MEDICAL ONCOLOGY- NEUROENDOCRINE TUMOURS IN THE LUNG

DR. SUNIL R CHOPADE

CONSULTANT MEDICAL ONCOLOGIST ,MUMBAI

LUNG NET

Heterogenous malignancy originating in amine precursor uptake and decarboxylation **(APUD) neuroendocrine cells from Kulchitsky cells (argentaffin cells)** .

The first description of carcinoid tumors belongs to **Siegfried Oberndorfer** who considered these tumors to have a slow growth, being cancer-like tumors.

TYPICAL CARCINOID (TC) : is a tumor with carcinoid histology, with <2 mitosis/2 mm^2 [10 high-power fields (HPF)] lack of necrosis and a size of 0.5 cm or greater.

ATYPICAL CARCINOID (AC) is a tumor with carcinoid morphology, with 2-10 mitosis/2 mm^2 (10 HPF) or necrosis (spotted).

LCNEC is a tumor of neuroendocrine morphology (organoid clusters, palisades, trabecular cells) with a high mitotic rate of >11/2 mm^2 (10 HPF), with a median of 70/2 mm^2 and necrosis (often large areas).

Small cell lung carcinoma (SCLC) presents with small cells, scant cytoplasm and fine, granular chromatin, absent nucleoli and a high mitotic rate (>11/2 mm^2 10 HPF; and median of 80/2 mm^2 10 HPF) and frequently with large zones of necrosis.

Variable	Typical carcinoid	Atypical carcinoid	Large-cell neuroendocrine carcinoma	Small-cell carcinoma
Neuroendocrine morphology	yes (organoid)	yes (organoid)	yes (organoid)	yes (nuclear features)
Cytological criteria	no	no	yes	yes
Mitoses/2 mm^2	1	2-10	≥ 11	≥ 11
Necrosis	no	punctate	extensive	extensive
Use of immunohistochemistry	recommended	recommended	defining	recommended
Combined variant	no	no	yes	yes
Chromogranin A and synaptophysin	positive	positive	positive 80-90%	positive 80-90%

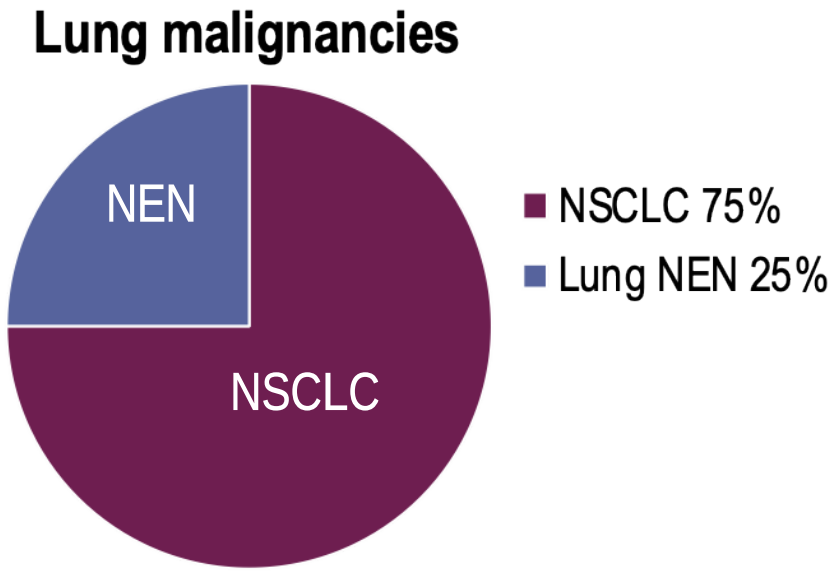
LUNG NET DIAGNOSIS

First step ❾ separating non small cell lung cancer (NSCLC) from lung neuroendocrine neoplasms (NEN)

NSCLC

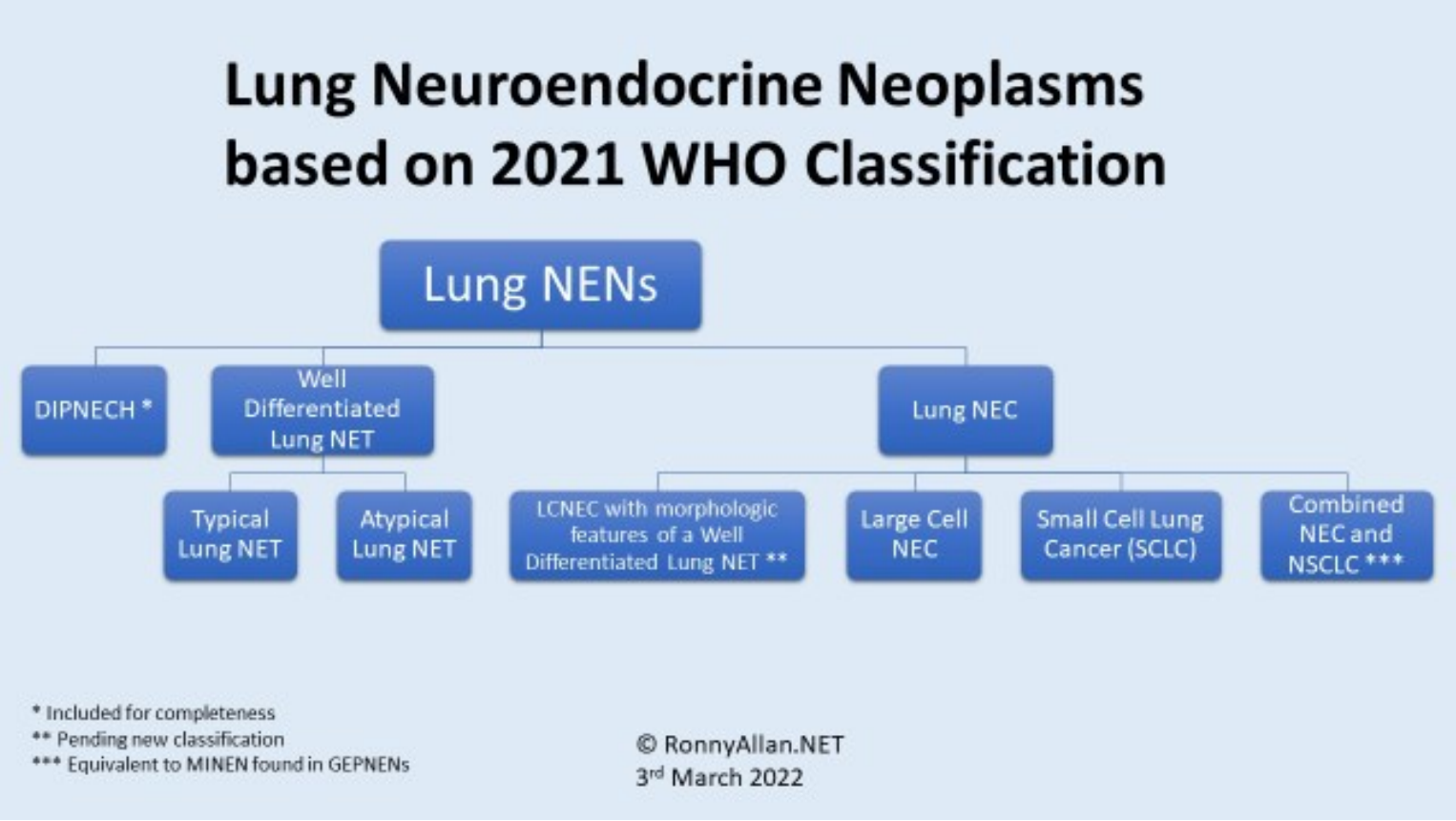
Vs.

Lung NEN



Rekhtman N. Arch Pathol Lab Med. 2010

WHO 2015 CLASSIFICATION OF LUNG/THYMUS NEUROENDOCRINE NEOPLASMS



- Mitosis and necrosis are necessary for classifying
- Ki-67 has no role to classify, but it has prognostic meaning

Travis WD, *et al.*, editors. WHO classification of tumours of the lung, pleura, thymus and heart. Lyon: IARC Press; 2019

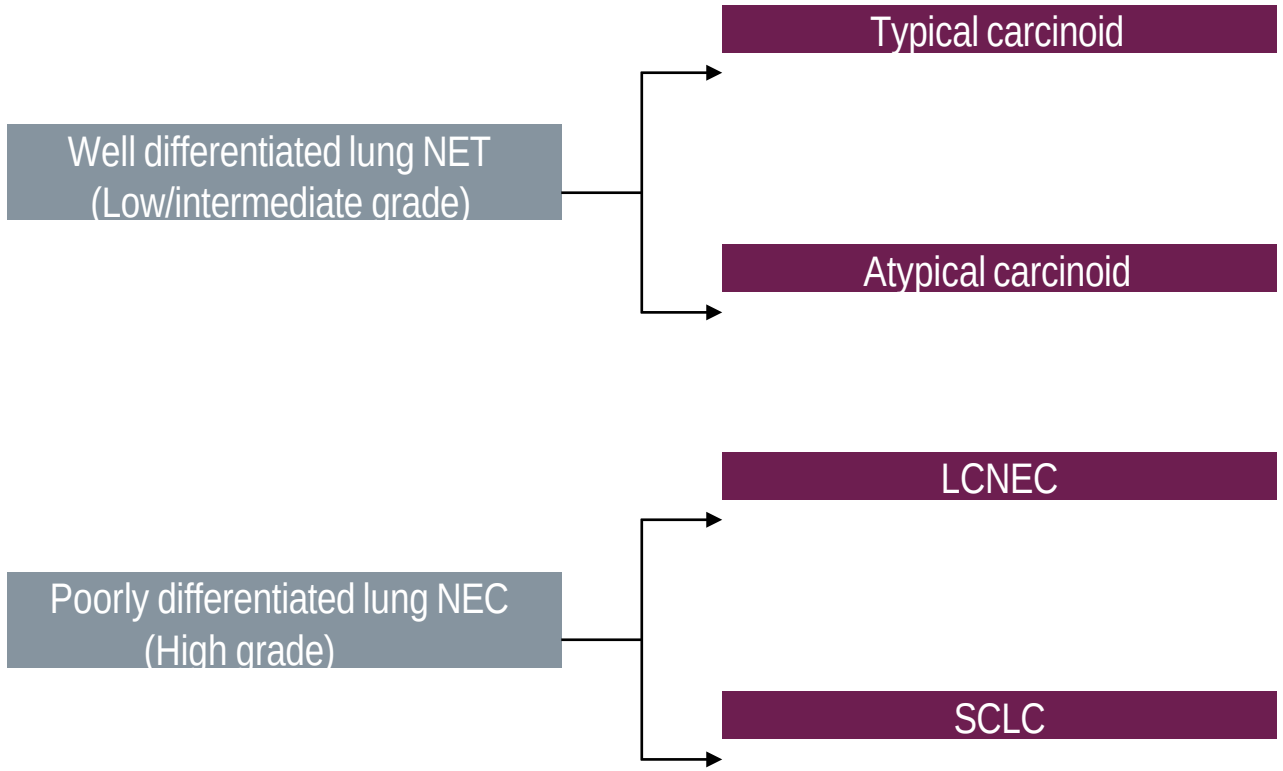
PATHOLOGISTS' PROPOSAL TO ADD KI-67 TO MITOSIS AND NECROSIS

Grade	Variable		
	Mitotic count (10 HPF)	Ki-67 (%)	Necrosis (%)
G1	2	< 4	No
G2	>2–47	4–< 25	<10
G3	>47	≥25	>10

All TC (n=105) were reclassified as G1;
of AC (n=75), 29 were G1, 45 were G2, and 1 was G3

Rindi G, *et al.* Endocr Relat Cancer. 2013;21:1-16.

