Κλινικό Φροντιστήριο Νευροενδοκρινών Νεοπλασμάτων

Η θέση των ανάλογων σωματοστατίνης στο νέο θεραπευτικό περιβάλλον των Νευροενδοκρινών όγκων

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No conflicts of interest to declare

NET: Wide Spectrum of Malignancies

NET arise from neuroendocrine cells throughout the body

Pancreatic NET
(formerly called islet cell tumors[a])

Functional (<10%)

- Gastrinoma
- Insulinoma
- Glucagonoma
- VIPoma
- Somatostatinoma

Nonfunctional (~60-90%)

Carcinoid tumors (other NET)

Foregut

- Lungs
- Stomach
- Duodenum

Midgut

- Jejunum
- Ileum
- Transverse, right colon
- Appendiceal

Hindgut

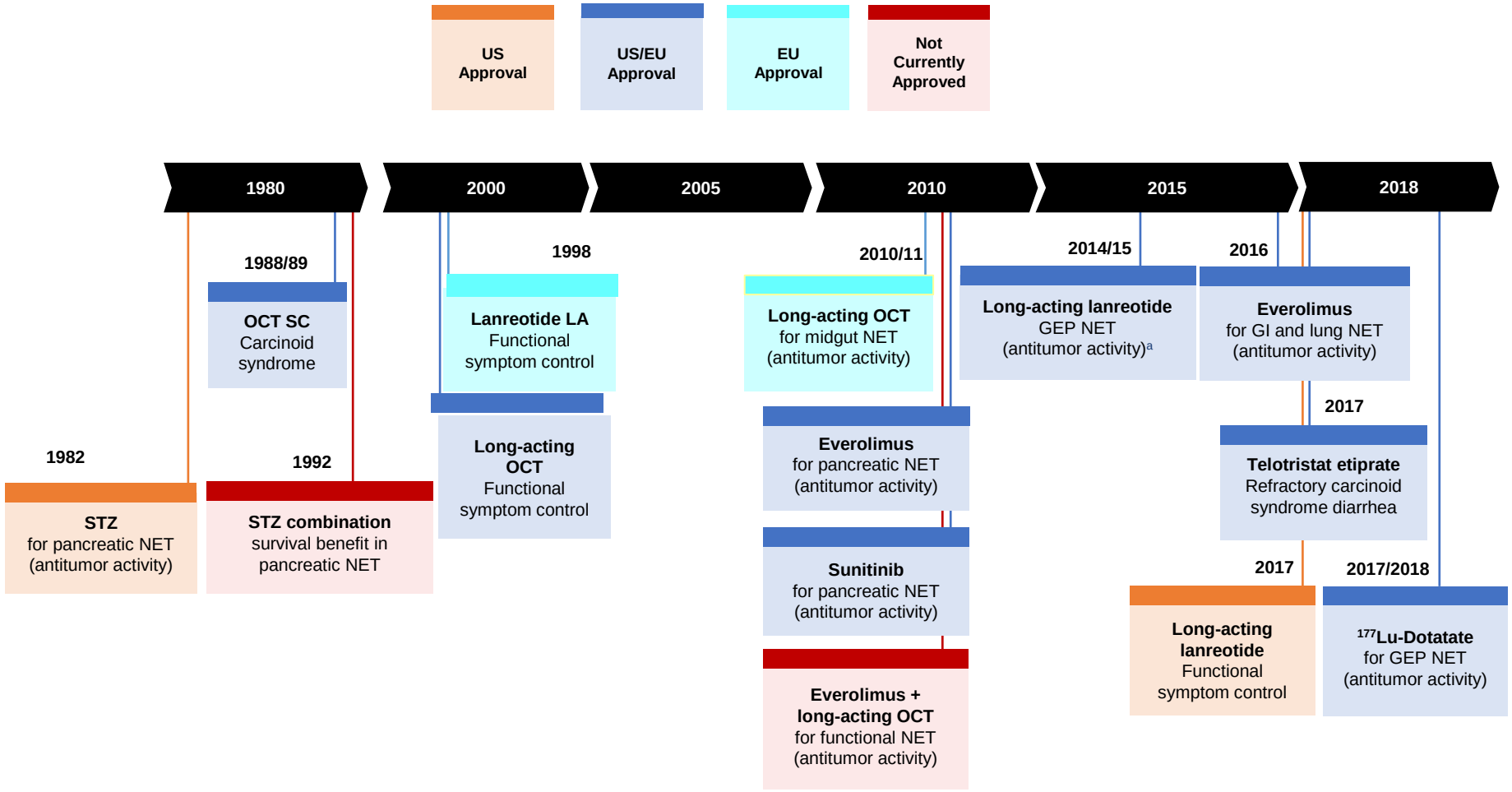
- Left, sigmoid colon
- Rectum

Additional Sites

- Ovary
- Medulla
- Adrenal medulla
- Paraganglia

Unknown Primary

Treatment Evolution for NEN Patients



What ARE the Treatment goals for NETs?

Eradication[1]
Resection of tumour/metastatic lesion if possible

Control tumour growth[1]
Prolong survival of the patients

Symptom control[1]
Symptoms from CS, functional pancreatic NETs, bulky tumours/metastasis etc

Improve/maintain QoL[2]

- CS, carcinoid syndrome; NET, neuroendocrine tumour; QoL, quality of life.
- 1. Oberg K, et al. *Ann Oncol* 2010;21(suppl 7):vii72–vii80; 2. Beaumont JL, et al. *Pancreas* 2012;41:461–466.

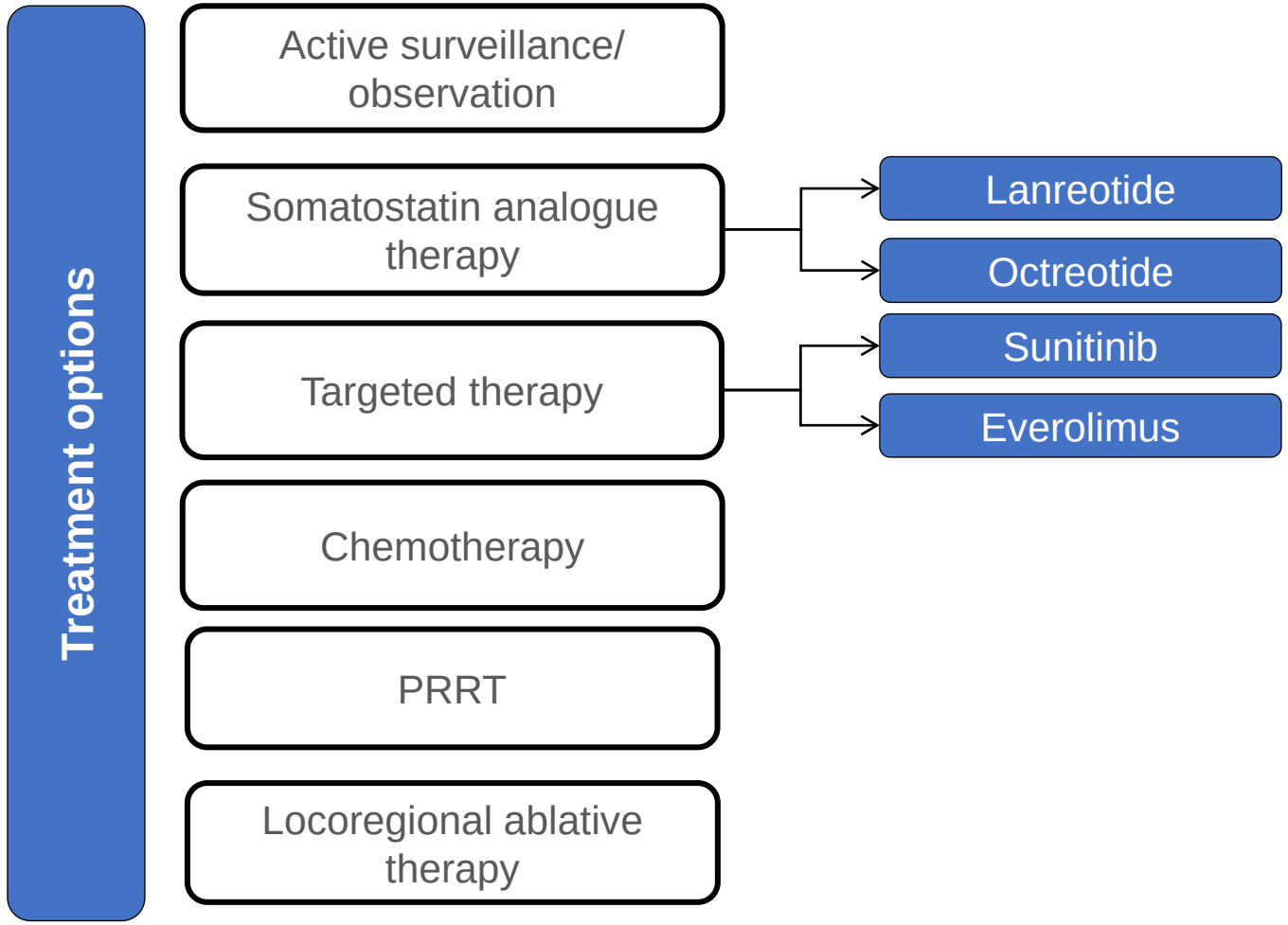
Key factors influencing treatment decisions

