94	86	80	75	70	67	61	42	21	13	5	0

17.Yao JC, et al Lancet. 2016 Mar 5;387(10022):968-977.

Summary of RADIANT-4

Prolong Survival

- Afinitor demonstrated a statistically significant and clinically meaningful prolongation of PFS in patients with **well-differentiated, advanced, progressive, nonfunctional NET of lung or GI origin**

	Afinitor	Placebo	HR
Median PFS	**11.0** months	3.9 months	**0.48** $p < 0.00001$

- Afinitor also had a favorable effect on overall survival

	HR
Overall survival	**0.64** $p = 0.037$

Reduce Tumor Size

- More patients who received Afinitor experienced tumor shrinkage

	Afinitor	Placebo
Tumor Shrinkage	**64** %	26 %

Safety

- Safety profile of Afinitor was consistent with known side effects

Baseline and Disease Characteristics of Patients with Lung NETs (1)

Characteristics		Lung (N = 90)	
		Everolimus n=63	Placebo n=27
Age, median (range)		67 (34-86)	61 (24-80)
Male, n (%)		32 (51)	15 (56)
WHO performance status, n (%)	0	46 (73)	18 (67)
	1	16 (25)	9 (33)
Race, n (%)	Caucasian	53 (84)	24 (89)
	Asian	7 (11)	2 (7)
	Others	3 (5)	1 (4)
Tumor grade, n (%)	Grade 1	26 (41)	13 (48)
	Grade 2	26 (57)	14 (52)
Proliferation index by primary tumor, n (%)	< 2 mitoses/ 10 HPF	2 (3)	1 (4)
	> 2-10 mitoses/ 10 HPF	7 (11)	7 (26)
	≤ 2% Ki-67 index	6 (9)	2 (7)
	3-20 % Ki-67 index	37 (59)	15 (56)
	> 20% Ki-67 index	3 (5)	0
	Not done	8 (13)	2 (7)

18.Fazio N, et al. Presented at ENETS, March 9 to 11, 2016, Barcelona, Spain.

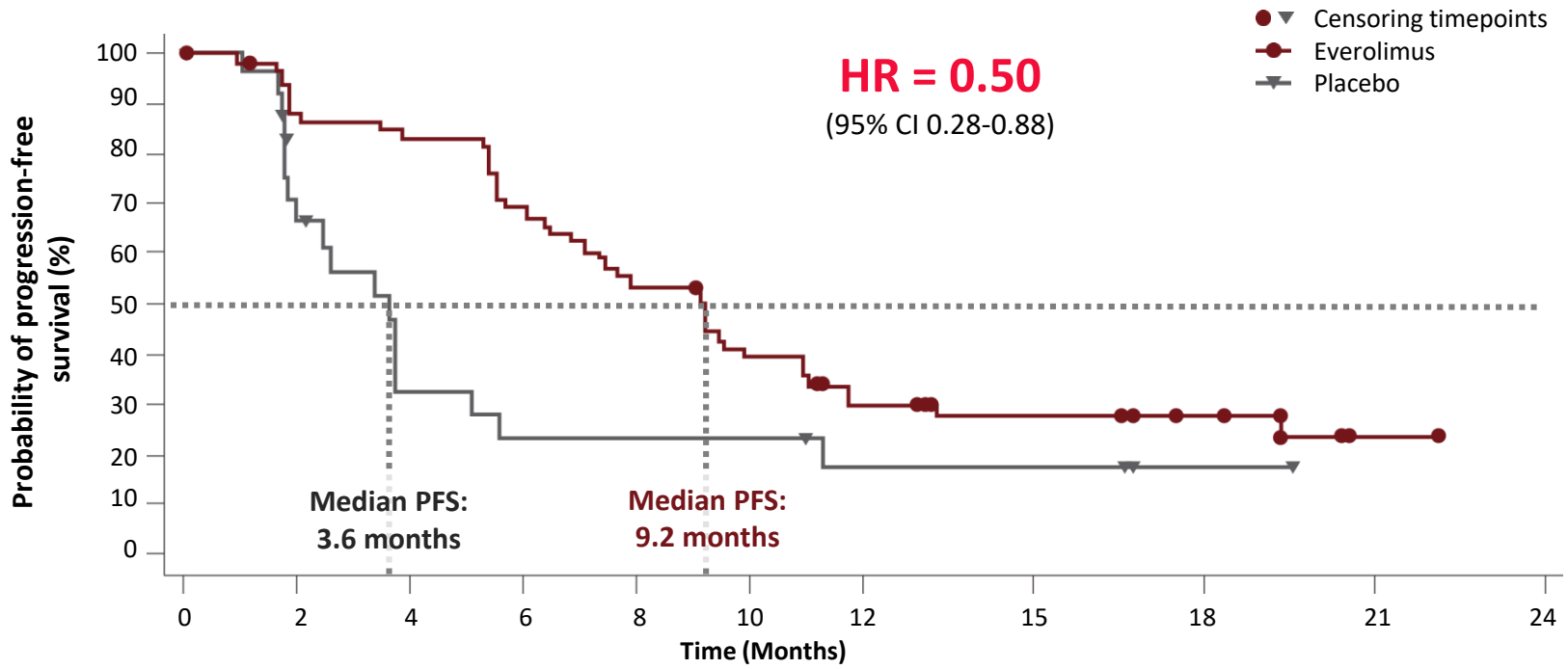
Baseline and Disease Characteristics of Patients with Lung NETs (2)