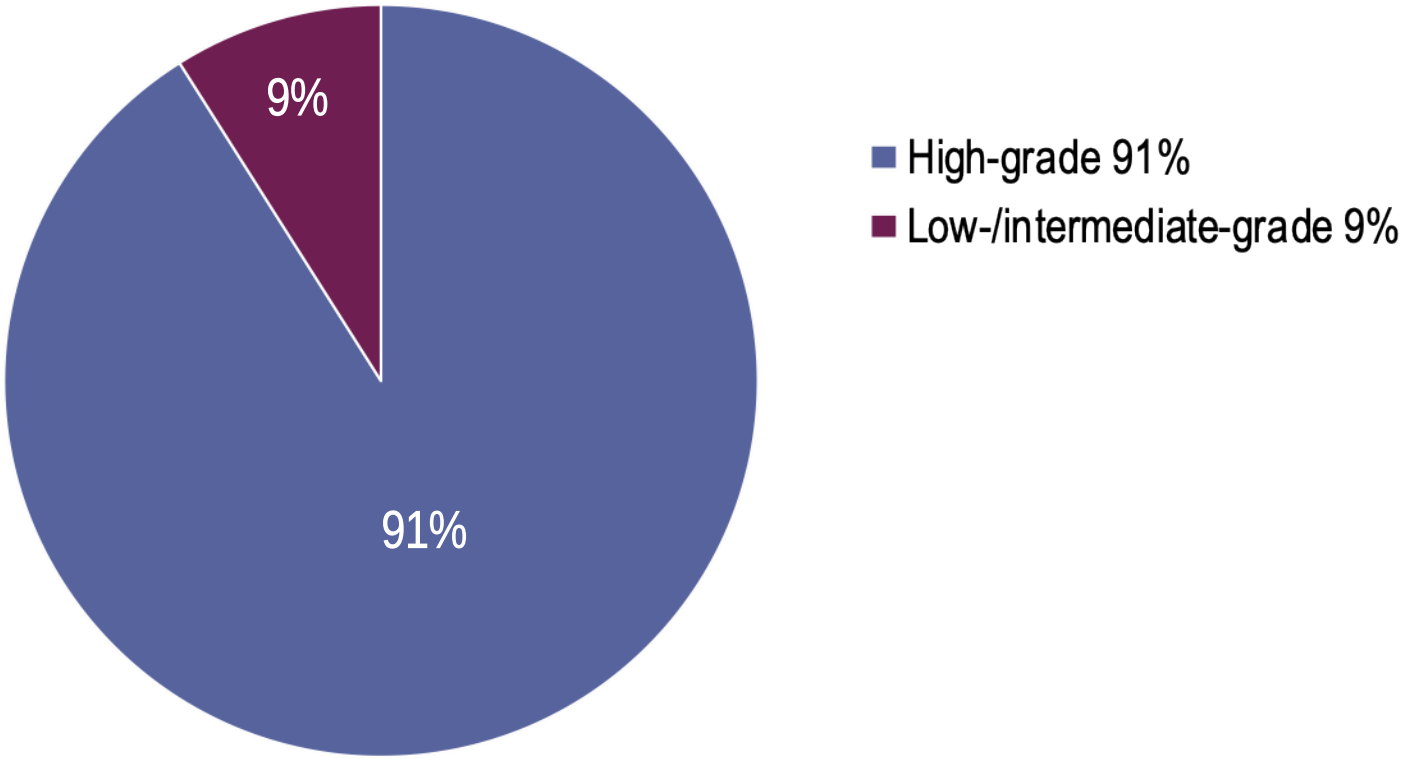
LUNG NEN: PATHOLOGICAL CLASSIFICATION AND TERMINOLOGY



TC: typical carcinoid; AC: atypical carcinoid; LCNEC: large cell neuroendocrine carcinoma; SCLC: small cell lung cancer; NET: neuroendocrine tumour; NEC: neuroendocrine carcinoma; WD: well differentiated; PD: poorly differentiated.

Fazio N, J Thoracic Dis 2017, 9 (Suppl 15): 1501-1510.

LUNG NEN

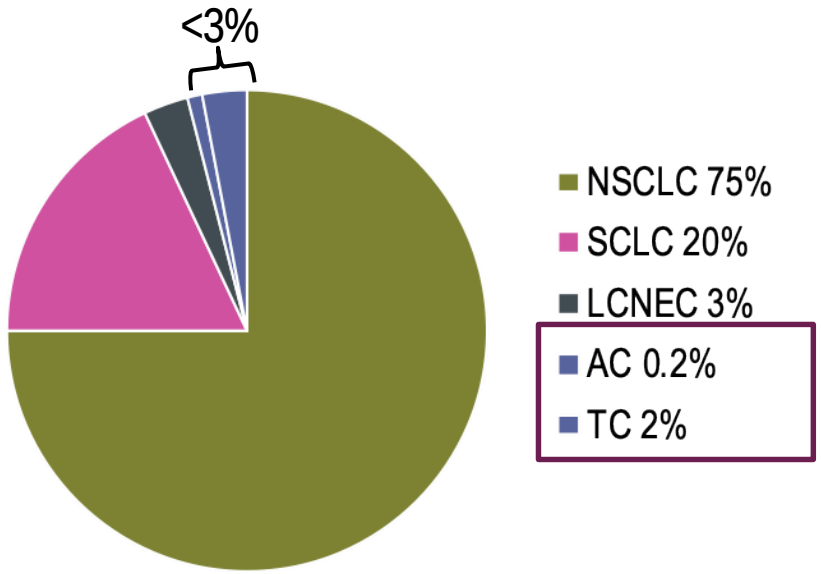


Rekhtman N. Arch Pathol Lab Med. 2010

LUNG NET EPIDEMIOLOGY

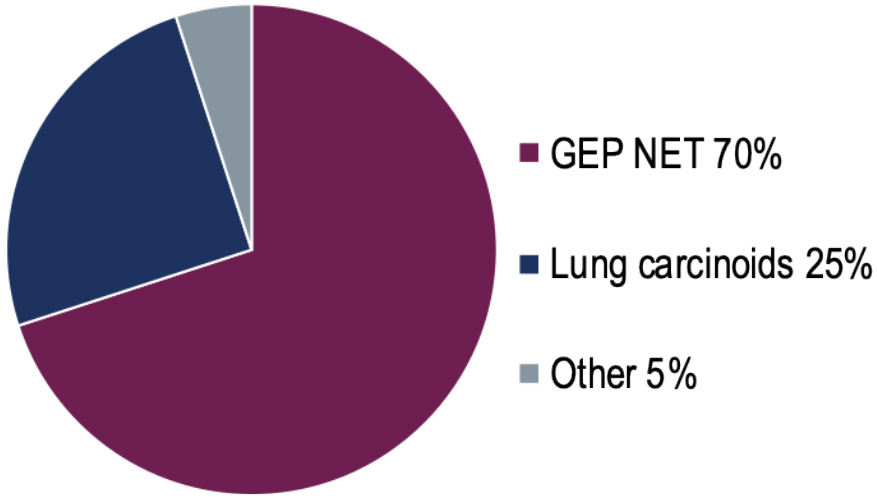
Two different perspectives <3% of all lung cancers and 25% of all NET

Lung cancers[1]



Thoracic medical oncologist's clinical practice

Neuroendocrine tumours[2]



NEN-dedicated medical oncologist's clinical practice

Fazio N, J Thoracic Dis 2017, 9 (Suppl 15): 1501-1510
1. Rekhtman N. Arch Pathol Lab Med. 2010;134:1628-1638;
2. Modlin IM, *et al.* Cancer. 2003;97:934-959.

LUNG NET:

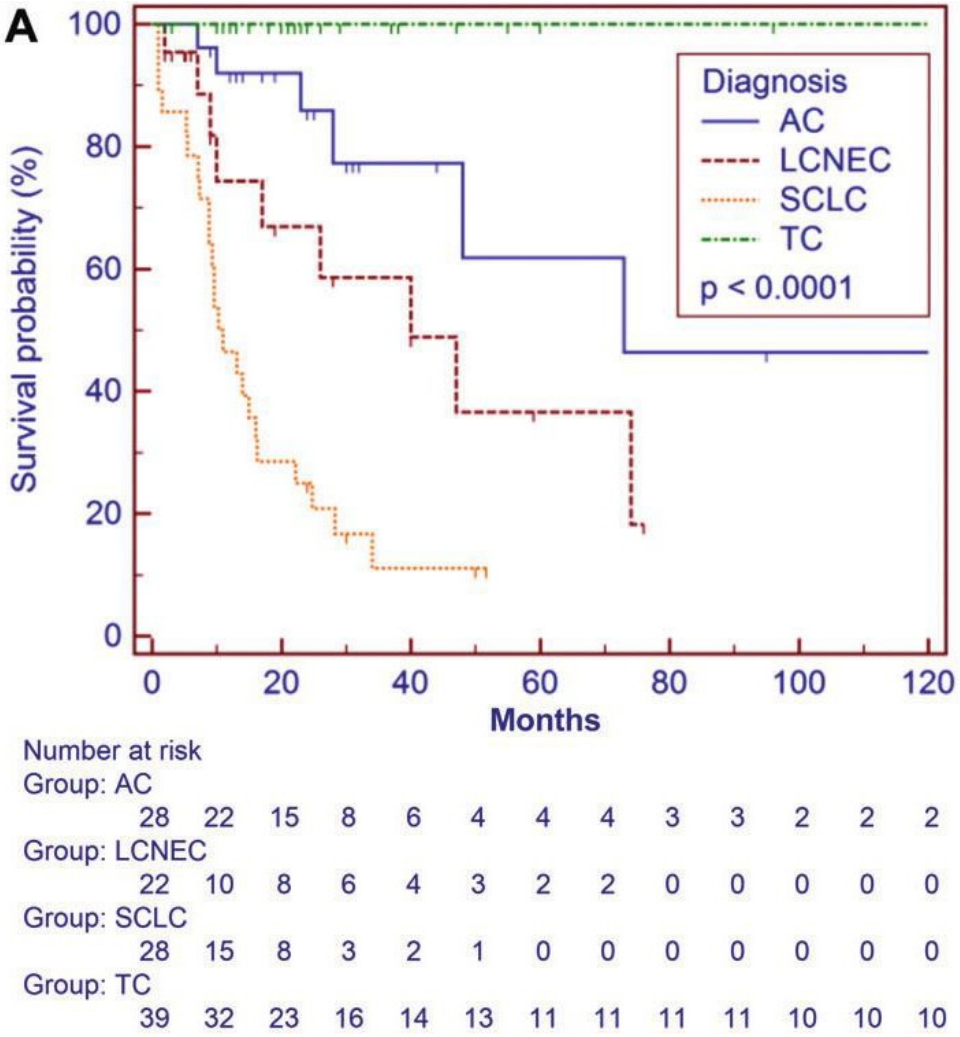
Associated clinical syndromes

- Carcinoid syndrome: 10%[1]

- Ectopic ACTH[2]
- Acromegaly[2]

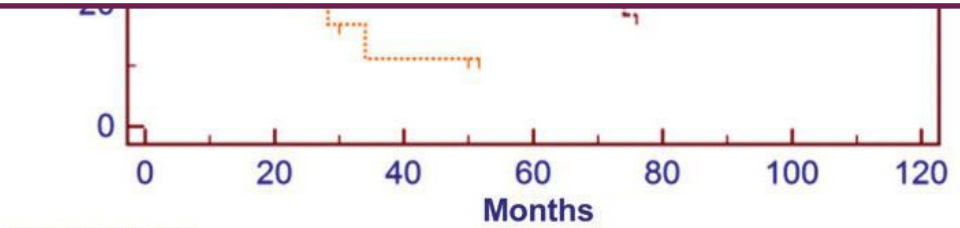
1. Halperin DM, Shen C, Dasari A, *et al.*. Lancet Oncol. 2017, 18, 525–534.
2. Ejaz S, Vassilopoulou-Sellin R, Busaidy NL, *et al.* Cancer 2011, 117, 4381–4389.

LUNG NET: MOLECULAR BIOLOGY



LUNG NET: MOLECULAR BIOLOGY

When mutations and copy number changes were combined, MEN1 alterations were almost exclusive to carcinoids, whereas alterations of TP53 and RB1 cell cycle regulation genes and PI3K/AKT/mTOR pathway genes were significantly enriched in carcinomas



Number at risk

Group: AC												
	28	22	15	8	6	4	4	4	3	3	2	2	2
Group: LCNEC												
	22	10	8	6	4	3	2	2	0	0	0	0	0
Group: SCLC												
	28	15	8	3	2	1	0	0	0	0	0	0	0
Group: TC												
	39	32	23	16	14	13	11	11	11	11	10	10	10

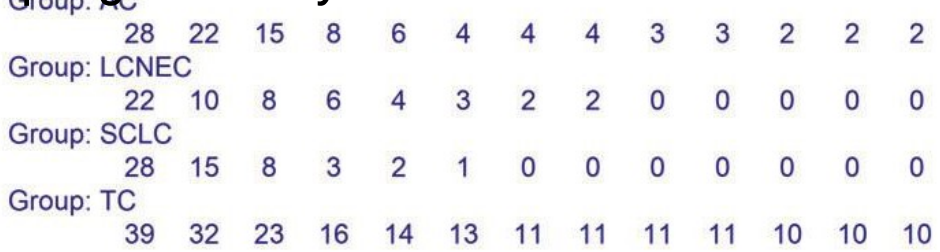
Simbolo M, *et al*. J Pathol 2017;241(4):488–500..

LUNG NET: MOLECULAR BIOLOGY

When mutations and copy number changes were combined, MEN1 alterations were almost exclusive to carcinoids, whereas alterations of TP53 and RB1 cell cycle regulation genes and PI3K/AKT/mTOR pathway genes were significantly enriched in carcinomas

RB1 and TERT impacted on survival regardless of subtype

KMT2D was prognostically relevant for SCLC and MEN1 for AC



Simbolo M, *et al*. J Pathol 2017;241(4):488–500..

LUNG NEN STAGING AND CHARACTERISATION

Type of Lung NEN	Morphological imaging	Functional imaging	Circulating markers
Well differentiated Very low Ki-67 Low grade TC	Total-body CT scan	^{68}GaPET-CT-DOTA-peptide	CgA
Well/moderately differentiated Intermediate Ki-67 (eg, 3–20) AC	Total-body CT scan	^{68}GaPET-CT-DOTA-peptide + ^{18}FDGPET-CT	CgA + NSE

Caplin ME, *et al.* Ann Oncol. 2015; 26:1604-20. Gasparri R, *et al.* Q J Nucl Med Mol Imaging. 2015;59:446-54. Wolin ME. Oncologist. 2015;20:1123-31.