Tumour grade (Ki-67)	• High grade/low grade • Progressive or stable disease – Pace of progression

Tumour stage	• Extent/burden of disease
	  – Localised or metastatic disease
	  – Low tumour burden/high tumour burden

Tumour functionality	• Functional tumour • Non-functional tumour

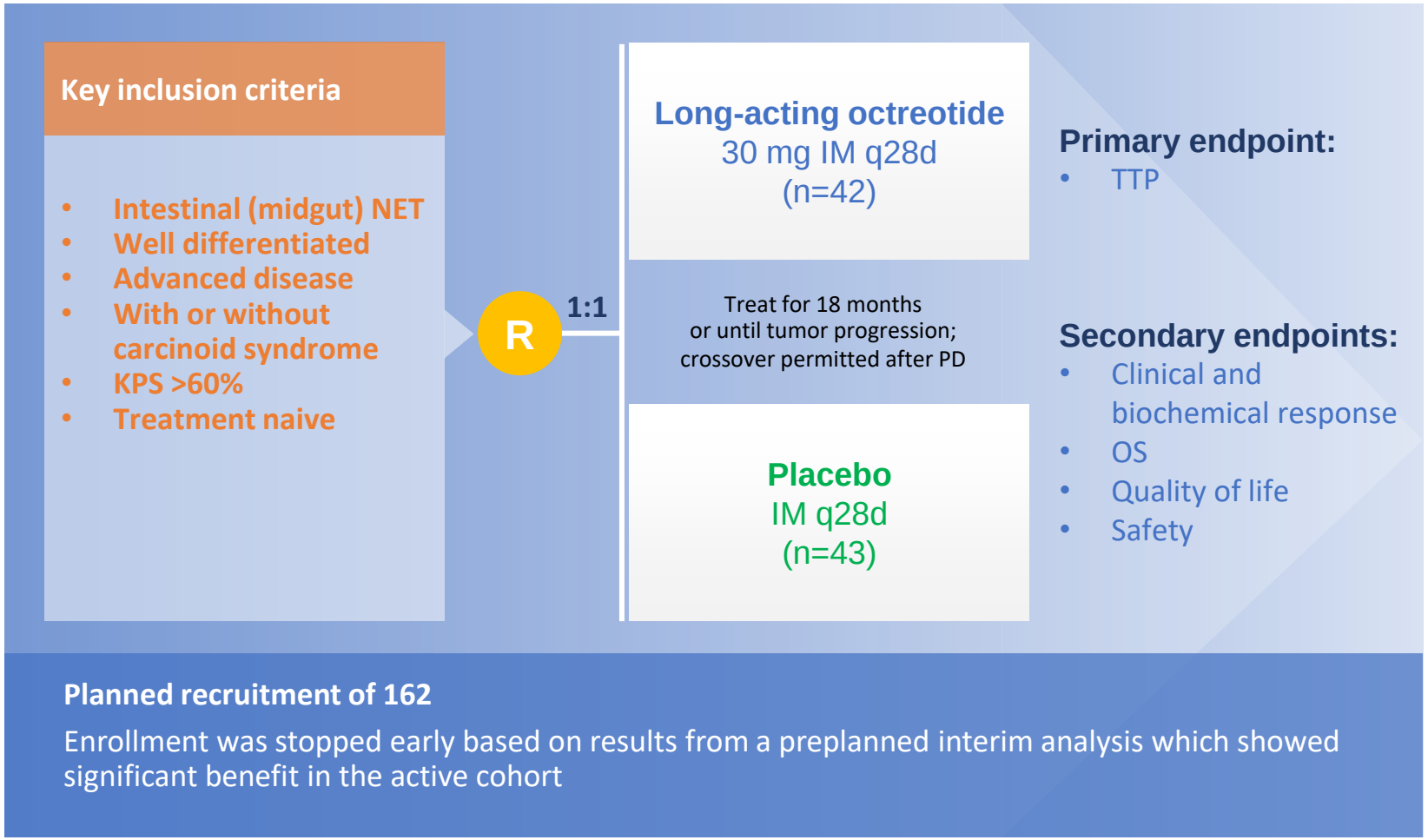
Treatment options available for the management of patients with unresectable, advanced NET



Treatment decisions: criteria for choosing treatment for advanced NETs

Criteria for choosing somatostatin analogues	• Functional tumours • Low-volume disease • G1 and subset of G2 (Ki-67 <10%) • Non-progressive disease • **Aim is to delay time to disease progression**
Criteria for choosing targeted therapies	• Moderate–low volume disease • G1/G2 tumours (Ki-67 <20%) • Moderate-low rate of disease progression • **Aim is to delay time to disease progression**
Criteria for choosing chemotherapy	• Bulky disease/high volume disease • More rapid disease progression • G2/G3 tumours (occasionally G1 tumours) • **Response required**