Characteristics		Lung (N = 90)	
		Everolimus n=63	Placebo n=27
Median time from initial diagnosis to randomization months (range)		25.8 (2.2-258.4)	37.5 (3.7-303.3)
Metastatic extent of disease, n (%)	Hepatic (with or without other organ) involvement	43 (68)	20 (74)
	Extra-hepatic	20 (32)	7 (26)
Prior treatments, n (%)	Surgery	33 (52)	18 (67)
	Somatostatin analogs	27 (43)	11 (41)
	Chemotherapy	25 (40)	13 (48)
	Radiotherapy including peptide receptor radionuclide therapy	25 (40)	13 (48)
Liver tumor burden	None	14 (22)	5 (18)
	> 0 to 10%	33 (52)	17 (63)
	> 10% to 25%	10 (16)	2 (7)
	> 25%	6 (10)	3 (11)

18.Fazio N, et al. Presented at ENETS, March 9 to 11, 2016, Barcelona, Spain.

Progression Free Survival by Central Review

Afinitor reduced the relative risk of progression or death by 50%

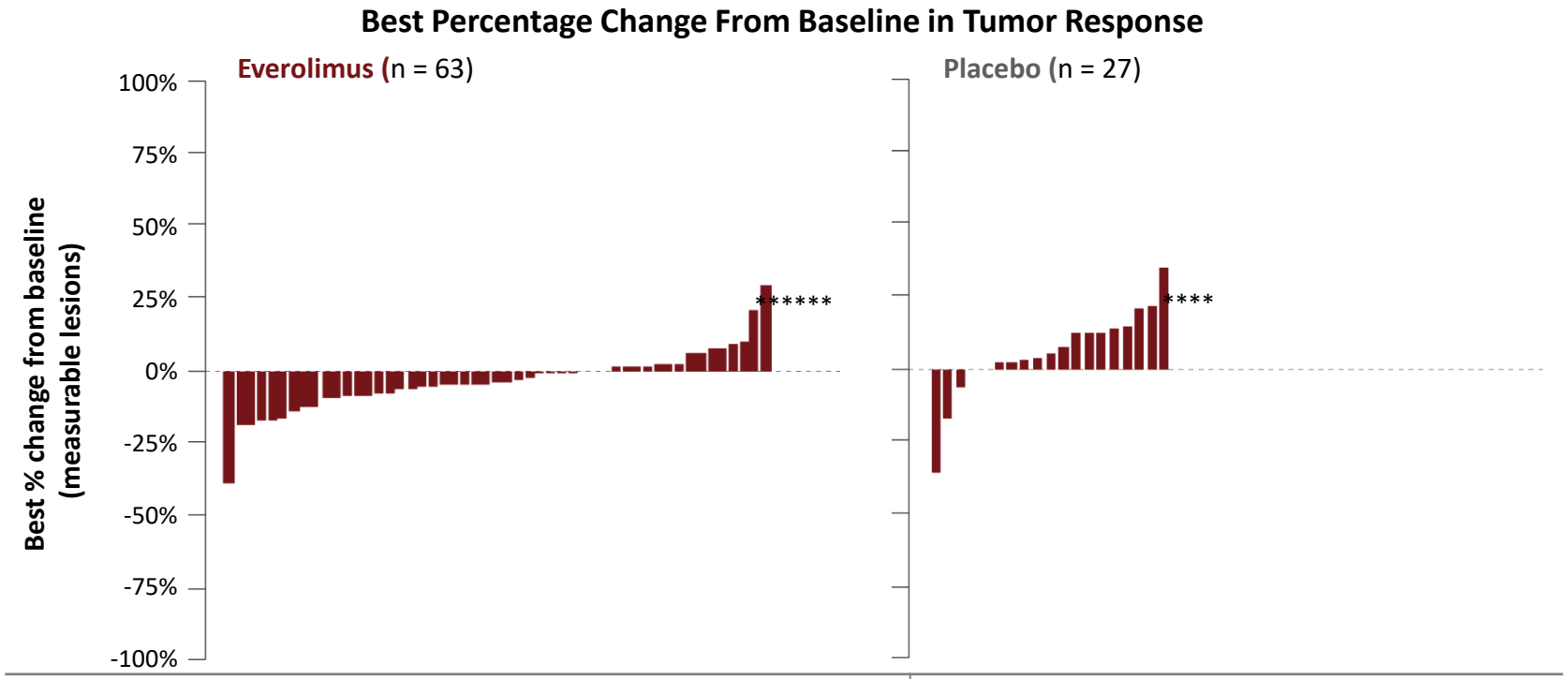


No.of patients still at risk

Everolimus	63	51	48	40	31	22	16	13	8	1	0
Placebo	27	15	7	5	5	5	3	3	1	0	0

18.Fazio N, et al. Presented at ENETS, March 9 to 11, 2016, Barcelona, Spain.