LUNG NEUROENDOCRINE NEOPLASM STAGING

Type of Lung NEN	Morphological imaging	Functional imaging	Circulating markers
Well differentiated Very low Ki-67 Low grade TC	Total-body CT scan	^{68}GaPET-CT-DOTA-peptide	CgA
Well/moderately differentiated Intermediate Ki-67 (eg, 3–20) AC	Total-body CT scan	^{68}GaPET-CT-DOTA-peptide + ^{18}FDGPET-CT	CgA + NSE
Poorly differentiated, High Ki-67 (eg, >20%) LCNEC/SCLC	Total-body CT scan	^{18}FDGPET-CT	NSE

Caplin ME, *et al.* Ann Oncol. 2015; 26:1604-20. Gasparri R, *et al.* Q J Nucl Med Mol Imaging. 2015;59:446-54. Wolin ME. Oncologist. 2015;20:1123-31.

LUNG NET:

Resectable local or locally advanced disease

Complete anatomical resection (segmentectomy, lobectomy, pneumonectomy)

Adequate lymphadenectomy: a minimum of six nodes/stations, three of which should be mediastinal including the subcarinal station (ESTS/IASLC 2006)

Caplin M, *et al.* Ann Oncol 2015; 26:1604-1620.

LUNG NET:
Adjuvant therapy?

RADICALLY RESECTED LUNG NETS:

No role for adjuvant therapy

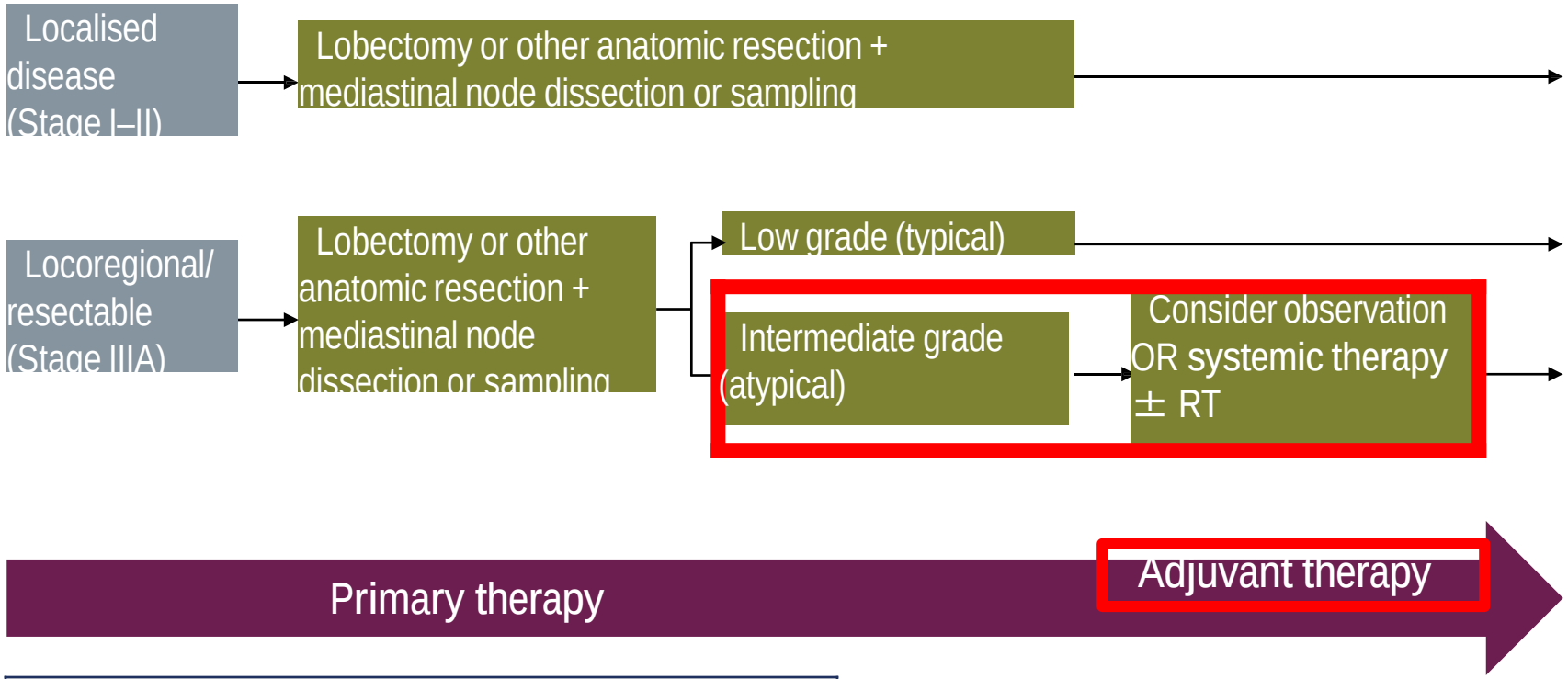
For locoregionally advanced and/or metastatic NETs of the GI tract, lung and thymus (carcinoid tumours):

❾ there is no known role for systemic treatment of the adjuvant setting for NETs

NCCN Guidelines Version 4.2018. Neuroendocrine and Adrenal Tumors. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

ADJUVANT CHEMO +/– RT IN SELECTED CASES

Bronchopulmonary



Stage IIIA	T1a.c, T2a,b	N2	M0
	T3	N1	M0
	T4	N0, N1	M0

RT, radiotherapy

NCCN Guidelines Version 4.2018. Neuroendocrine and Adrenal Tumors. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

2016

2021

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

M. E. Caplin[1*], E. Baudin[2], P. Ferolla[3], P. Filosso[4], M. Garcia-Yuste[5], E. Lim[6], K. Oberg[7], G. Pelosi[8], A. Perren[9], R. E. Rossi[1,10] & W. D. Travis[11] the ENETS consensus conference participants[†]

Annals of Oncology 26: 1604–1620, 2015

adjuvant tumor control

Currently, there is no consensus on adjuvant therapy in PCs after complete resection. Indeed, both prognostic studies and trials in the adjuvant setting are lacking. Only patients with AC with positive lymph nodes, especially if there is a high proliferative index, should be considered for adjuvant therapy and discussed on an individual patient basis in the context of multidisciplinary tumor board meeting. Clinical trials are needed in this setting.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

E. Baudin[1], M. Caplin[2], R. Garcia-Carbonero[3], N. Fazio[4], P. Ferolla[5], P. L. Filosso[6], A. Frilling[7], W. W. de Herder[8], D. Hörsch[9], U. Knigge[10], C. M. Korse[11], E. Lim[12], C. Lombard-Bohas[13], M. Pavel[14], J. Y. Scoazec[15], A. Sundin[16] & A. Berruti[17], on behalf of the ESMO Guidelines Committee*

No routine adjuvant therapy is recommended in LCs [IV, C for AC; IV, D for TC]. However, cytotoxic ChT (dacarbazine/temozolomide- or oxaliplatin-based ChT) ± RT may be considered in selected fit patients with a particularly high risk of relapse (i.e. AC N2) after multidisciplinary discussion [IV, C]

RADICALLY RESECTED LUNG NET:

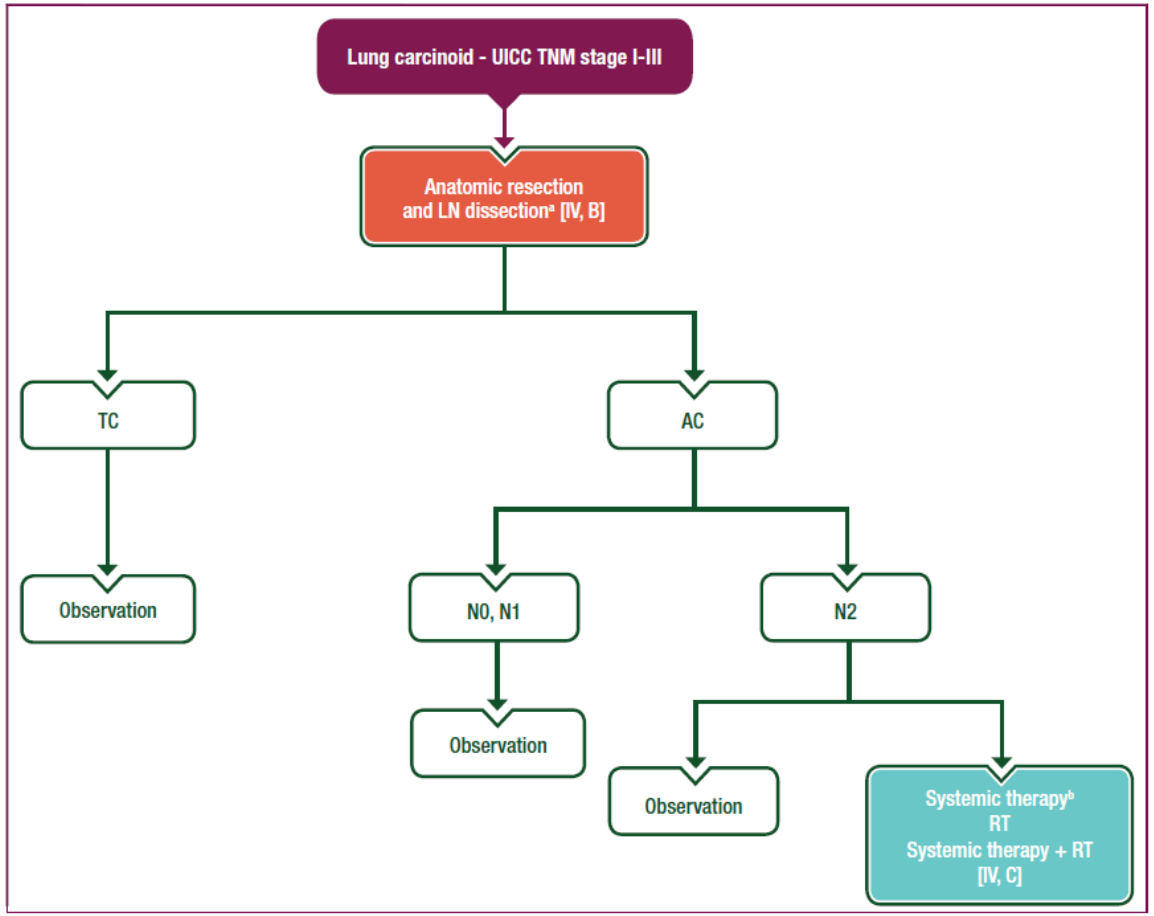
Adjuvant therapy

On an individual patient basis, a systemic therapy (mainly chemotherapy) can be discussed after multidisciplinary discussion in intermediate grade (atypical carcinoid) and intermediate stage (pN2)

ESMO
ANNALS OF ONCOLOGY
SPECIAL ARTICLE

Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

E. Baudin[1], M. Caplin[2], R. Garcia-Carbonero[3], N. Fazio[4], P. Ferolla[5], P. L. Filosso[6], A. Frilling[7], W. W. de Herder[8], D. Hörsch[9], U. Knigge[10], C. M. Korse[11], E. Lim[12], C. Lombard-Bohas[13], M. Pavel[14], J. Y. Scoazec[15], A. Sundin[16] & A. Berruti[17], on behalf of the ESMO Guidelines Committee*



SYSTEMIC THERAPIES IN ADVANCED DISEASE

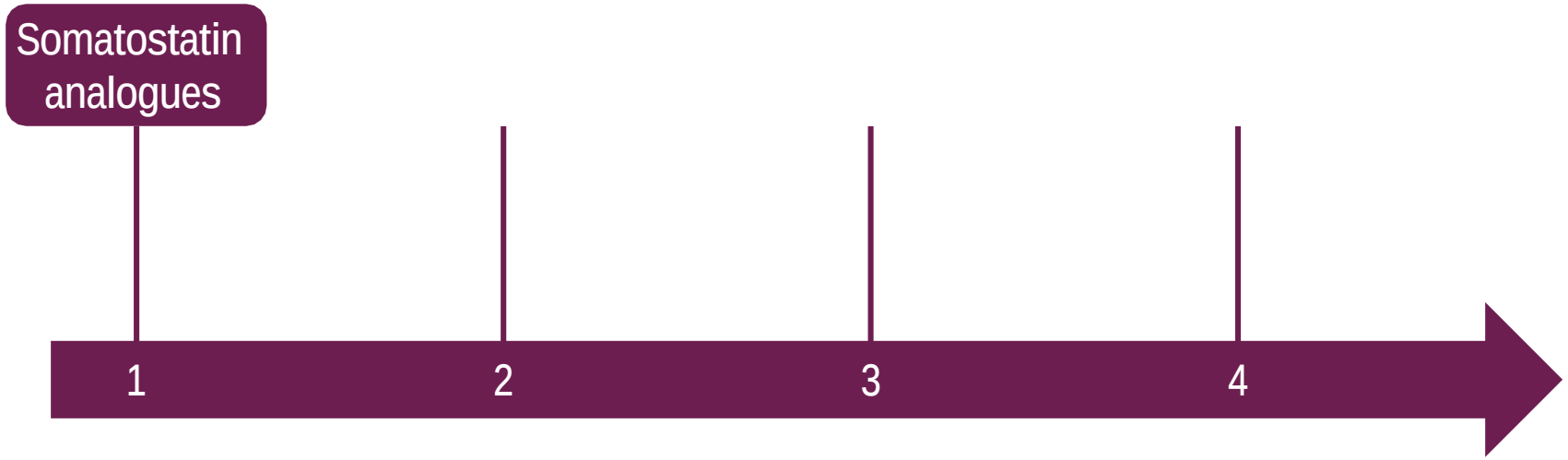
ADVANCED WELL-DIFFERENTIATED LUNG NET

- Octreotide or Lanreotide
- Everolimus
- Chemotherapy
- Peptide Receptor Radionuclide Therapy (PRRT)
- Liver-directed treatments