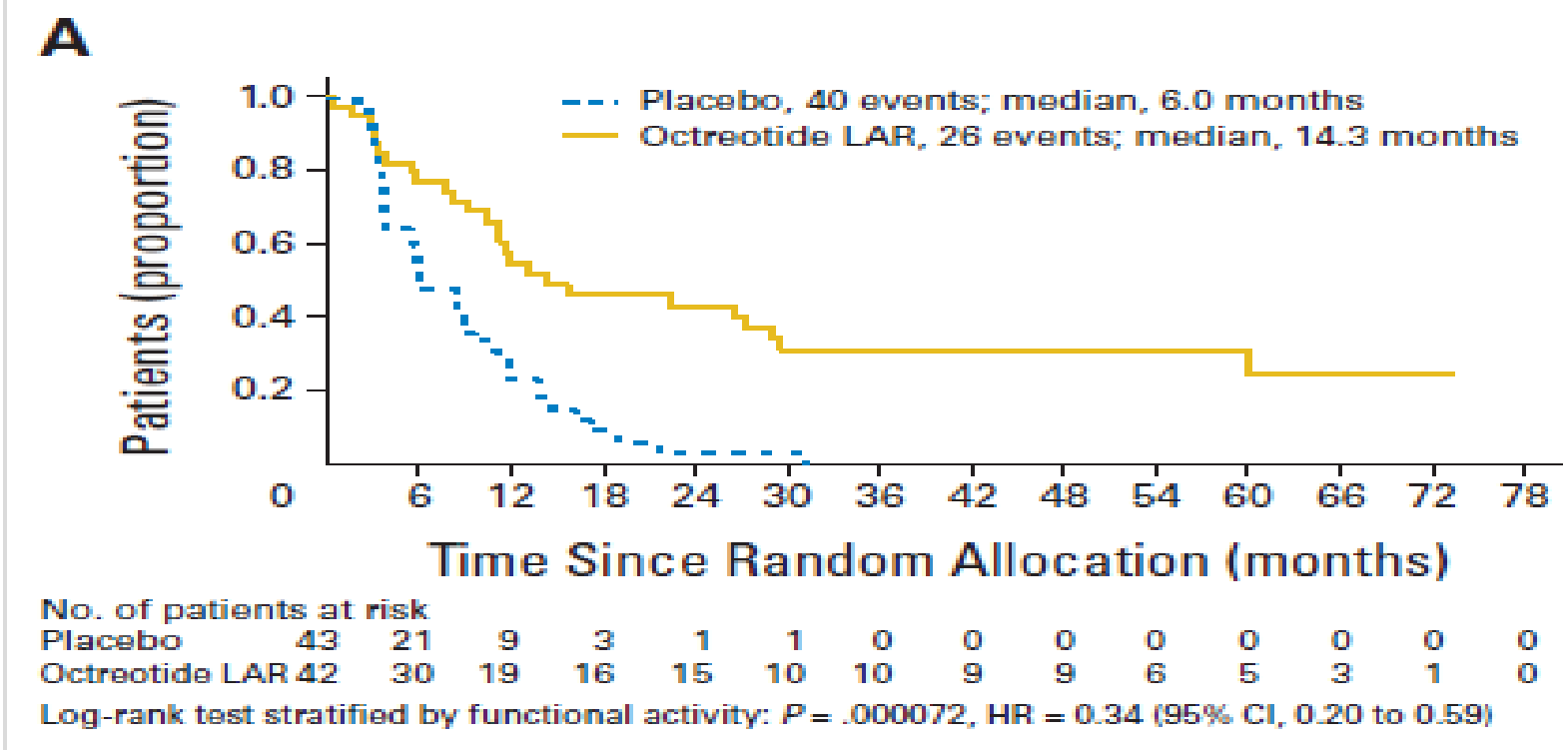
PROMID: Evaluation of the antiproliferative effect of octreotide LAR



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

PROMID: Octreotide LAR 30 mg significantly extends TTP compared to placebo

66% reduction in the risk of tumor progression[1]



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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D., Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*

N Engl J Med 2014;371:224-33.
DOI: 10.1056/NEJMoa1316158

CLARINET : Study aim and design

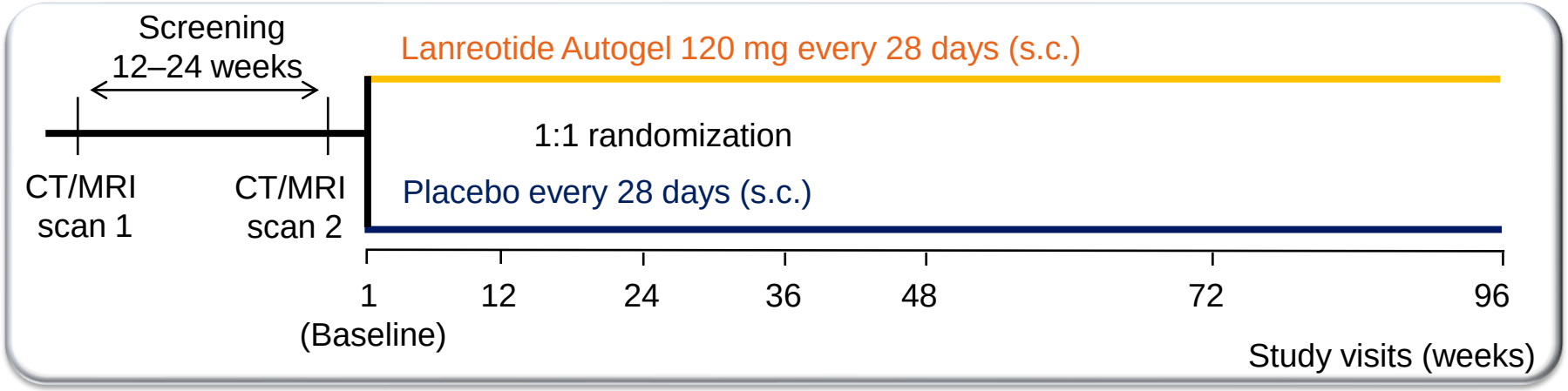
CLARINET
Controlled study of **L**anreotide **A**ntiproliferative **R**esponse **I**n **NET**

Aim

- To compare effect of lanreotide Autogel 120 mg vs. placebo on PFS in non-functioning enteropancreatic NETs

Design

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



Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

CLARINET: Patient population

- Adults with sporadic non-functioning* enteropancreatic NETs
- Well-/moderately differentiated tumours with Ki-67 <10%
- Tumours measurable according to RECIST 1.0 (centrally assessed)
- Unresectable locally advanced tumours or metastatic disease (or patients declined surgery)
- Target lesion(s) classified as grade ≥2 on somatostatin receptor scintigraphy
- No use of interferon, chemoembolization, or chemotherapy in previous 6 months, and SSA naïve (unless >6 months previously and <15 days in duration)

•*Including gastrinomas adequately controlled by proton pump inhibitors and NETs of unknown primary origin

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

CLARINET: Study endpoints

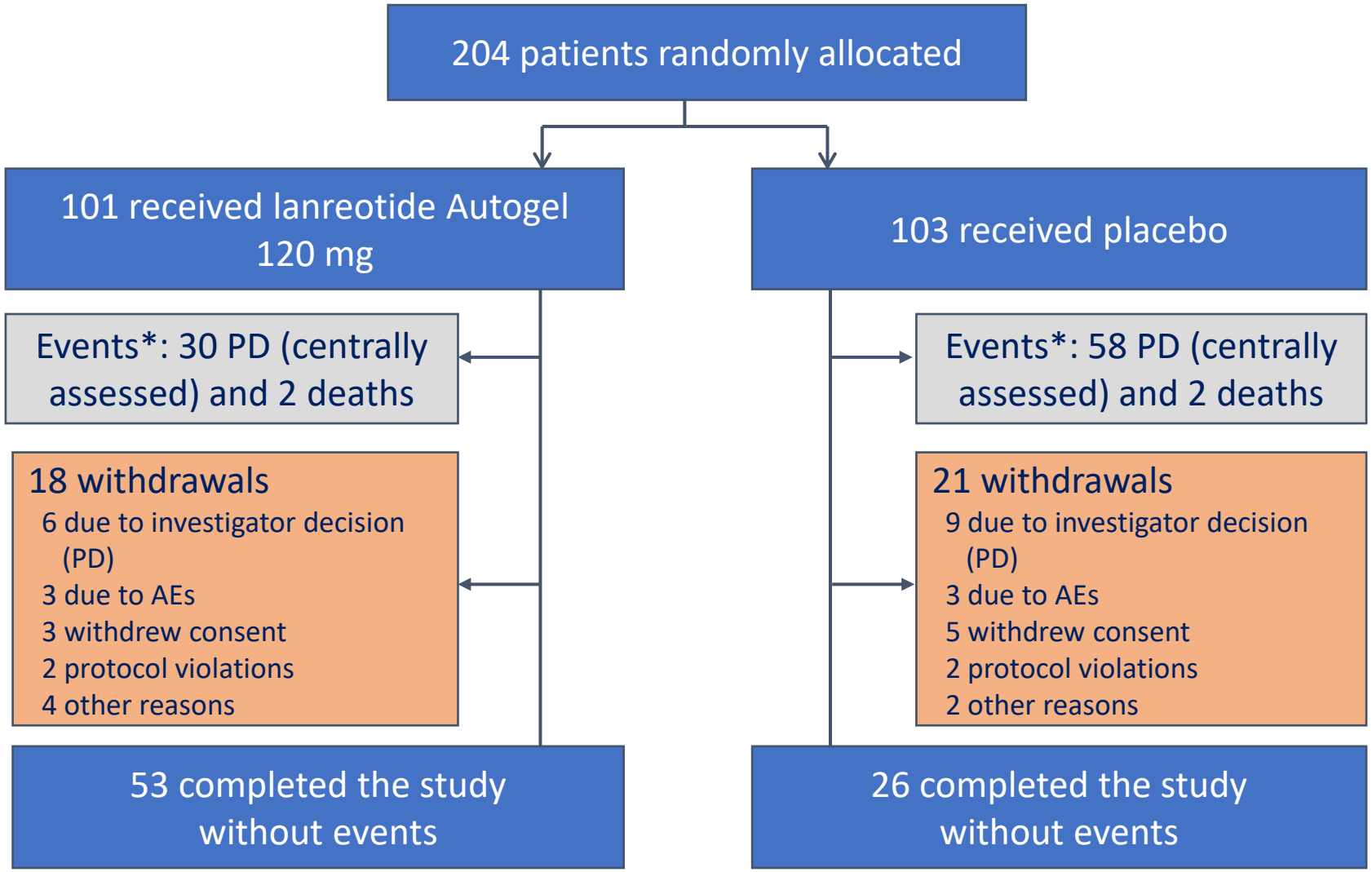
- Primary endpoint
- PFS (time to death or PD) within 96 weeks of first injection
  - PD assessed centrally with RECIST 1.0
  - PFS was also examined in pre-defined subgroups (e.g. tumour origin, tumour grade, and hepatic tumour volume)