More Patients who Received Afinitor Experienced Tumor Shrinkage



	Everolimus, n (%)	Placebo, n (%)
Decrease in size of target lesion from baseline	57.9	13.0
Increase in size of target lesion from baseline	31.6	69.6
Percentage change in size of target lesion contradicted by overall lesion response = progressive disease (dented by*)	10.5	17.4

18.Fazio N, et al. Presented at ENETS, March 9 to 11, 2016, Barcelona, Spain.

Similar Safety Profile in Patients with Lung NETs

Lung	Everolimus n=62*		Placebo n=27	
Preferred Term, n (%)	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Stomatitis†	38 (61)	7 (11)	7 (26)	0
Rash	22 (35)	0	1 (4)	0
Fatigue	20 (32)	2 (3)	5 (22)	0
Peripheral edema	17 (27)	2 (3)	0	0
Diarrhea	16 (26)	3 (5)	2 (7)	0
Infections‡	14 (23)	5 (8)	1 (4)	0
Asthenia	14 (23)	1 (2)	0	0
Anemia	13 (21)	2 (3)	1 (4)	0
Decreased appetite	13 (21)	0	2 (7)	0
Nausea	12 (19)	2 (3)	3 (11)	0
Pyrexia	12 (19)	2 (3)	1 (4)	0
Hyperglycemia	11 (18)	6 (10)	2 (7)	0
Dyspnea	9 (14)	1 (2)	3 (11)	1 (4)
Non-infectious pneumonitis	8 (13)	1 (2)	1 (4)	0
Dysgeusia	8 (13)	0	1 (4)	0
Cough	8 (13)	0	1 (4)	0
Pruritus	7 (11)	1 (2)	0	0
Dry mouth	7 (11)	0	0	0
Weight decreased	5 (8)	1 (2)	3 (11)	0

*In everolimus arm, 1 patient withdraw the consent. †Includes stomatitis, aphthous stomatitis, mouth ulceration, and glossitis. ‡Includes all infections.

18.Fazio N, et al. Presented at ENETS, March 9 to 11, 2016, Barcelona, Spain.

Summary of RADIANT-4 in Lung NETs

Prolong Survival

- Afinitor was associated with clinically meaningful improvement of PFS in patients with **advanced, progressive, well-differentiated, non-functional lung NET**

	Afinitor	Placebo	HR
Median PFS	**9.2** months	3.6 months	**0.50** (95% CI 0.28-0.88)

Reduce Tumor Size

- More patients who received Afinitor experienced tumor shrinkage

	Afinitor	Placebo
Tumor Shrinkage	**57.9** %	13.0%

Well Tolerated

- Afinitor was well tolerated with no new safety signals

「藥品給付規定」修訂對照表

第9節 抗癌瘤藥物 Antineoplastics drugs

（自108年10月1日生效）

使用於無法切除、局部晚期或轉移之胃腸道或**肺部來源之非功能性神經內分泌腫瘤**成人病患，需同時符合下列條件：（108/10/1）（1)腫瘤分化程度為良好者。（2)為進展性腫瘤，即過去12個月影像檢查為持續惡化者（RECIST定義為疾病惡化者）。(3)**不可合併使用化學藥物或其他標靶藥物。**

Treatment Choices

Tools	Evidence level
- SSA	SPINET (early terminated), LUNA (Can extrapolate to other SSA?)
- Everolimus	RADIANT4
- Chemotherapy	
- PRRT	

Chemotherapy

Study	C/T regimen	n	ORR	PFS
Forde, et al	Etoposide+ cisplatin	17	23.5%	7 mon
Faure, et al	Folfox	31 (lung n=8)	29%	14.1 mon
Spada, et al	Oxaliplatin based (G+O, Xeloda+O, Folfox)	78 (lung=19)	26%	8 mon
Al-Toubah T et al.	Temozolamide+ Xeloda	20	30%	13 mon

- Very little data, no RCT, limited numbers…
- The best regimen ?

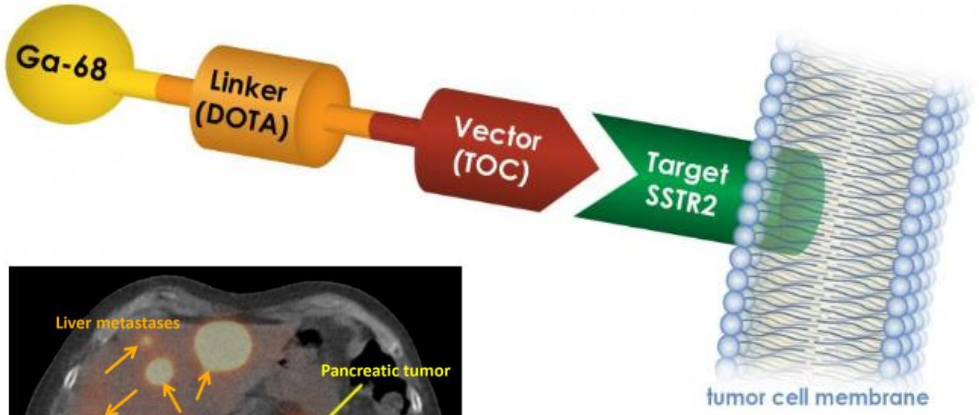
Forde, et al. J Thorac Oncol. 2014 Mar;9(3):414-8.
Faure M, etal. Mol Clin Oncol. 2017 Jan;6(1):44-48.
Spada F, et al. Neuroendocrinology. 2016;103(6):806-14.
Al-Toubah T, et al. Oncologist. 2019