ADVANCED WELL-DIFFERENTIATED LUNG NET

First-line therapy

Functioning and/or SSTR functional expression
and/or low tumour grade and/or slowly progressing

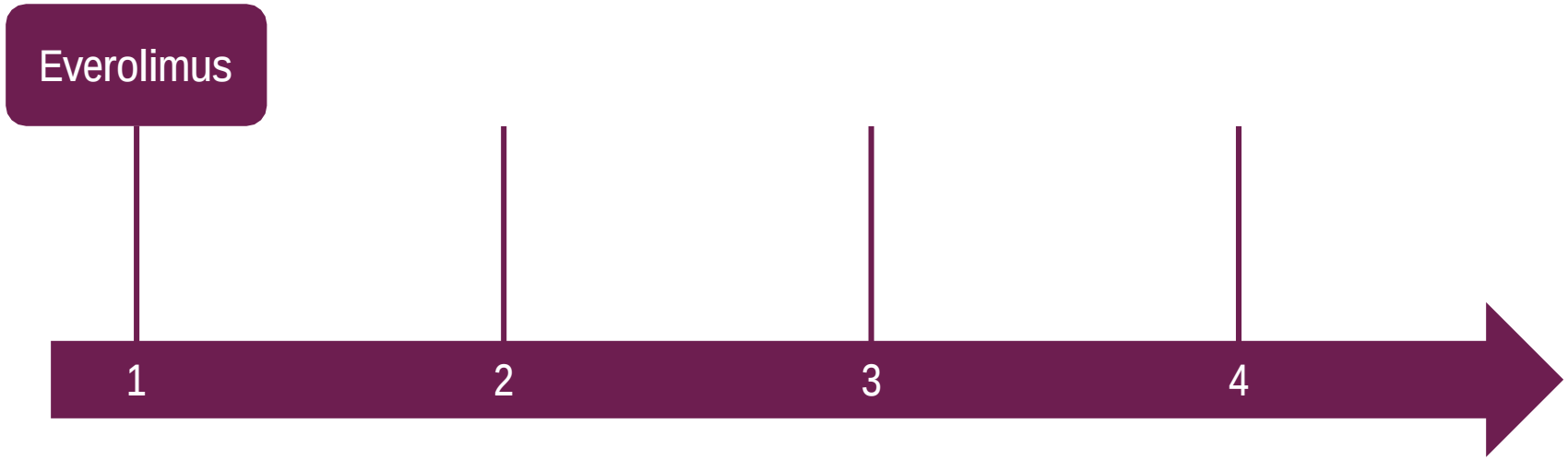


SSTR = somatostatin receptor
ENETS 2016 guidelines; NCCN 2018 guidelines.

ADVANCED WELL-DIFFERENTIATED LUNG NET

First-line therapy

Non functioning and intermediate tumour grade and/or
Negative/unhomogeneous SSTR functional expression and/or
fast progressing



ENETS 2022 guidelines; NCCN 2018 guidelines.

ESMO 2021 guidelines

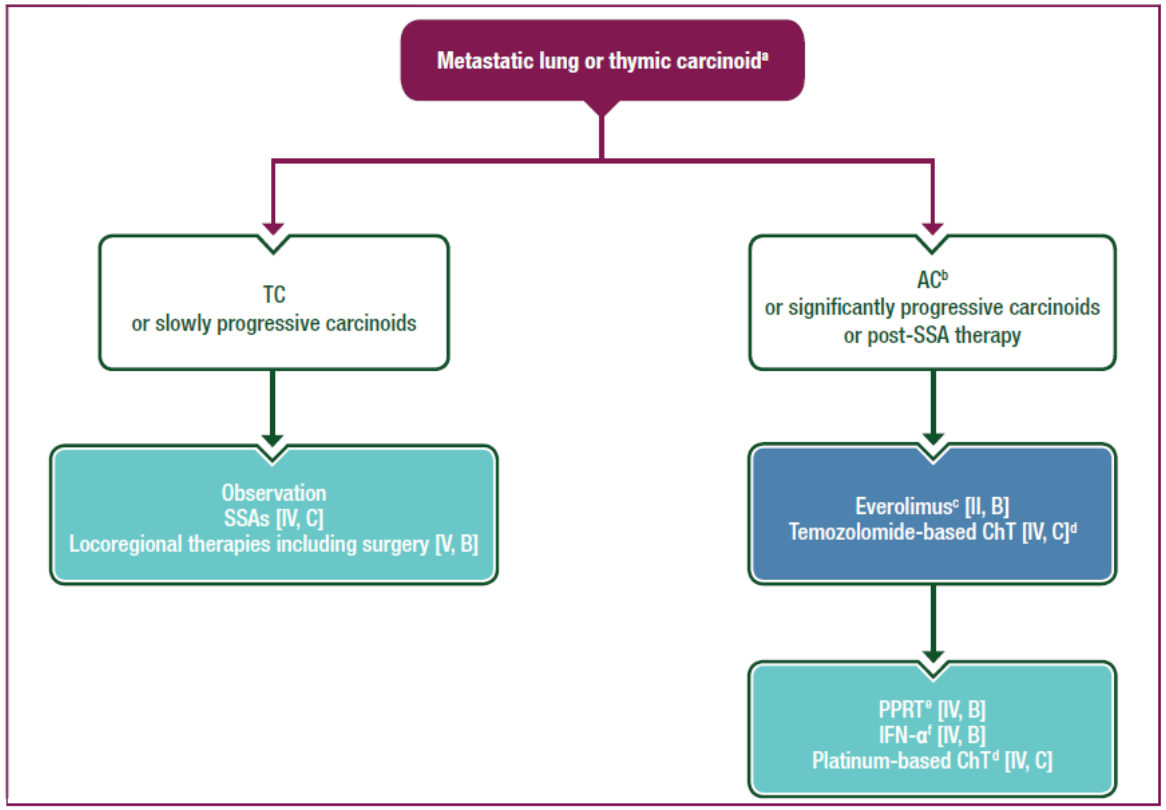
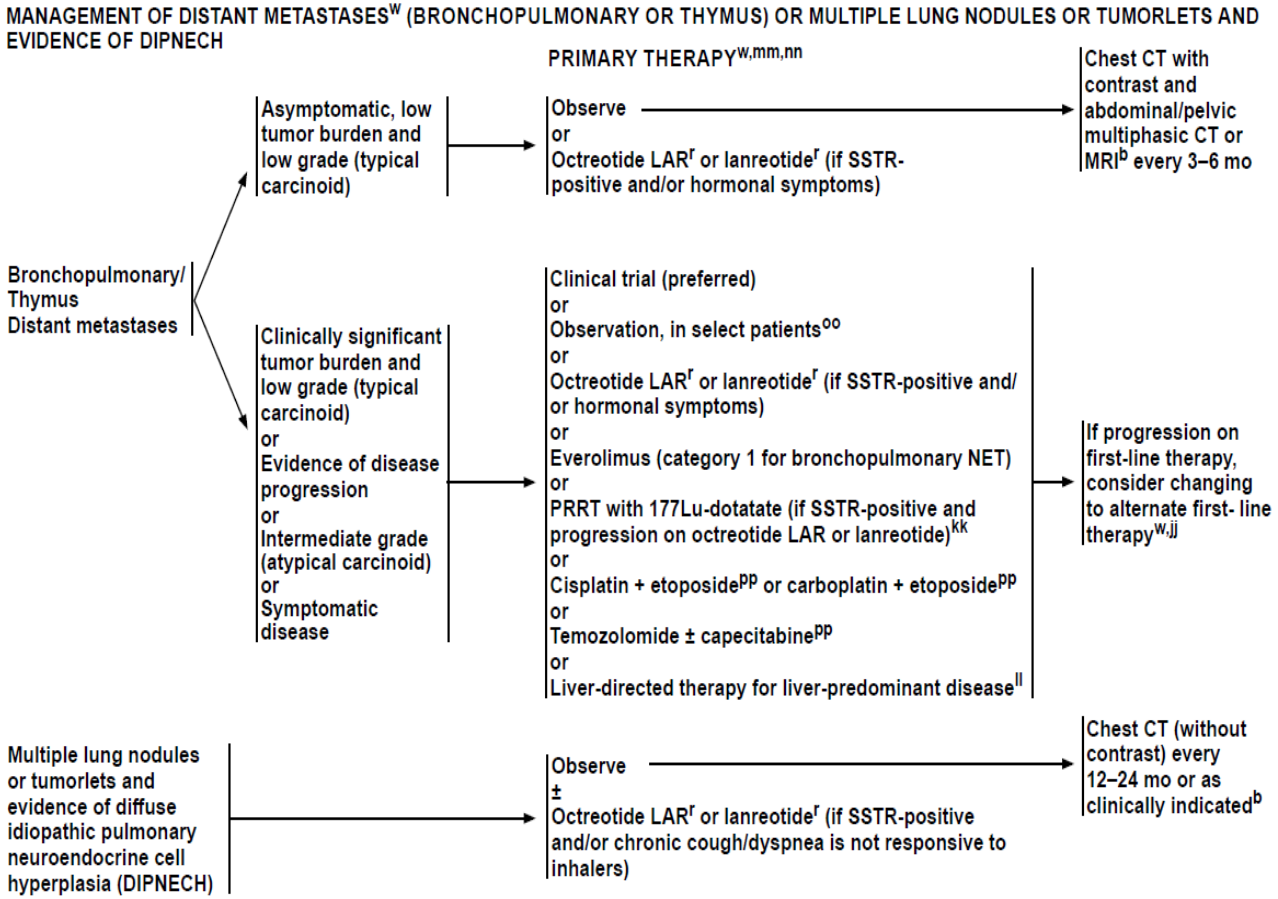


Figure 3. Treatment of functioning syndromes.
In patients with refractory CS, a variety of options exist but there is no consensus on the best strategy, due to the lack of specific LC studies.
ChT, chemotherapy; CS, carcinoid syndrome; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; IFN-α, interferon-α; LC, lung carcinoid; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue.
[a] Telotristat ethyl is the only second-line EMA- and FDA-approved agent in patients with refractory diarrhoea due to the carcinoid syndrome. When second-line treatment is given for controlling CS, distinct from increased SSA dose or pasireotide, SSA therapy should be maintained until a significant improvement of CS is observed.