- Key secondary endpoints
  - Overall survival
  - % patients alive and without PD at weeks 48 and 96
  - Time to tumour progression
  - Quality of life
  - % patients with ≥50% reduction in CgA*
  - PK
  - Antibodies
  - Safety

*For subgroup of patients with baseline levels >ULN. CgA, chromogranin A; PD, progressive disease; ULN, upper limit of normal.

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

CLARINET: Patient disposition



*Two deaths occurred in lanreotide group after withdrawal for another reason and two deaths occurred and two PDs detected in placebo group after withdrawal for another reason; †despite a central assessment of PD. AEs, adverse events.

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

CLARINET: Baseline characteristics

	Lanreotide (n=101)	Placebo (n=103)
Men, n (%)	53 (52)	54 (52)
Age in years, mean (SD)	63.3 (9.8)	62.2 (11.1)
Time since diagnosis in months		
Mean (SD)	32.6 (46.1)	34.4 (41.4)
Median	13.2	16.5
Primary tumour resected, n (%)	40 (40)	39 (38)
NET origin, n (%)		
Pancreas	42 (42)	49 (48)
Midgut	33 (33)	40 (39)
Hindgut	11 (11)	3 (3)
Unknown/other	15 (15)	11 (11)
Tumour progression, n (%)	4 (4)	5 (5)
Prior treatment, n (%)	16 (16)	16 (16)
Tumour grade, n (%)*		
1 (Ki-67: 0–2%)	69 (68)	72 (70)
2 (Ki-67: 3–10%)	32 (32)	29 (28)
Unknown	0	2 (2)
Hepatic tumour volume, n (%)		
0%	16 (16)	18 (17)
>0–10%	33 (33)	40 (39)
>10–25%	13 (13)	17 (17)
>25–50%	23 (23)	12 (12)
>50%	16 (16)	16 (16)
Chromogranin A, n (%)		
≤1 × ULN	33 (33)	34 (33)
1–2 × ULN	25 (25)	18 (17)
>2 × ULN	41 (41)	48 (47)
Unknown	2 (2)	3 (3)

Data from NEJM online appendix

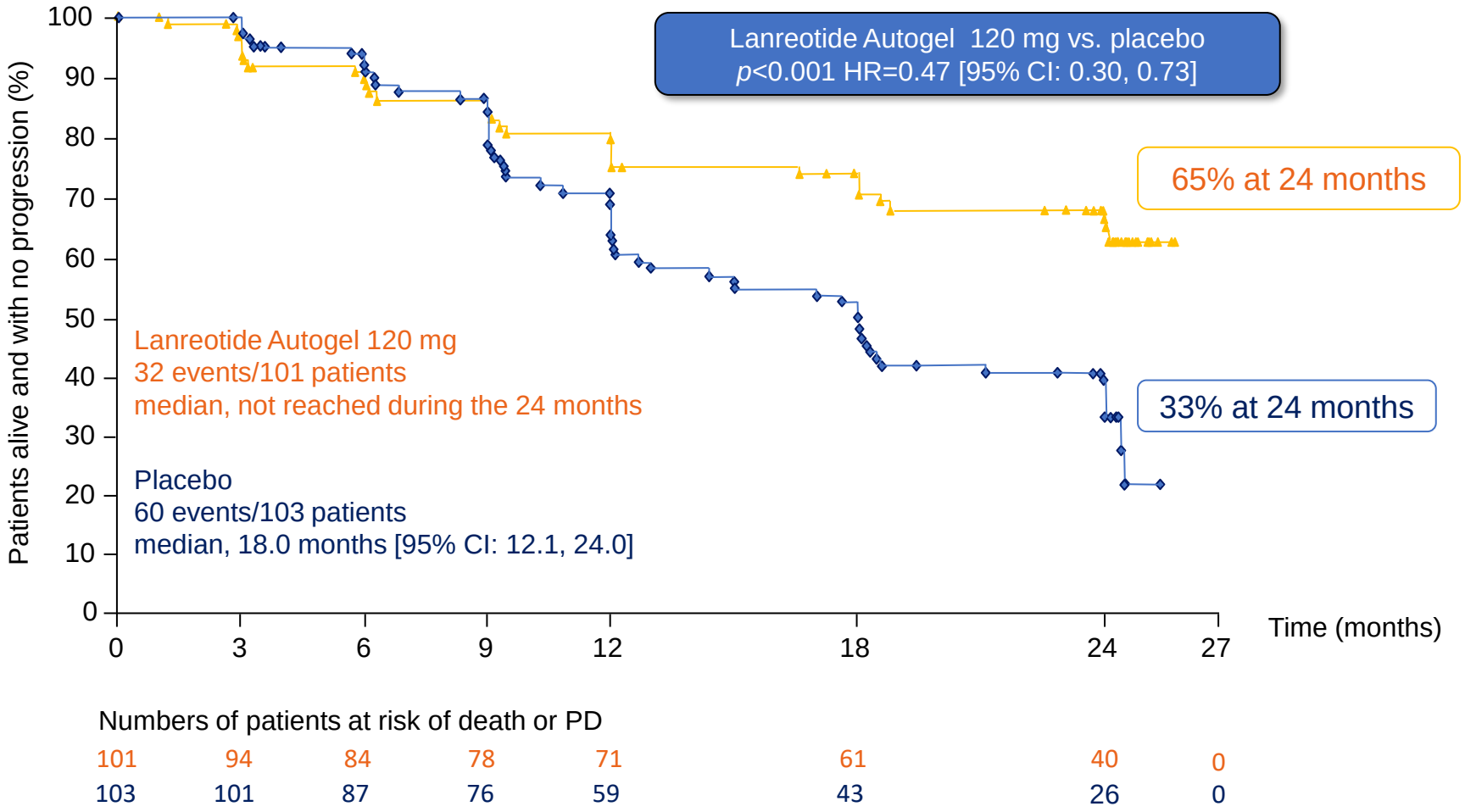
Data from NEJM online appendix

*Ki-67 thresholds as per World Health Organization (WHO) 2010 classification with values >2–≤10% assigned to grade 2.