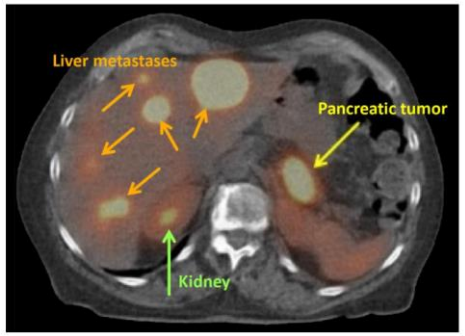
Treatment Choices

Tools	Evidence level
- SSA	SPINET (early terminated), LUNA (Can extrapolate to other SSA?)
- Everolimus	RADIANT4
- Chemotherapy	Case series
- PRRT	

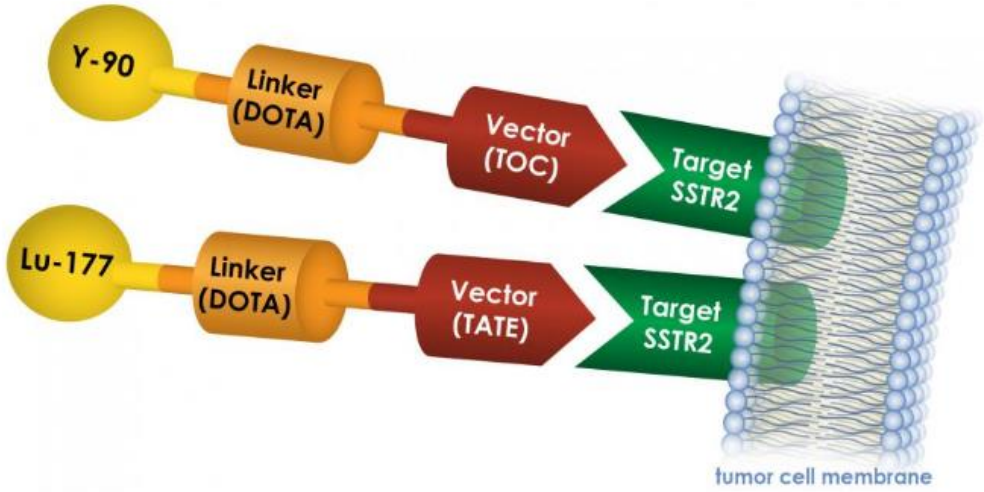
Peptide Receptor Radionuclide Therapy (PRRT)

- **Theranostics: A Combination of Diagnosis and Therapy**
- Targeted delivery of **cytotoxic radioactivity** to tumors that strongly express **somatostatin receptors (SSTRs)**
- **Only One phase 3 study (NETTLER study) demonstrated efficacy in midgut NET.**





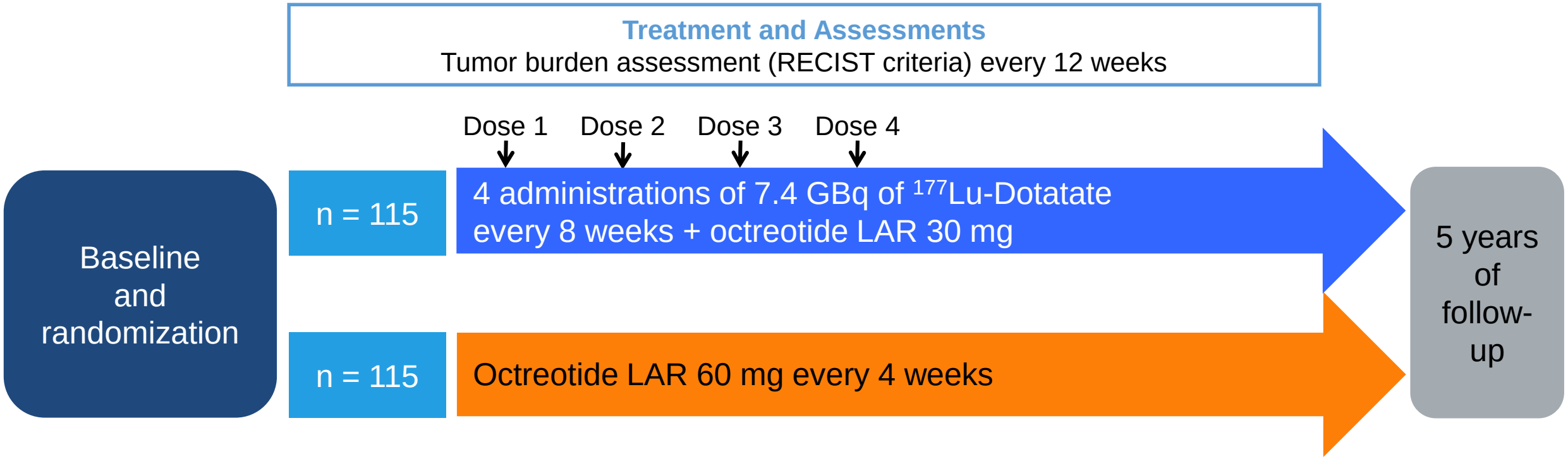
Ga68 DOTA-TOC scan.



https://uihc.org/health-topics/what-theranostics

Midgut NET: NETTER 1—Phase 3 Study of ^{177}Lu-Dotatate + Octreotide vs. High-Dose Octreotide

MidGut !!, **no lung NET**



RECIST, Response Evaluation Criteria in Solid Tumors.