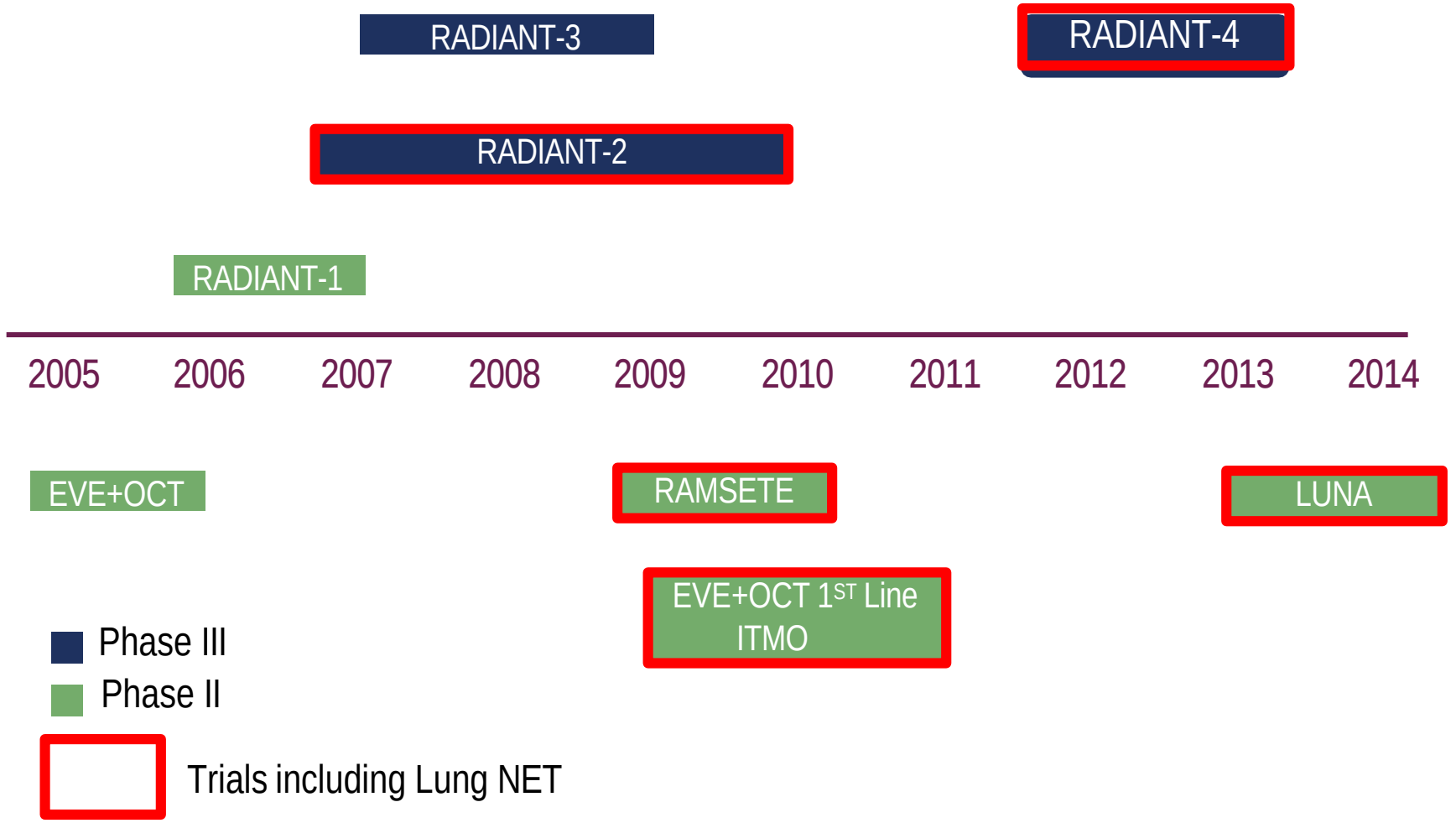
NCCN 2022 guidelines



EVEROLIMUS INVESTIGATION IN NETS

RADIANT

(RAD001 in Advanced Neuroendocrine Tumours)



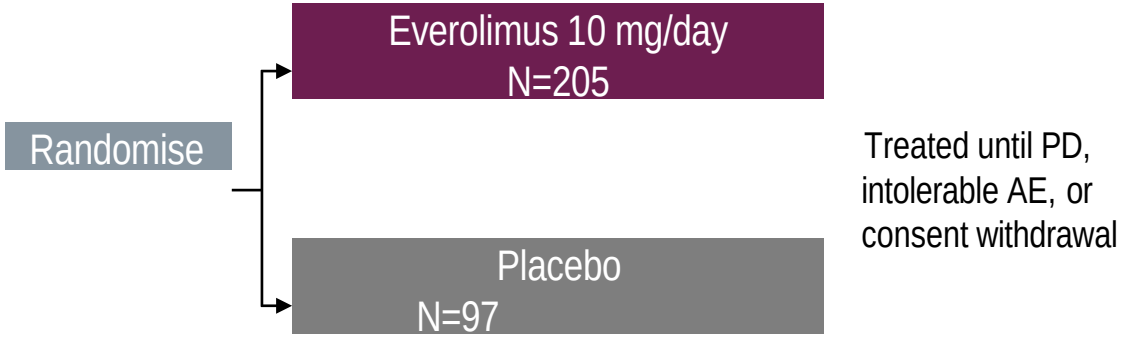
TRIALS WITH EVEROLIMUS IN LUNG NETS

Trial	Experimental arm	Control arm	Type of study	Lung subgroup	Number of lung patients	Author
RAMSETE	EVE	No	Phase II	Non-functioning	22/73	Pavel M, ESMO 2014
RADIANT-2	EVE + Oct LAR	Oct LAR + Placebo	Phase III	Carcinoid syndrome	44/429	Fazio N, Chest 2013
RADIANT-4	Everolimus	Placebo	Phase III	Non-functioning	90/302	Yao JC, Lancet 2015
LUNA	Pasireotide *vs.* EVE *vs.* Pasireotide/EVE	No	Phase II	Functioning and non-functioning	121/121	Ferolla P, Lancet Oncol 2017

RADIANT-4 STUDY DESIGN

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N=302)

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



Treated until PD, intolerable AE, or consent withdrawal

Endpoints:

- **Primary:** PFS (central)
- **Key secondary:** OS

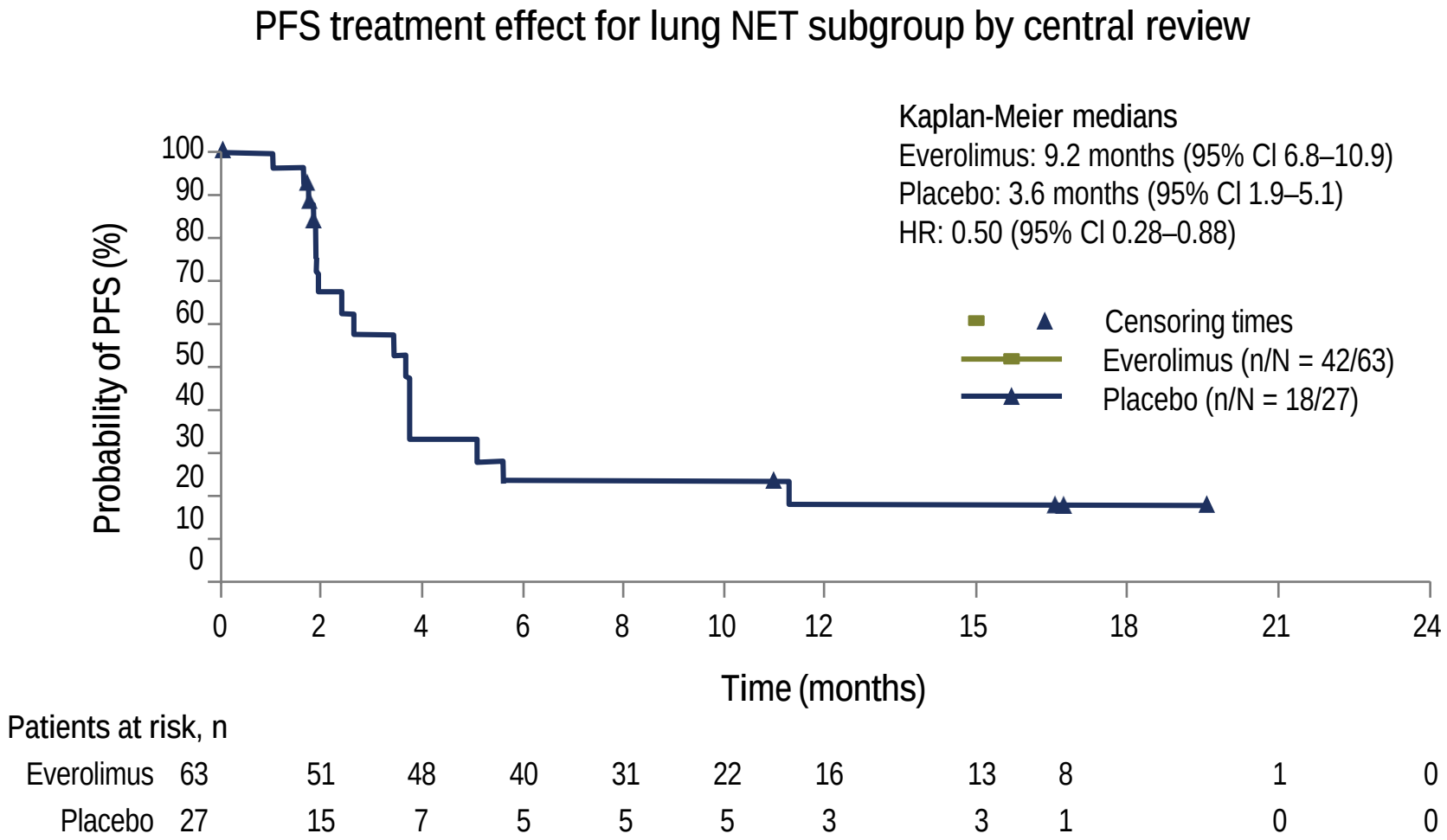
Stratified by:

- Prior SSA treatment (yes *vs.* no)
- Tumour origin (stratum A *vs.* B)*
- WHO PS (0 *vs.* 1)

Approximately 176 PFS events needed to detect a HR of 0.59 with 91.3% power at one-sided significance level of 2.5%

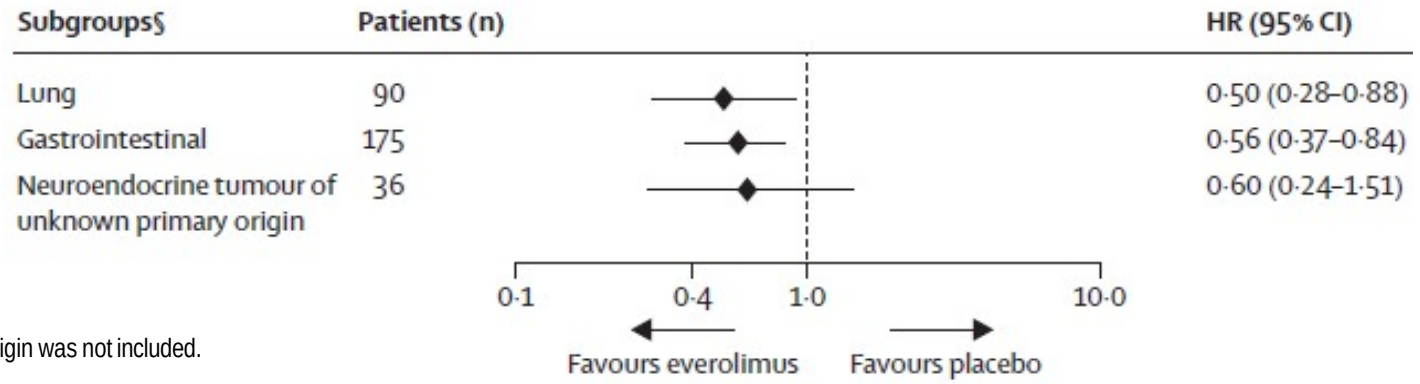
*Based on prognostic level, grouped as: **Stratum A (better prognosis)** – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worse prognosis)** – lung, stomach, rectum, and colon except caecum. Crossover to open label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

RADIANT-4 TRIAL: LUNG SUBGROUP, 90 PTS



RADIANT-4 TRIAL: LUNG SUBGROUP, 90 PTS

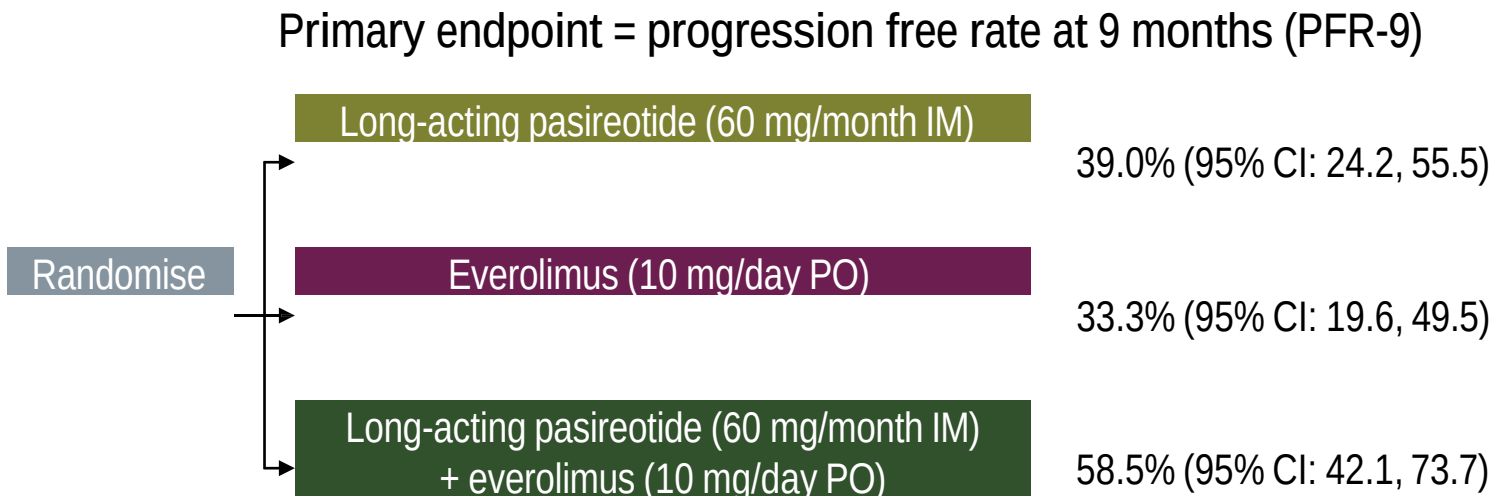
Tumour grade, n (%)		
	Everolimus (n=63)	Placebo (n=27)
Low	26 (41)	13 (48)
Intermediate	37 (59)	14 (52)
Prior antineoplastic therapy		
	Everolimus (n=63)	Placebo (n=27)
Yes	56 (86)	24 (89)
No	9 (14)	3 (11)



§ One patient with thymus as primary tumour origin was not included.