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

PFS significantly prolonged with lanreotide Autogel 120 mg vs. placebo

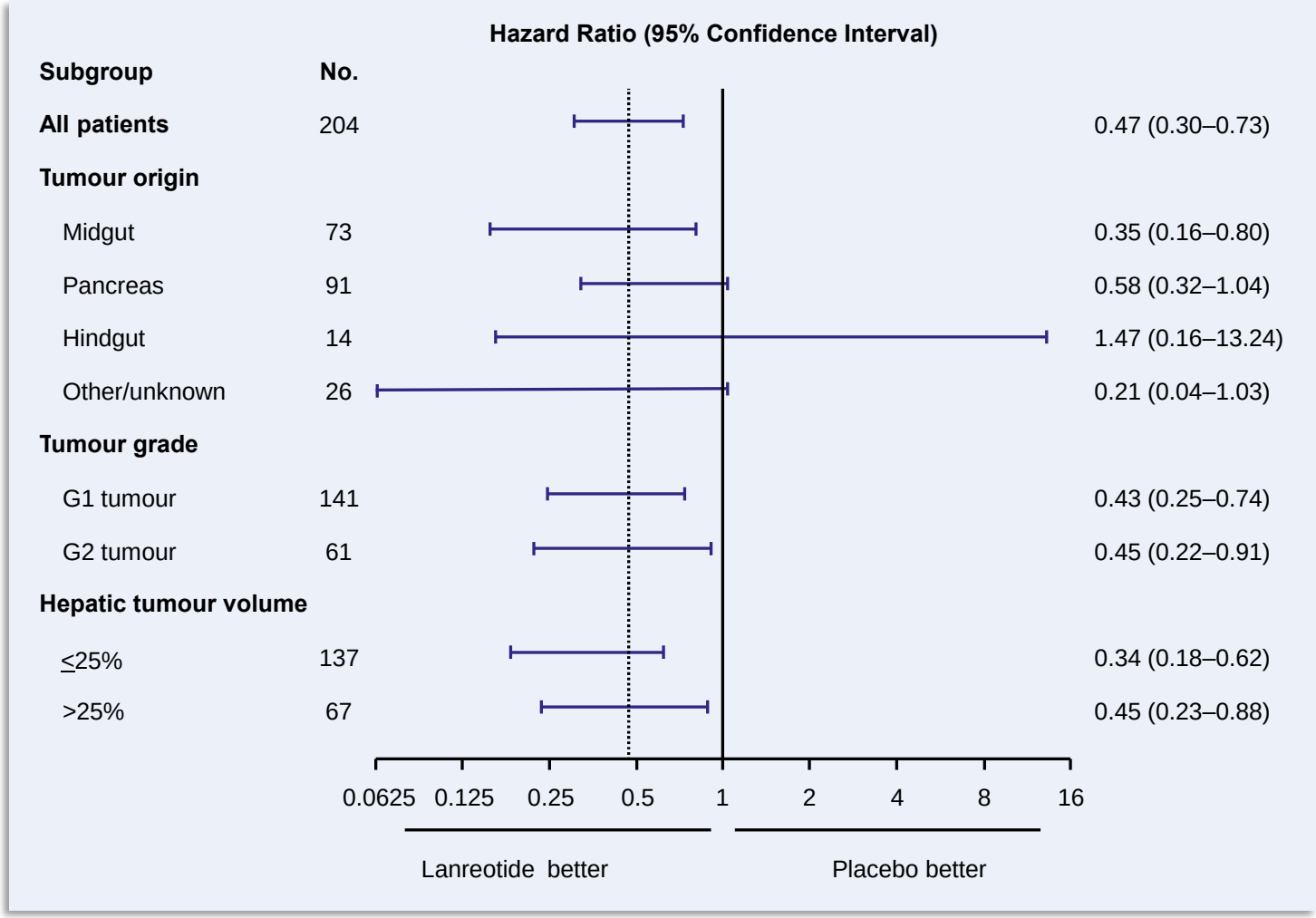
with 53% risk reduction of disease progression or death with Somatuline 120mg versus placebo



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

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

Therapeutic effect in pre-defined subgroups generally consistent with overall population

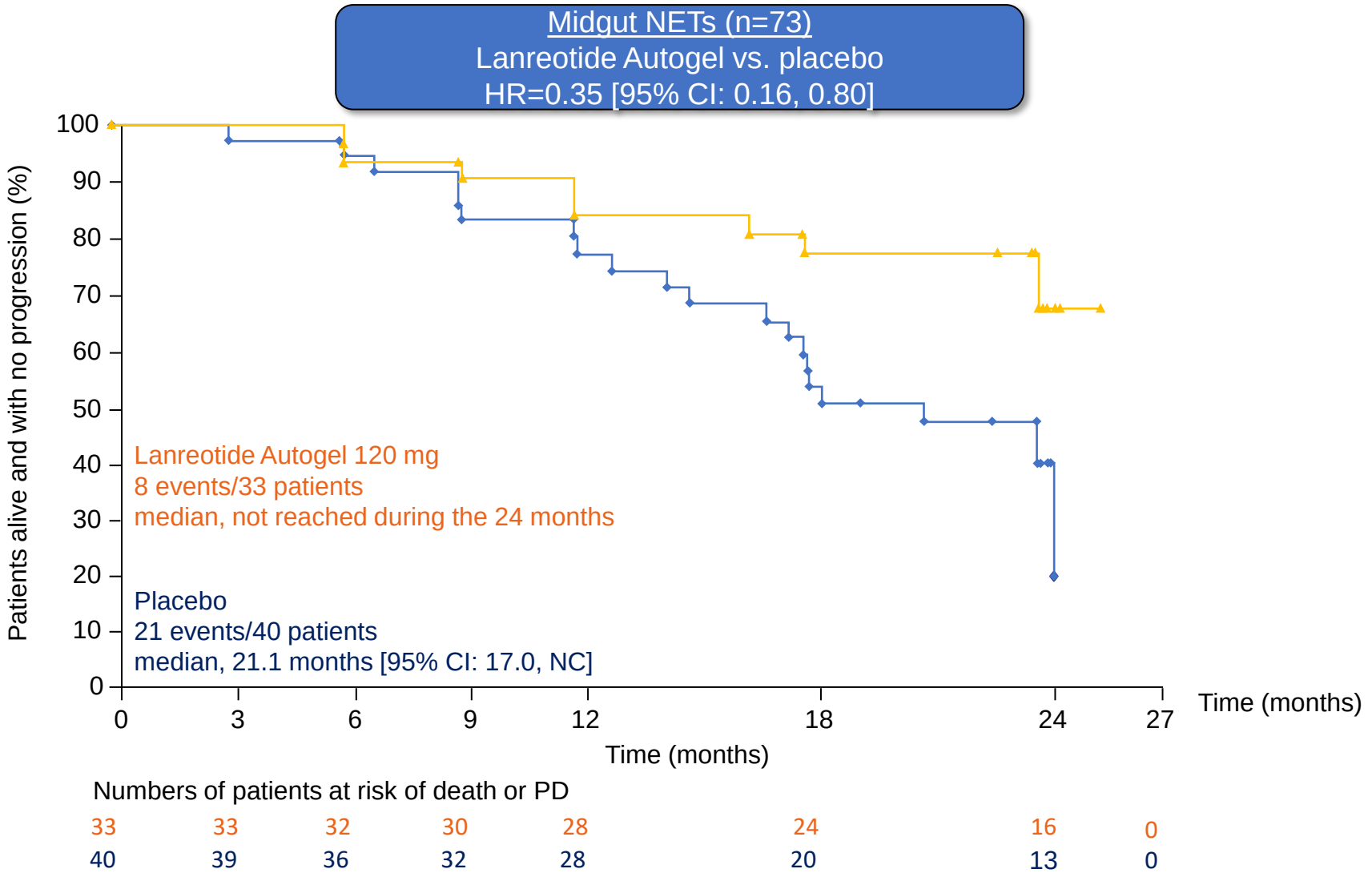


Learning point from CLARINET trial
Lanreotide Autogel can control tumour growth in G1/G2 (Ki-67≤10%) advanced midgut and pancreatic NETs even with substantial hepatic tumour load

Subgroups pre-defined although number of categories for hepatic tumour volume was simplified *post hoc* from five to two.