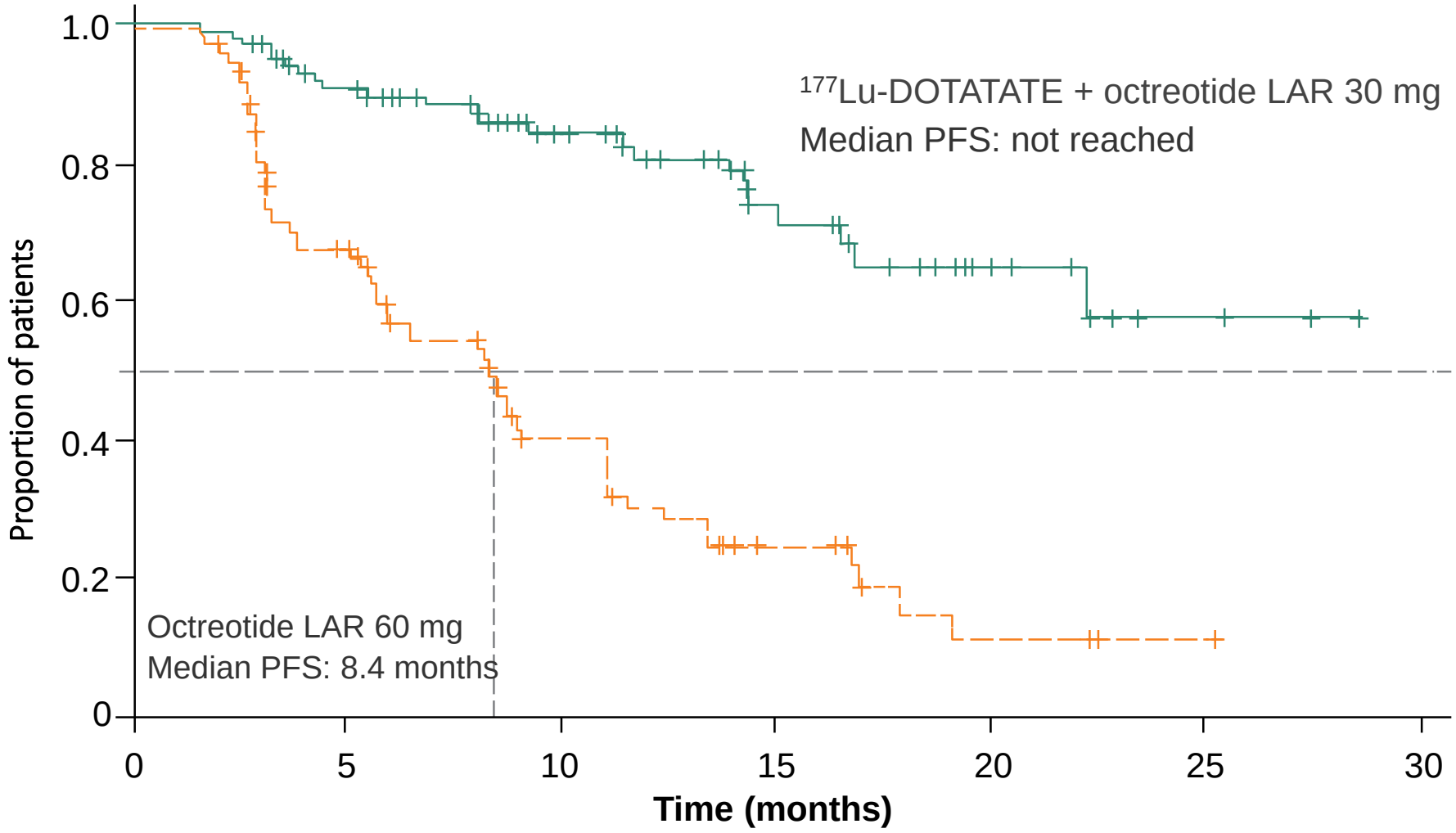
Strosberg J et al. Presented at: European Cancer Congress 2015; September 25-29, 2015; Vienna, Austria.

NETTER-1: PFS

N = 229 (ITT)

Number of events: 90
- ^{177}Lu-DOTATATE: 23
- Octreotide 60 mg LAR: 67

HR 0.209; 95% CI: 0.129, 0.338
***P* < 0.0001**



ITT, intention to treat.

Strosberg J et al. Presented at: European Cancer Congress 2015; September 25-29, 2015; Vienna, Austria.