Fazio N, *et al.* Cancer Sci 2017;109(1):174-181; reprinted from The Lancet , 387(10022), Yao JC, *et al.* Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study; 968-77, Copyright 2016, with permission from Elsevier.

LUNA TRIAL: THREE-ARM RANDOMISED PHASE 2

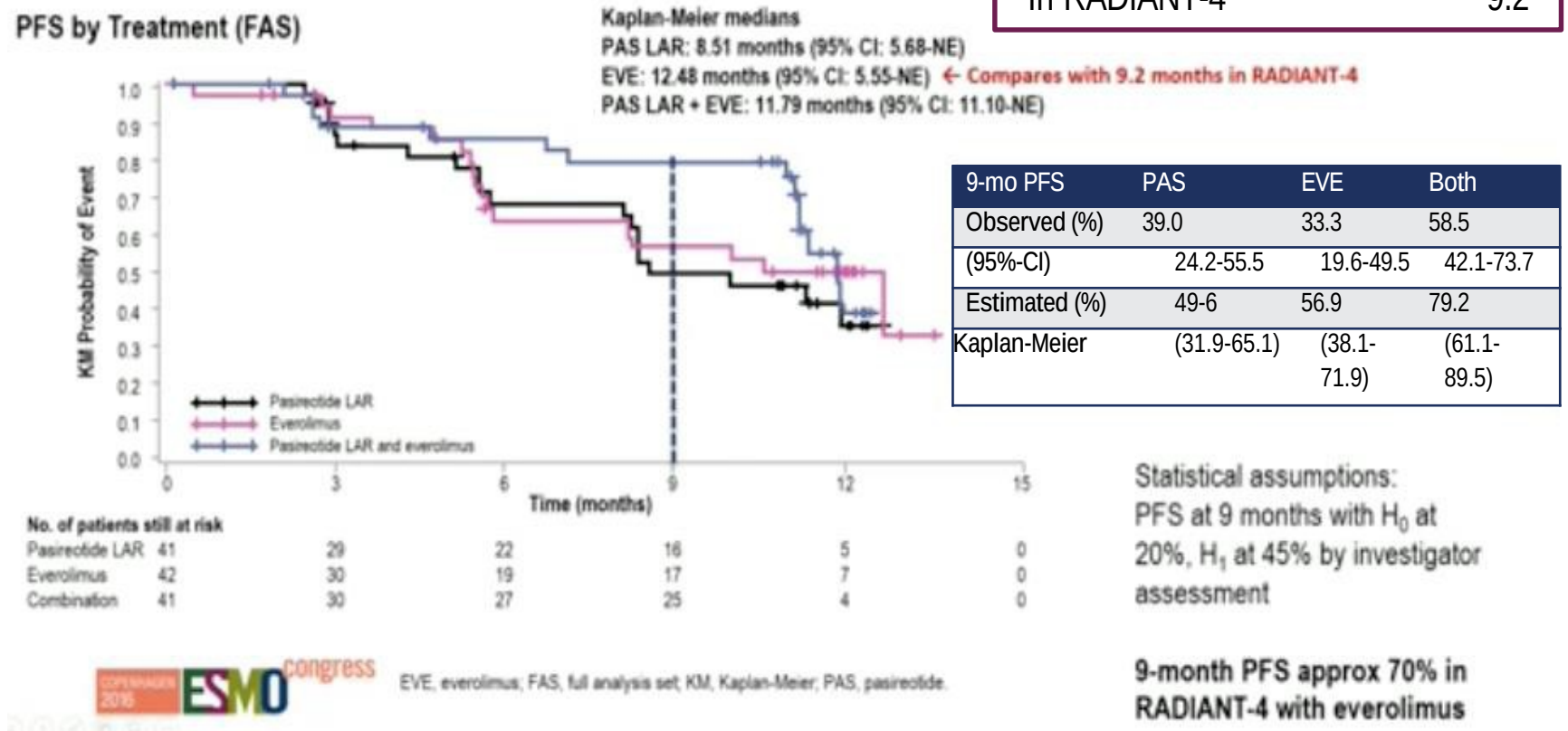


The most common treatment-emergent AEs (incidence >40%)

- **Combination arm:** hyperglycaemia (87.8%), diarrhoea (78.0%), and weight decreased (56.1%)
- **Everolimus arm:** stomatitis (61.9%), diarrhoea (47.6%), and weight decreased (40.5%)
- **Long-acting pasireotide arm:** hyperglycaemia and weight decreased (both 43.9%)

LUNA STUDY – EFFICACY

	mPFS (mo)
PAS LAR	8.5
EVE	12.5
PAS LAR + EVE	12
*In RADIANT-4	9.2



9-mo PFS	PAS	EVE	Both
Observed (%)	39.0	33.3	58.5
(95%-CI)	24.2-55.5	19.6-49.5	42.1-73.7
Estimated (%)	49-6	56.9	79.2
Kaplan-Meier	(31.9-65.1)	(38.1-71.9)	(61.1-89.5)

Statistical assumptions:
PFS at 9 months with H_0 at 20%, H_1 at 45% by investigator assessment

9-month PFS approx 70% in RADIANT-4 with everolimus

Ferolla P, *et al.* Ann Oncol 2016; 27 (suppl 6): abstr 416O. Oral presentation ESMO 2016. Valle J, Highlights ESMO 2016

CHEMOTHERAPY IN ADVANCED LUNG NET

- ✓ Temozolomide-based
- ✓ Oxaliplatin-based

MOST PULMONARY CARCINOIDS DO NOT RESPOND TO CIS/CARBOPLATIN-BASED CHEMOTHERAPY

Study (n)	Design / Drug	Pathology/PI Terminology	Primary	PR	Duration, months
Moertel CG, 1986 (15)	Phase II / Cisplatin	Carcinoids	Not specified	7%	3
Jodrell D, 1990 (13)	Phase II / Carboplatin	Carcinoids	Various	0%	-
Saltz L, 1993 (20)	Phase II / Carboplatin	Carcinoids	Not specified	0%	-
Mitry E, 1999 (12)	Retro./ Cisplatin-Etoposide	Well diff.	Various	9%	2.3
Fjällskog MLH, 2001 (32)	Retro./ Cisplatin-Etoposide	Well diff./ carcinoids	Various	33%	-
Wirth LJ, 2004 (22)	Retro./ Cisplatin-Etoposide	Carcinoids	Pulmonary	22%	-
Kulke MH, 2006 (14)	Phase II / Cisplatin-Irinotecan	Well diff.	Various	0%	-
Hentic O, 2011	Retro./ Cisplatin-Etoposide				
Vélayoudom-Céphise FL, 2013 (4)	Retro./ Cisplatin-Etoposide	NET G3	Various	0%	-
Heetelfd M, 2015 (12)	Retro./ Cisplatin-Etoposide	NET G3	Digestive, CUP	17%	2.4

By courtesy of Prof Eric Baudin

TEMOZOLOMIDE IN THORACIC NEUROENDOCRINE NEOPLASMS

TMZ regimens and responses in thoracic NENs assessed by RECIST criteria

Study	Type of study	Regimen	No. of pts with thoracic NENs/no. of total NEN pts	Pretreated pts with chemotherapy, %	CR+PR, %	SD, %	TTP or PFS, months
Ekeblad S, *et al.* [34], 2007	Retrospective	TMZ 200 mg/m^2/d, d1-5, q4wk	20/36 (7 thymic, 13 bronchial)	NA	0/31	25	TTP: 7
Welin S, *et al.* [16], 2011	Retrospective	TMZ 150-200 mg/m^2/d, d1-5 CAP 750-1000 mg x2, d1-14 BVZ 5 mg/kg, d14, d28	3/25 (bronchial)	100	32	40	PFS: 6
Koumarianou A, *et al.* [46], 2012	Retrospective	TMZ 100 mg/d, d1-21 BVZ 7.5 mg/kg, d1, q3wk	1/15 (bronchial)	80	0	0	TTP: 9
Chan JA, *et al.* [47], 2012	Prospective	-	4/34 (bronchial)	NA	NA	NA	NA
Crona J, *et al.* [65], 2013	Retrospective	TMZ 150-200 mg/m^2/d, d1-5, q4wk (±sorafenib 1 patient, ±CAP/BVZ 1 patient)	10/28 (thymic)	NA	0/20	70	TTP:20
Crona J, *et al*. [63], 2013	Retrospective	TMZ 150-200 mg/m^2/d, d1-5, q4wk	31/31 (bronchial)	35	0/14	52	PFS: 5
Saranga-Perry V, *et al.* [64], 2013	Retrospective	TMZ 170-190 mg/m^2/d, d10-14 CAP 600-750 mg/d x2, d1-14	3/3 (thymic)	100	67	33	NA
Chong CR, *et al.* [66], 2014	Retrospective	TMZ 150-200 mg/m^2/d, d1-5, q4wk	14/300 (bronchial)	NA	14	57	PFS: 10
Pietanza MC, *et al.* [67], 2012	Phase II	TMZ 75 mg/m^2/d, d1-21, q4wk	64 (SCLC)	100	1.5/19	9	TTP: 1.6
Zauderer MG, *et al.* [68], 2014	Phase II	TMZ 200 mg/m^2/d, d1-5, q4wk	25/25 (SCLC)	100	0/12	NA	NA

Koumarianou A, *et al.* Neuroendocrinology 2015

OXALIPLATIN-BASED CHEMOTHERAPY IN THORACIC NETS

Temozolomide-based and oxaliplatin-based chemotherapy in advanced lung NETs

Author	Regimen	Prospective/retrospective	No. of patients	Results
Walter T, (26)	Oxaliplatin-based	Retrospective	45	PFS: 15 months
Bajetta E, (27)	Capecitabine and oxaliplatin	Phase II	5/40	PFS: 20 months
Spada F, (28)	Oxaliplatin based	Retrospective	19/78	PFS: 8 months
Crona J, (29)	Temozolomide	Retrospective	31	PFS: 5.3 months
Chan JA, (30)	Temozolomide + bevacizumab	Phase II	19/34	PFS: 7.3 months
Kunz PL, (31)	Oxaliplatin based + bevacizumab	Phase II	42/76	PFS: 19 months

Fazio N, J Thoracic Dis 2017, 9 (Suppl 15): 1501-1510

PRRT IN THORACIC NETS

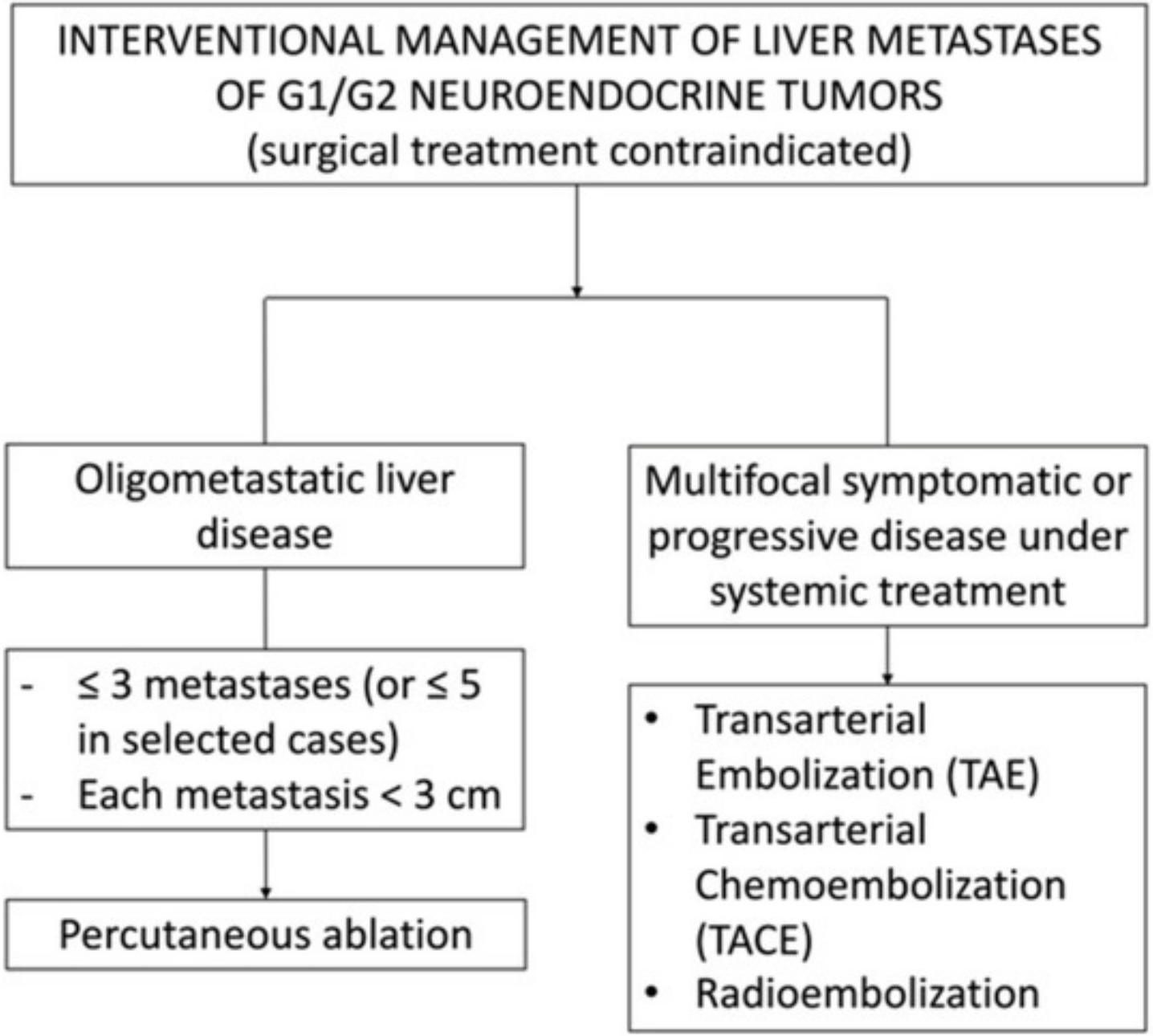
Studies of PRRT including more than 10 patients with advanced lung NETs