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

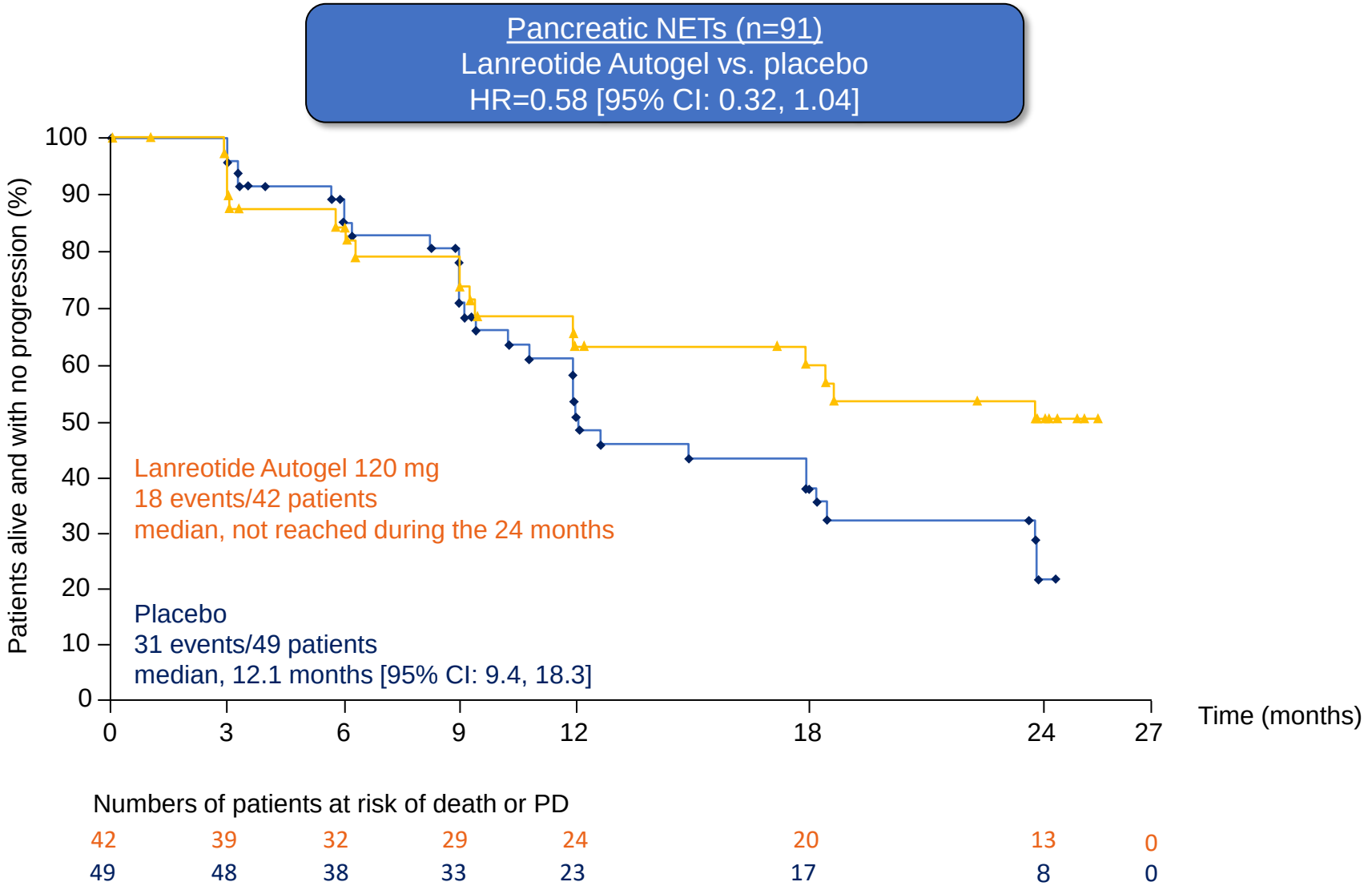
Effect in midgut tumors consistent with overall population



HR derived from Cox proportional hazards model. NC, not calculable.

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

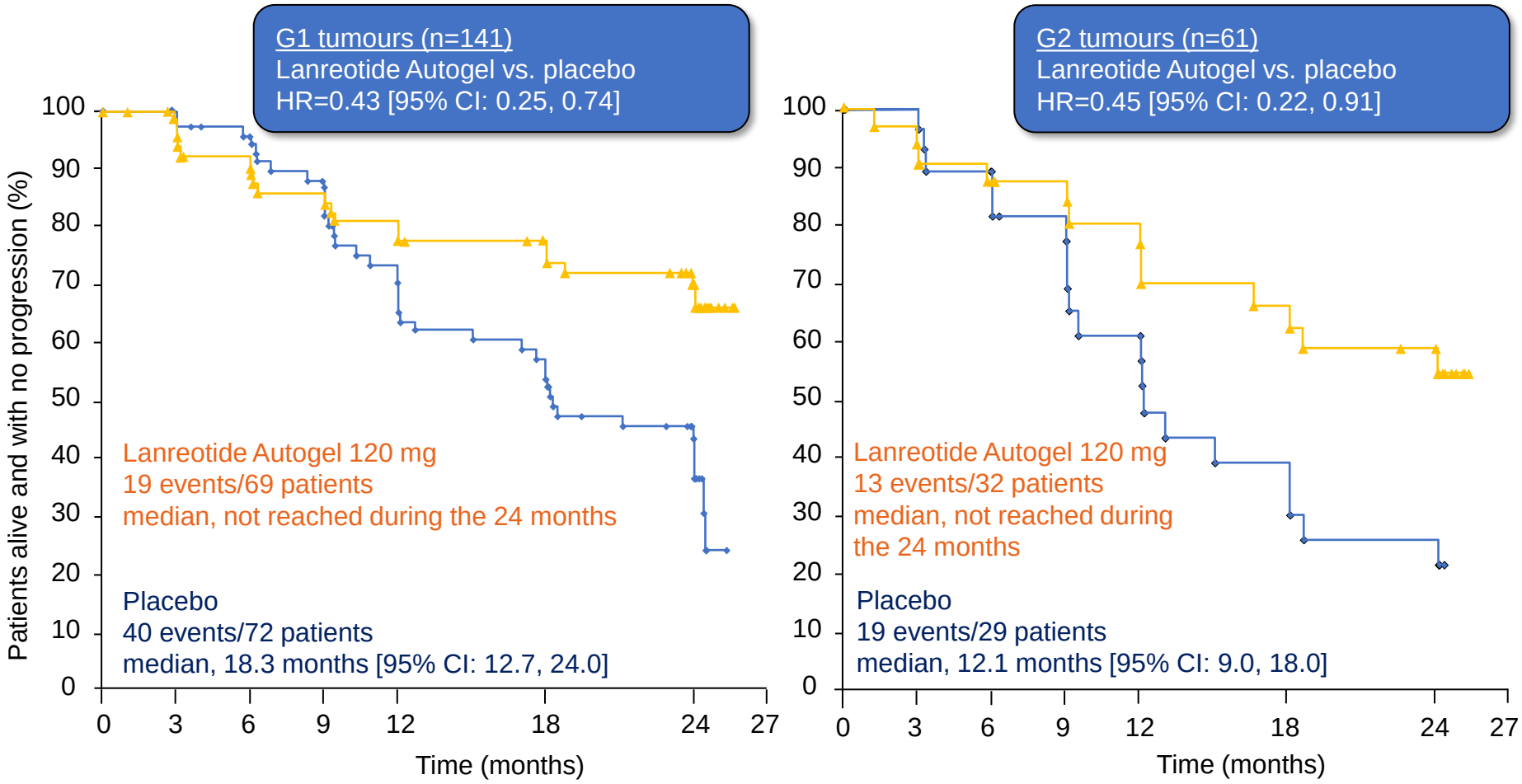
Effect in pancreatic tumors consistent with overall population



HR derived from Cox proportional hazards model.