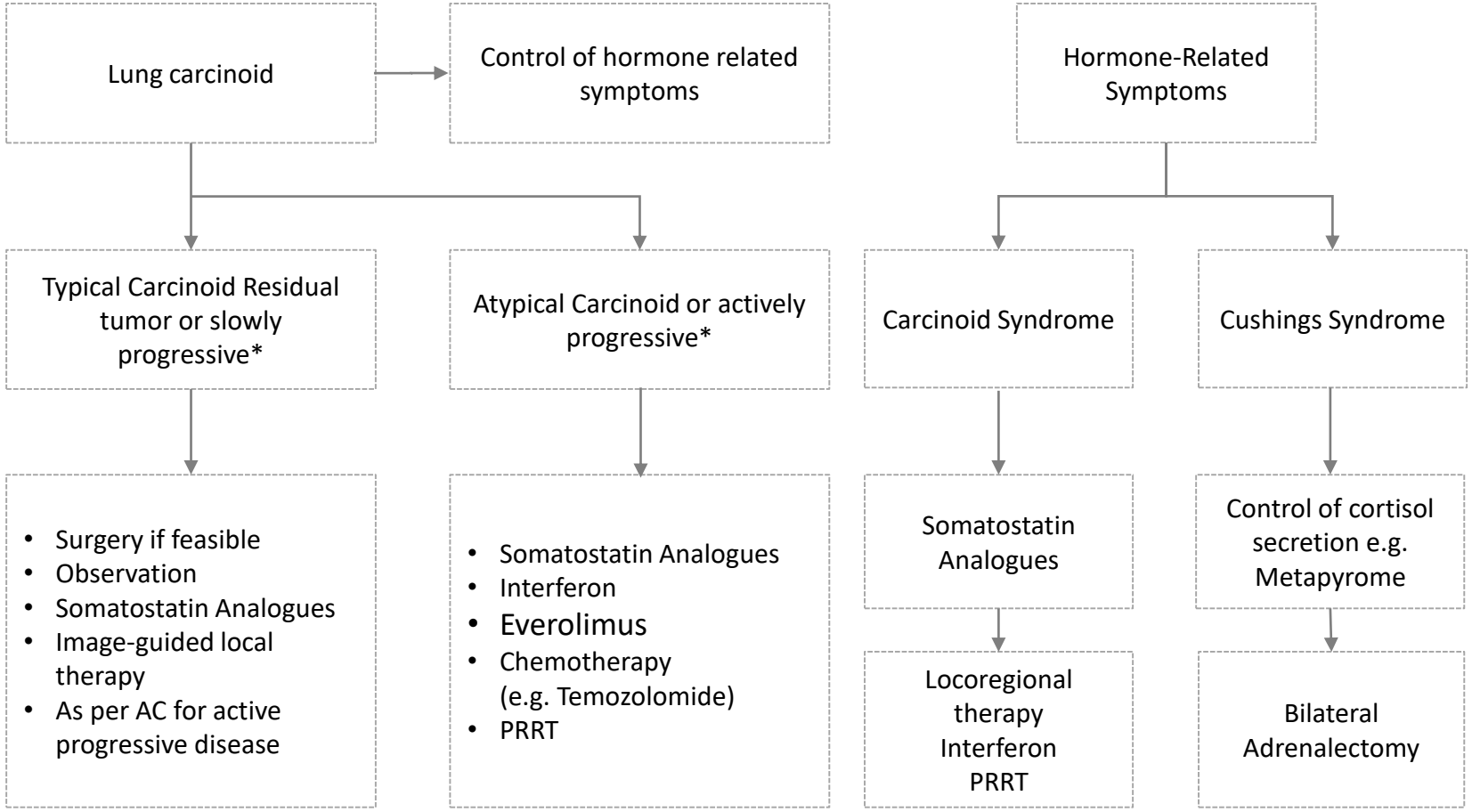
PRRT series n LNET		n other NET	Isotope	Major findings
Mariniello A, 2016	114	-	^{90}Y; ^{177}Lu; ^{90}Y + ^{177}Lu	PR/minor response in 26.5%, associated with longer OS, PFS
Ianniello A, 2016	34	-	Prospective sequential pts with PD; ^{177}Lu	DCR for TC = 80%: CR=6%, PR=27%, SD=47%) mPFS = 20m (95%CI 12 – 27) FDG –PET may predict non responders; TTF-1 prognostic
Lim, 2019	35	-	^{177}Lu	mOS= 33m (range 2-91)
Brabander T, 2017 (Erasmus)				PR= 7, SD= 7, PD =6, 3= N/E
Imnof, 2011				th CR= 0
Demirci E, 2019				
Koffas, 2016				6m (abstract only)
Baum, 2018				T = 40m
Villard, 2012				0 y; HR: 0.64; p=0.006
Parghane 2017 (India)				
Horsch D, 2016 (German registry)				val data for LNET only)
Bodei L, 2016				
Mandair D, 2017				
Sharma, 2018	18	135 all sites well-diff NET	^{90}Y (83%), ^{177}Lu	mTTP all = 23.9m mTTP LNET = 18.6m
van Essen, 2007	9	5 gastric, 2 thymic	^{177}Lu	mTTP = 31m
Khan S, 2011	?	265 GEP + LNET	^{177}Lu	Improved QOL, PS
Sabet, 2017	22		^{177}Lu	Med PFS = 27m PR= 6, SD= 9, PD= 7
Garske-Roman, 2018	6	200 all sites, mainly GEP	^{177}Lu	Med PFS for lung = 18m
Gabriel, 2019	4	34 GEP, 2 UP, 2 non-NET	^{90}Y	12 year f/u (retrospective), mOS= 79m, 32% of all pts still alive