Author	Type of study	Radionuclide	No. of patients	Results
Imhof A, (22)	Phase II	Y^{90}-Octreotide	84/1, 109	RR 28.6% (morphological response*)
Bodei L, (23)	Phase II	Y^{90}-Octreotide	11/141	PR: 1; SD: 8
Ianniello A, (24)	Retrospective	Lu^{177}-Octreotide	34	PFS: 20.1 months
Marinello G, (21)	Retrospective, single institution	Y^{90}-Octreotide or Lu^{177}-Octreotate orY^{90}-Octreotide + Lu^{177}-Octreotate	114	PFS: 28 months; OS: 58.8 months

PFS, progression free survival; OS, overall survival; RR, response rate; mo, months

Fazio N, J Thoracic Dis 2017, 9 (Suppl 15): 1501-1510

LIVER DIRECTED THERAPY


INTERVENTIONAL MANAGEMENT OF LIVER METASTASES OF G1/G2 NEUROENDOCRINE TUMORS (surgical treatment contraindicated)
Oligometastatic liver disease
- ≤ 3 metastases (or ≤ 5 in selected cases)
- Each metastasis < 3 cm
Percutaneous ablation
Multifocal symptomatic or progressive disease under systemic treatment
• Transarterial Embolization (TAE)
• Transarterial Chemoembolization (TACE)
• Radioembolization

Immunotherapy in Neuroendocrine tumors

SCLC Low grade lung NEN Pancreatic NEC	KEYNOTE 028, 2019 [61]	Exp: pembrolizumab	≥II line	Ib	mOS: 9.7 months mOS: 21.1 months mOS:21.0 months	mPFS: 1.9 months mPFS: 5.7 months mPFS: 4.5 months	33% 12% 6%
Low grade GEP and lung NEN GEP NEC	CPDR001E2201, 2019 [62]	Exp: spartalizumab	≥II line	II			ORR overall 7.4% ORR in GEP NEC 4,8% ORR in thoracic NET 20%
NEN with Ki67 >10%	NCT03167853, 2020 [63]	Exp: toripalimab	≥II line	Ib	mOS: 9.1 months in PD-L1 ≥10% mOS: 7.2 months in PD-L1 <10% (HR 0.55; 95% CI: 0.24–1.23)	mPFS: 3.8 months in PD-L1 ≥10% mPFS: 2.2 months in PD-L1 <10% (HR 0.50; 95% CI: 0.24–1.06)	ORR was 42.9% (in PD-L1 expression ≥10%: 50.0%; in high TMB: 75.0%) ORR was 8.3% (in PD-L1 expression <10%)
NEN (no p-NEN)	DART/SWOG 1609, 2020 [64]	Exp: ipilimumab plus nivolumab	Any line (median II previous lines)	II	mOS: 11 months	mPFS: 4 months	25% (45% in high-grade and 0% in low-intermediete grade)
NET and NEC (any site)	NCT03074513, 2020 [65]	Exp: atezolizumab plus bevacizumab	≥II line	II		mPFS: 19.6 months in pNET mPFS: 14.9 months in extra-pNET	ORR: 20% in pNET ORR: 15% in extra-pNET

Maggio I, Manuzzi L, Lamberti G, Ricci AD, Tober N, Campana D. Landscape and Future Perspectives of Immunotherapy in Neuroendocrine Neoplasia. ***Cancers****.*
2020; 12(4):832. https://doi.org/10.3390/cancers12040832

SCLC Is a High-Grade Neuroendocrine Tumor[1]

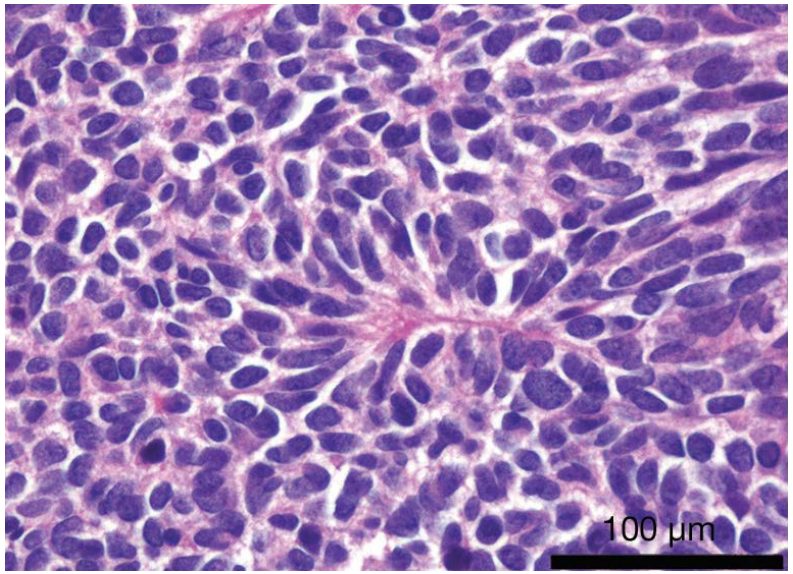
Pathologic diagnosis is made according to WHO Classification by morphology[1-3]

- Uniform round to spindled-shaped small cells
- Ill-defined borders
- Sparse cytoplasm
- High mitotic index
- Frequent nuclear molding

IHC panels may be used to confirm diagnosis; cells may be positive for epithelial and/or neuroendocrine markers[2,4-6]

- Synaptophysin
- Chromogranin A
- CD56
- **TTF-1**
- Ki67
- **Keratin**
- **Epithelial membrane antigen**

H&E Stain of SCLC Specimen[5]



Cells are small with fine, granular chromatin and scarce cytoplasm

Markers of neuroendocrine differentiation can be found in approximately 75% of SCLC cases[4]

SCLC can also develop from histologic transformation of NSCLC; case series have found histologic transformation in 5-14% of NSCLC adenocarcinoma cases[7]

CD, cluster of differentiation; H&E, hematoxylin and eosin; IHC, immunohistochemistry; TTF-1, thyroid transcription factor 1; WHO, World Health Organization.

1. Farago AF et al. *Transl Lung Cancer Res*. 2018;7(1):69-79. 2. Früh M et al. *Ann Oncol*. 2013;24 Suppl 6:vi99-vi105. 3. Brambilla E et al. *Eur Respir J*. 2001;18(6):1059-1068. 4. Guinee DG Jr et al. *Am J Clin Pathol*. 1994;102(4):406-414. 5. Dorantes-Heredia R et al. *Transl Lung Cancer Res*. 2016;5(4):401-412. 6. Thunnissen E et al. *J Thorac Oncol*. 2017;12(2):334-346. 7. Oser MG et al. *Lancet Oncol*. 2015;16(4):e165-e172.

Tumor markers in SCLC

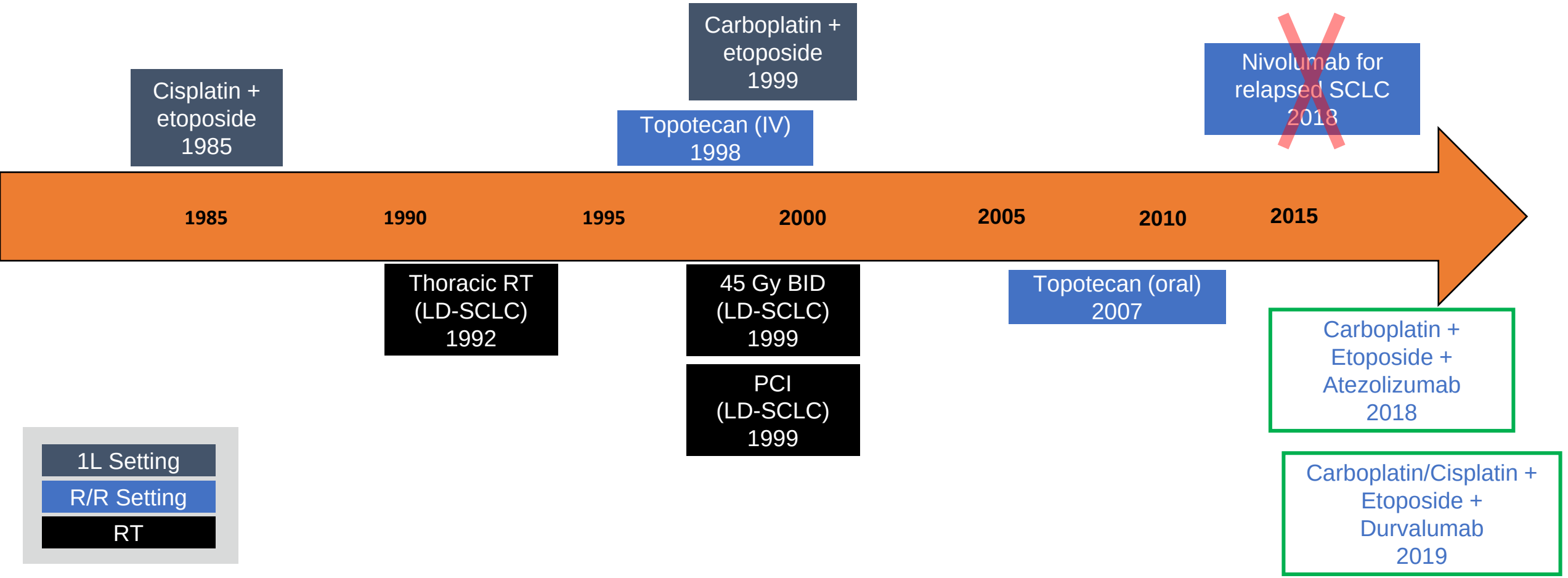
No molecular markers that are recommended for treatment selection for SCLC outside of clinical trials

Markers reflecting neuroendocrine and neural differentiation	synaptophysin, chromogranin, and CD56 (neural cell adhesion molecule [NCAM])

Neuron-specific enolase (NSE), dopa decarboxylase, calcitonin, gastrin-releasing peptide (GRP), and insulin-like growth factor-I (IGF-1)

SCLC cells can also produce several polypeptide hormones ❾ resulting in various paraneoplastic endocrinologic syndromes	ACTH, vasopressin (antidiuretic hormone)

The SoC for treatment of ES-SCLC, often given palliatively, is a standard combination regimen of cisplatin or carboplatin + etoposide or irinotecan and had not changed in more than 30 years.



Adapted from Sabari JK et al. *Nat Rev Clin Oncol*. 2017;14(9):549-561.