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

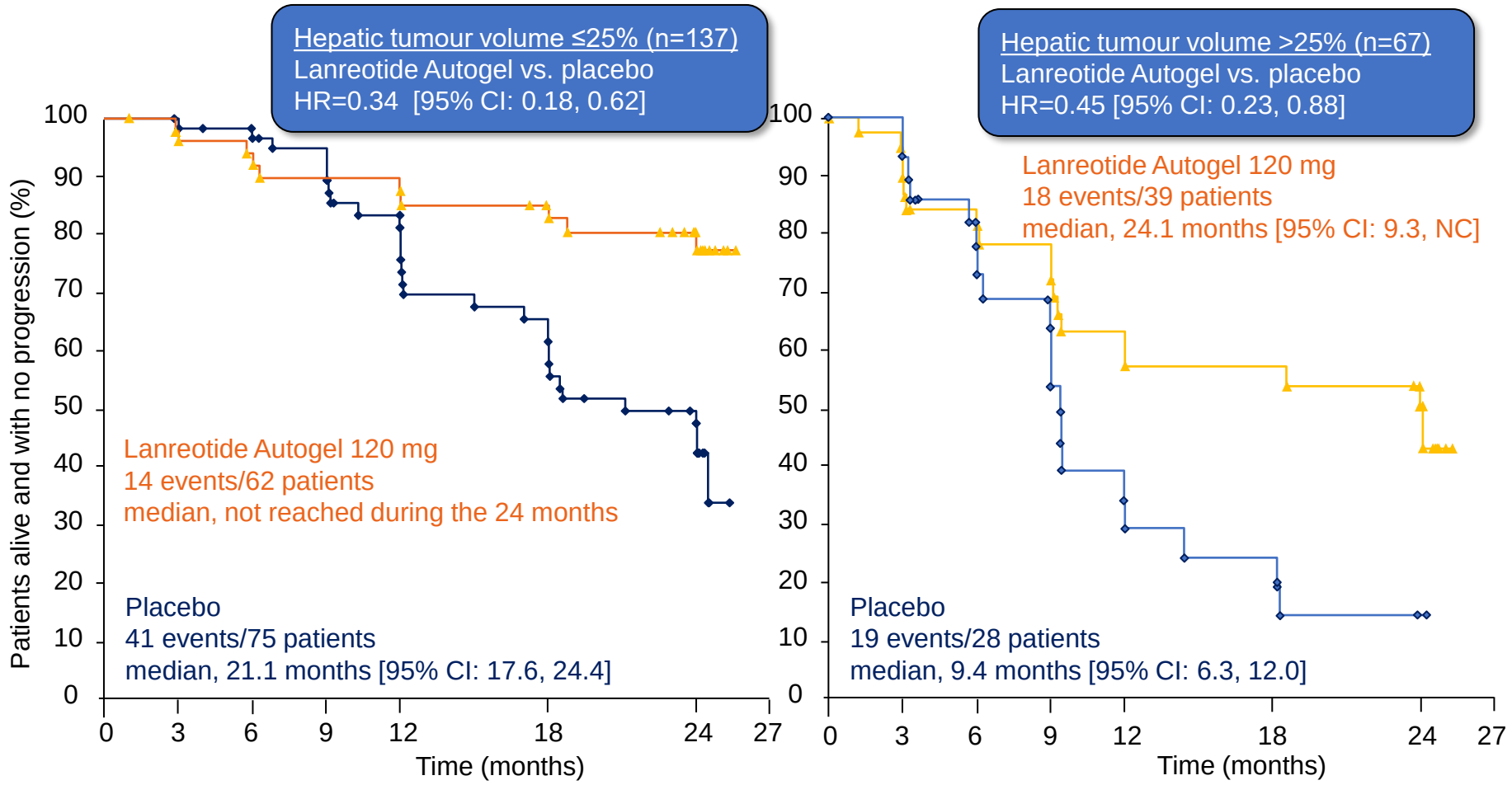
Effect in G1 and G2 tumours consistent with overall population



HR derived from Cox proportional hazards model.

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

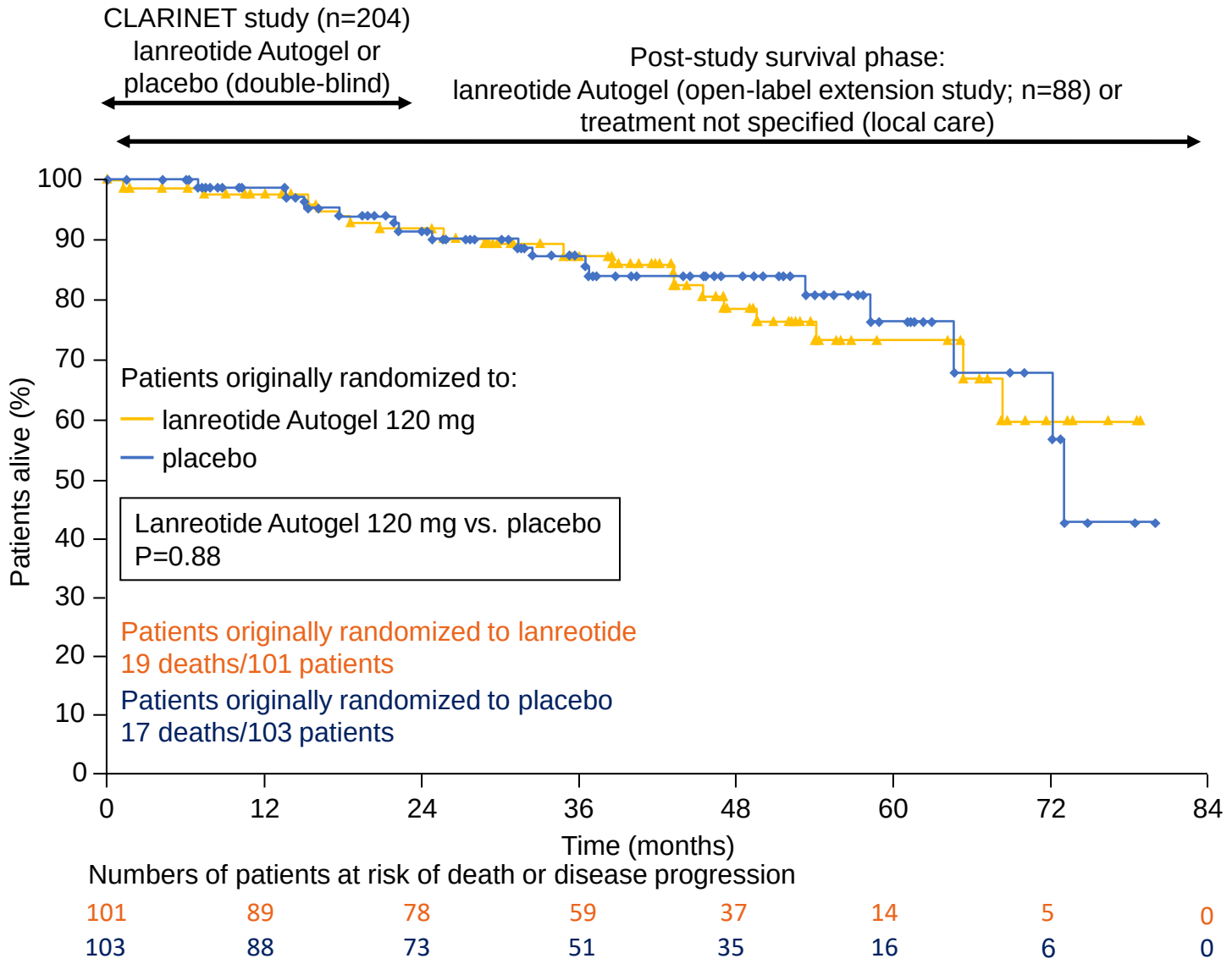
Effect in low and high hepatic tumour volume consistent with overall population



HR derived from Cox proportional hazards model.