- Sounds rationale !! (Theranostics)
- Case series only; retrospective; highly selected
- No randomized phase 3 study

Treatment Choices

Tools	Evidence level
- SSA	SPINET (early terminated), LUNA (Can extrapolate to other SSA?)
- Everolimus	RADIANT4
- Chemotherapy	Cases Series
- PRRT	Cases Series (NETTLER study only limited in midgut NET)

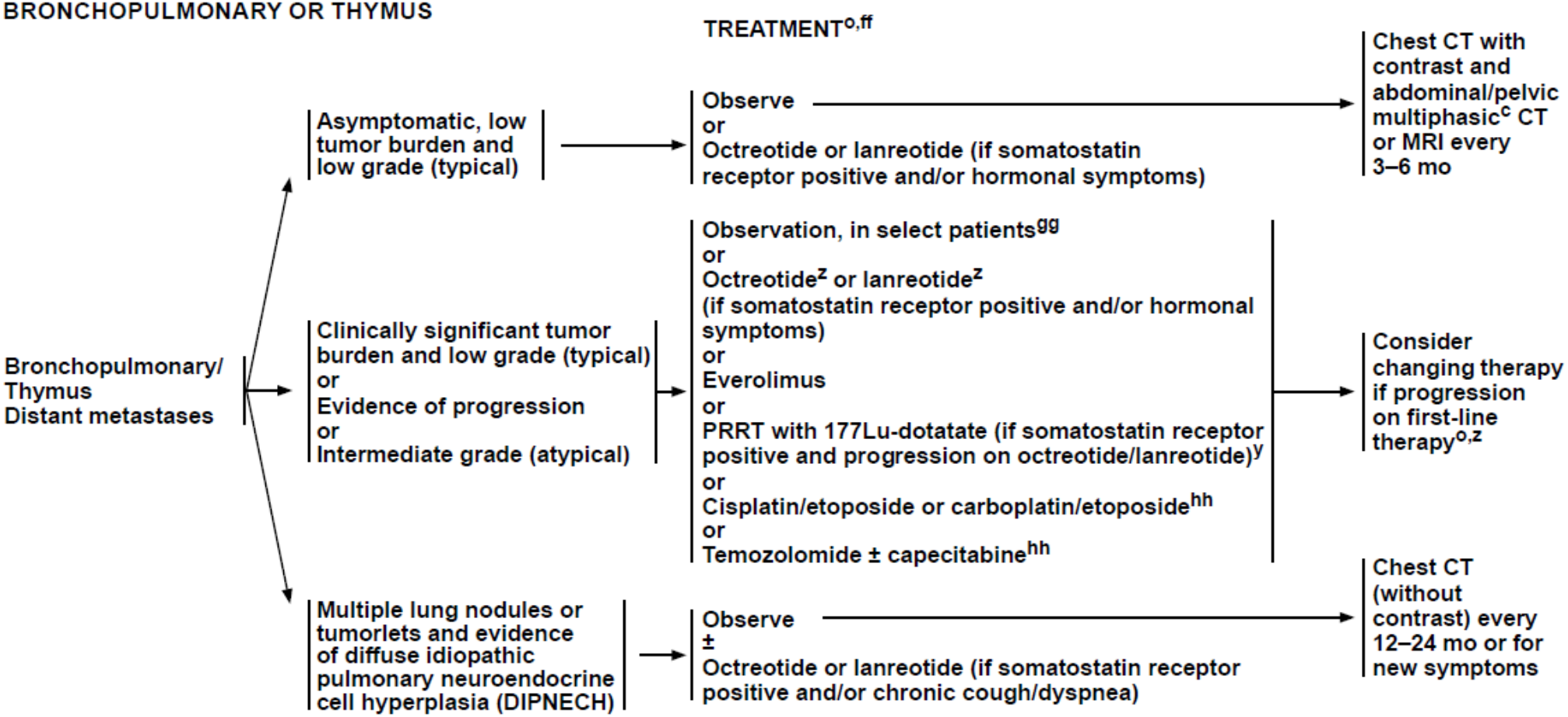
ENETS Consensus & Recommendations for Pulmonary Carcinoids (2015)



*Progression is defined according to RECIST criteria. **PRRT:** peptide radiolabeled receptor radiotherapy.

Caplin ME, et al. Ann Oncol. 2015 Aug;26(8):1604-20.