Systemic Therapy in SCLC

The mainstay of systemic treatment in SCLC

combination of platinum etoposide both in LS & ES disease

Cisplatin

preferred for younger fit patients

Carboplatin

older patients

with comorbidities (concern of potential toxicity from cisplatin)

Irinotecan-platinum

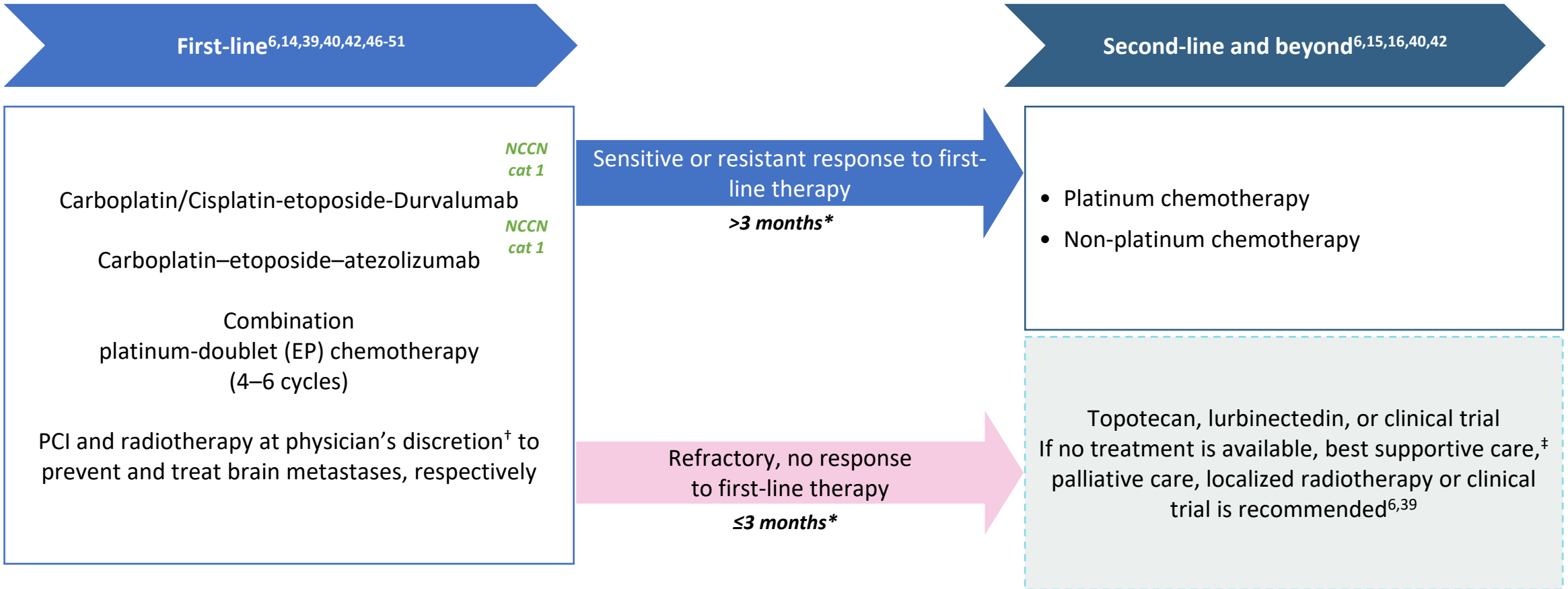
alternative to etoposide-platinum (especially in ES-SCLC wherein cCRT is not done)

PD-L1 ICIs

atezolizumab and durvalumab - in ES-SCLC with platinum-etoposide

Lung Cancer in India - https://doi.org/10.1016/j.jtho.2021.02.004

IO for 1L ES-SCLC



*NCCN Guidelines: **≤6 months - refractory or resistant disease, > 6 months sensitive disease**

* ESMO Guidelines: **≥ 3 months - sensitive SCLC** and **<3 months - resistant SCLC**

† Some patients with limited stage SCLC may not benefit from PCI and PCI is not recommended for patients with poor performance status or impaired neurocognitive function; ‡ Pain medications and other non-specific palliative treatments, including radiotherapy with explicitly palliative intention (<5 0 Gray of radiation).[9,10]

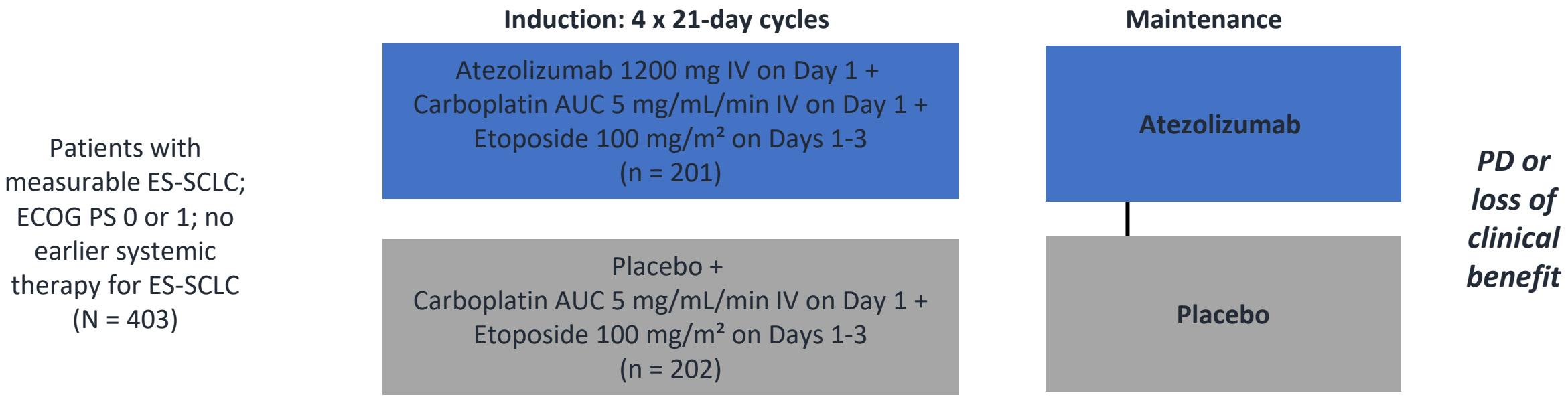
DoR: duration of response; ES-SCLC: extensive-stage small cell lung cancer; EP: platinum-etoposide; FDA: food and drug administration; IO: immuno-oncology; NCCN: National Comprehensive Cancer Network; ORR: objective response rate; PCI: prophylactic cranial irradiation; SCLC: small cell lung cancer

6. Oronsky B, et al. Neoplasia 2017; 14. "Resources for Information on Approved Drugs." U.S. Food and Drug Administration, FDA, 2021; 15: ESMO press release. 3 September 2018. 16: MERCK News Release, June 201939: "NCCN Guidelines for SCLC, Version 1.2022."; 40: "Lung & Chest Tumors." *ESMO Interactive Guidelines*; 42: "Download Medicine Data." European Medicines Agency, 13 Oct. 2021; 46: The ASCO Post Staff. "Nivolumab Indication in Small Cell Lung Cancer Withdrawn in U.S. Market." 2021; 47: The ASCO Post Staff. "Pembrolizumab's Indication in Small Cell Lung Cancer Is Withdrawn." 2021; 48: "Review Report Pharmaceuticals and Medical Devices ... - PMDA."; 49: "Pharmaceuticals and Medical Devices Agency - PMDA.GO.JP." 50: "Durvalumab Approved in China for the Treatment of Extensive-Stage Small Cell Lung Cancer." 51: "China National Medical Products Administration Grants Approval of Roche's Tecentriq in Combination with Chemotherapy as First-Line Treatment of People with Extensive-Stage Small Cell Lung Cancer." Ganti et al. NCCN, Small Cell Lung Cancer, Version 2.2022

IMPOWER-133

IMpower133: Atezolizumab + Chemotherapy for Advanced SCLC

- Double-blind, randomized, placebo-controlled phase I/III trial



- Coprimary endpoints: OS, PFS by investigator assessment
- Secondary endpoints: ORR, DoR, safety

Liu. IASLC WCLC. 2018. Abstr. PL0-207. Horn. NEJM. 2018;379:2220.

CASPIAN trial

CASPIAN: Study Design

- Randomized, open-label, multicenter phase III study

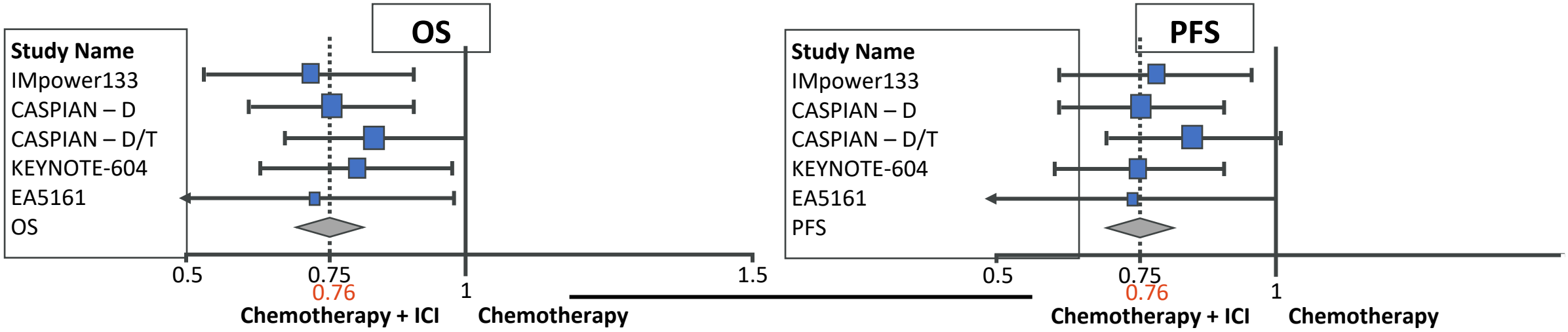
Treatment-naive, extensive-stage SCLC, WHO PS 0/1, measurable disease per RECIST v1.1, life expectancy ≥ 12 wks, asymptomatic or treated and stable brain metastases
(N = 805)

*Etoposide 80-100 mg/m^2 with either carboplatin AUC 5-6 or cisplatin 75-80 mg/m^2, durvalumab 1500 mg, tremelimumab 75 mg.
†Per investigator discretion, additional 2 cycles of EP (6 cycles total) and PCI

- Primary endpoint: OS
- Secondary endpoints: PFS and ORR (investigator-assessed per RECIST v1.1), safety and tolerability, PROs

Paz-Ares. ASCO 2020. Abstr 9002.

FRONTLINE CHEMOIMMUNOTHERAPY IN SCLC: SUMMARY OF EFFICACY



	IMpower133	CASPIAN		KEYNOTE-604	EA5161
		Durvalumab	Durvalumab/Trem		
Median PFS, mos ▪ HR (95% CI)	5.2 0.77 (0.62-0.96)	5.1 0.78 (0.65-0.94)	4.9 0.84 (0.70-1.01)	4.5 0.75 (0.61-0.91)	5.5 0.68 (0.48-1.0)
Median OS, mos ▪ HR (95% CI)	12.3 0.70 (0.54-0.91)	13 0.73(0.59-0.91)	10.4 0.82 (0.68-1.00)	10.8 0.80 (0.64-0.98)	11.3 0.67 (0.46-0.98)
12-mos OS, %	51.7	52.8	43.8	45.1	~ 48
24-mos OS, %	~ 22	22.2	23.4	22.5	NR

Owonikoko. ASCO 2020.

Cross-Trial Comparison: IMpower133 and CASPIAN

Parameter	IMpower133: Atezolizumab + EP → Atezolizumab[1]	CASPIAN: Durvalumab + EP → Durvalumab[2]
Blinding	Double blind	Open label
PS	ECOG PS 0/1	WHO PS 0/1
Brain mets	Treated, asymptomatic	Asymptomatic *or* treated and stable off steroids and anticonvulsants for ≥1 mo before study entry
Platinum agent	Carboplatin	Carboplatin *or* cisplatin
Dosing frequency	Q3W	Induction: Q3W Maintenance: Q4W
No. CT cycles	4	Durvalumab arm: 4 Control arm: 4-6
PCI	Permitted during maintenance	Durvalumab arm: not permitted Control arm: permitted

1. Horn. NEJM. 2018;379:2220. 2. Paz-Ares. Lancet. 2019;394:1929.

ARTICLES | VOLUME 21, ISSUE 5, P645-654, MAY 2020

Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial

José Trigo, MD • Vivek Subbiah, MD • Prof Benjamin Besse, MD • Victor Moreno, MD • Rafael López, MD • María Angeles Sala, MD • et al. Show all authors • Show footnotes

Published: March 27, 2020 • DOI: https://doi.org/10.1016/S1470-2045(20)30068-1 •

Summary

Background

Few options exist for treatment of patients with small-cell lung cancer (SCLC) after failure of first-line therapy. Lurbinectedin is a selective inhibitor of oncogenic transcription. In this phase 2 study, we evaluated the acti and safety of lurbinectedin in patients with SCLC after failure of platinum-based chemotherapy.

Findings

Between Oct 16, 2015, and Jan 15, 2019, 105 patients were enrolled and treated with lurbinectedin. Median follow-up was 17·1 months (IQR 6·5–25·3). Overall response by investigator assessment was seen in 37 patients (35·2%; 95% CI 26·2–45·2). The most common grade 3–4 adverse events (irrespective of causality) were haematological abnormalities—namely, anaemia (in nine [9%] patients), leucopenia (30 [29%]), neutropenia (48 [46%]), and thrombocytopenia (seven [7%]). Serious treatment-related adverse events occurred in 11 (10%) patients, of which neutropenia and febrile neutropenia were the most common (five [5%] patients for each). No treatment-related deaths were reported.

Interpretation

Lurbinectedin was active as second-line therapy for SCLC in terms of overall response and had an acceptable and manageable safety profile. Lurbinectedin could represent a potential new treatment for patients with SCLC, who have few options especially in the event of a relapse, and is being investigated in combination with doxorubicin as second-line therapy in a randomised phase 3 trial.

CONCLUDING REMARKS

- Lung NET patients should be managed within or in collaboration with a dedicated multidisciplinary team (MDT)
- A complete and radical anatomic resection + N1/N2 lymphadenectomy should be performed in resectable Lung NET
- Everolimus is the only approved drug for the advanced Lung NET
- Octreotide or lanreotide were not specifically approved but they are recommended for low grade indolent SSTR+ Lung NET
- Chemotherapy , PRRT, Liver directed therapies - option in advanced NET