MANAGEMENT OF DISTANT METASTASES[o] BRONCHOPULMONARY OR THYMUS

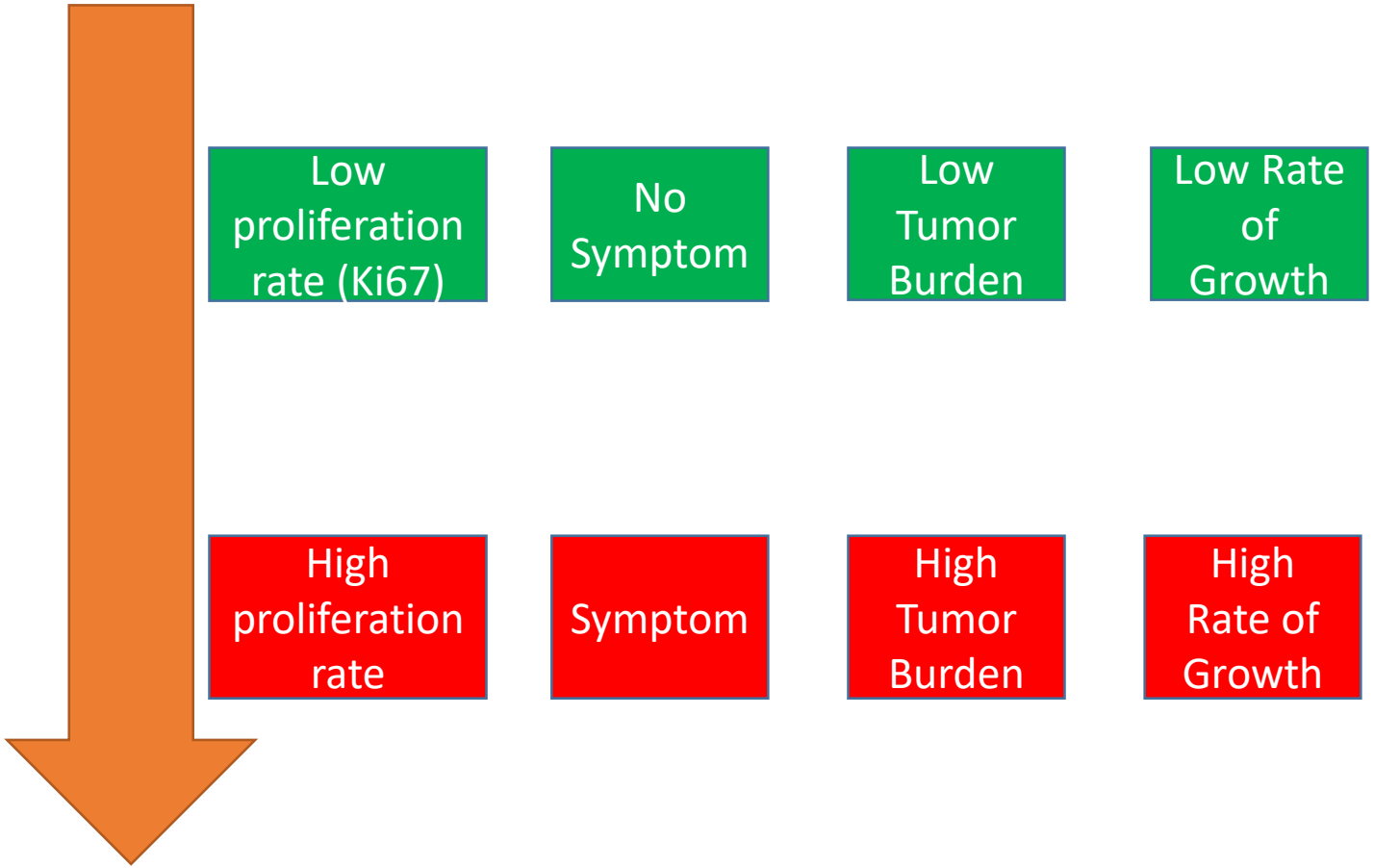


[c]Multiphasic imaging studies are performed with IV contrast.
[o]See Principles of Systemic Anti-Tumor Therapy (NE-D).
[y]See Principles of Peptide Receptor Radionuclide Therapy (PRRT) with 177Lu-dotatate (NE-E).
[z]If disease progression, treatment with octreotide or lanreotide should be discontinued for non-functional tumors and continued in patients with functional tumors; those regimens may be used in combination with any of the subsequent options. For details on the administration of octreotide or lanreotide with 177Lu-dotatate, see NE-E.

[ff]Neuroendocrine tumors are highly heterogeneous and all elements need to be considered (eg, burden of disease, symptoms, histopathology, rate of growth) when determining the best course of treatment.
[gg]Observation can be considered if asymptomatic or for tumors on the lower end of the spectrum.
[hh] Can be considered for intermediate-grade/atypical tumors with Ki-67 proliferative index and mitotic index in the higher end of the defined spectrum.

How I treat NET patients

Tools
- SSA
- Everolimus
- Chemotherapy
- PRRT



Take Home Message

1. **Lung NET WHO 2015 categories need urgent refinement**
2. **Lung NET/NEC are more heterogenous than expected**
3. **Biology is King. Patient selection is Queen.**
4. **RADIANT4 study demonstrated Afinitor prolongation of PFS in patients with well-differentiated, advanced, progressive, nonfunctional NET of lung (Most Evidence of any therapy).**
5. **We need more reliable clinical trials in pulmonary NETs.**