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

OS: no significant difference



•P-value derived from log-rank test.

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

CLARINET: Other secondary endpoints

- Change in QoL not significantly different between groups
- Other secondary endpoints significantly favoured lanreotide

	Lanreotide	Placebo	Lanreotide vs. placebo
Patients alive and progression-free at: n (%) Week 48 Week 96	(n=101) 67 (66) 53 (52)	(n=103) 50 (49) 26 (25)	Odds ratio [95% CI] 2.11 [1.19, 3.76]* 3.27 [1.81, 5.93]***
Time to tumour progression in months Median [95% CI]	(n=101) (30 events) Not reached	(n=103) (58 events) 18.0 [12.1, 24.0]	Logrank test ***
Change in EORTC QLQ-C30 global health status score from baseline to LVA, LS mean (SE)	(n=95) –5.18 (3.73)	(n=98) –4.87 (3.70)	LS mean (SE) [95% CI] –0.31 (2.74) [–5.73, 5.10]
Patients with ≥50% reduction in CgA between baseline and LVA, n (%)†	(n=64) 27 (42)	(n=64) 3 (5)	Odds ratio [95% CI] 15.20 [4.29, 53.87]***

Data from NEJM online appendix:

11 patients developed putative anti-lanreotide antibodies, but there was no evidence of reduced therapeutic effect

Steady-state serum lanreotide levels were reached after six injections; thereafter, levels were maintained

*p<0.05; *** p<0.001; †in subgroup with CgA levels >ULN at baseline. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire C30; LS, least squares; LVA, last post-baseline value available.

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

Safety: consistent with known profile

- No treatment-related deaths and few withdrawals due to AEs
- AEs consistent with known profile of lanreotide Autogel

	Lanreotide (n=101)	Placebo (n=103)
Any AEs	89 (88)	93 (90)
Related to treatment	50 (50)	29 (28)
Severe / moderate / mild	26 (26) / 44 (44) / 17 (17)	32 (31) / 44 (43) / 17 (17)
Any serious AEs	25 (25)	32 (31)
Related to treatment	3 (3)	1 (1)
Withdrawals due to AEs	3 (3)	3 (3)
Related to treatment	1 (1)	0
Treatment-related AEs occurring in ≥10% of patients		
Diarrhea	26 (26)	9 (9)
Abdominal pain	14 (14)	2 (2)
Cholelithiasis	10 (10)	3 (3)

Data are number (%) of safety population.

Caplin M., *et al.* Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. *New Engl J Med* 2014;371(3):224–33

CLARINET: Conclusions

- PFS was significantly prolonged with lanreotide Autogel 120 mg in patients with grade 1 or 2 (Ki-67 <10%) metastatic enteropancreatic NETs
  - Median PFS not reached with lanreotide during the 24-month study vs. 18 months with placebo (p<0.001)
  - 53% risk reduction for PD
- Safety profile consistent with previous studies

Caplin M., *et al. New Engl J Med* 2014;371(3):224–33

Implications for clinical practice

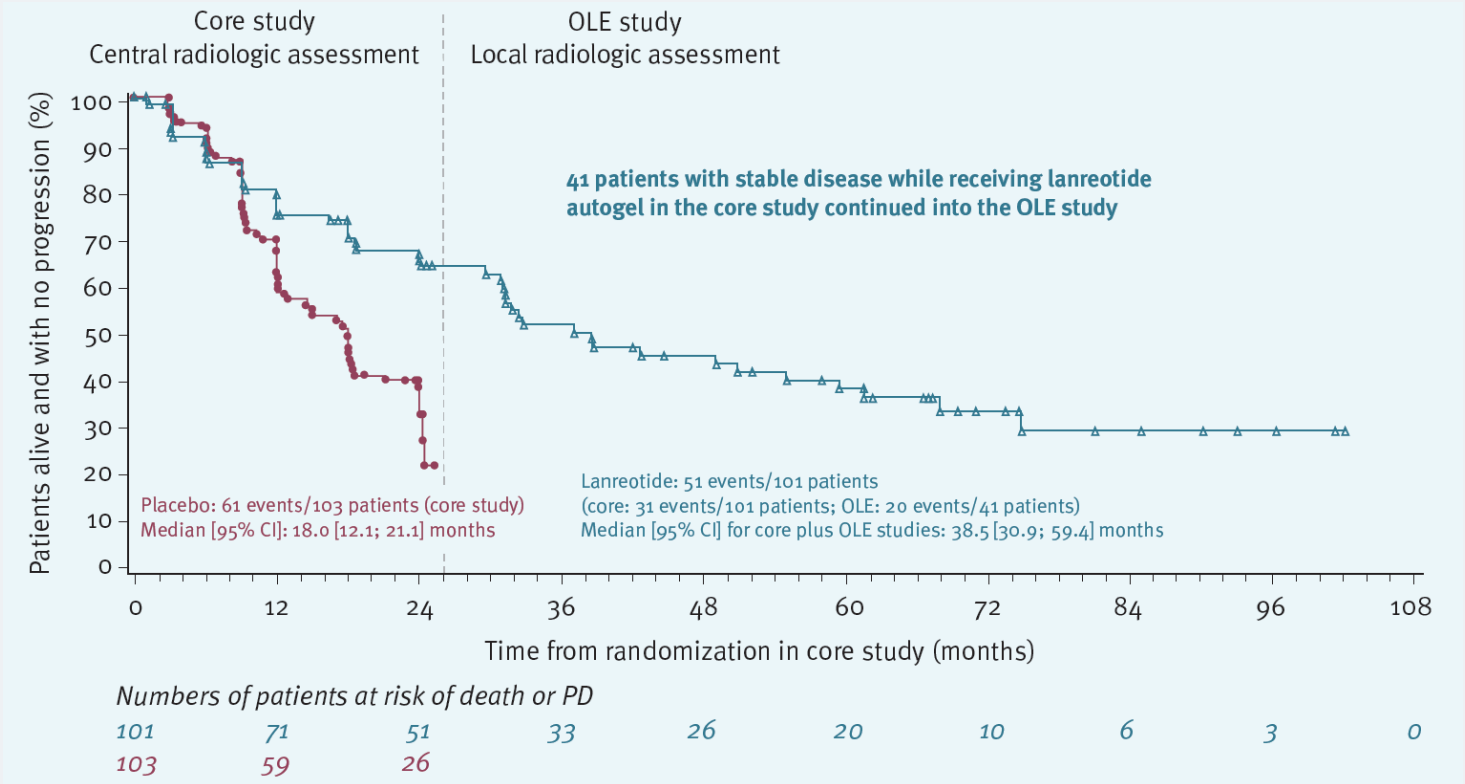
- “Lanreotide Autogel 120mg/4W is associated with prolonged PFS among patients with advanced, grade 1 or 2 (Ki-67 <10%) enteropancreatic, somatostatin receptor–positive NETs with prior stable disease, irrespective of the hepatic tumor volume”.

- CLARINET study represents the highest level of evidence demonstrating antiproliferative effects of Lanreotide Autogel 120 mg in patients with GEP NETs.

Caplin M., *et al. New Engl J Med* 2014;371(3):224–33

CLARINET OLE: Lanreotide 120 mg efficacy data consistent with continued anti-tumour effects[1]

Progression-free survival (PFS; intention-to-treat population)



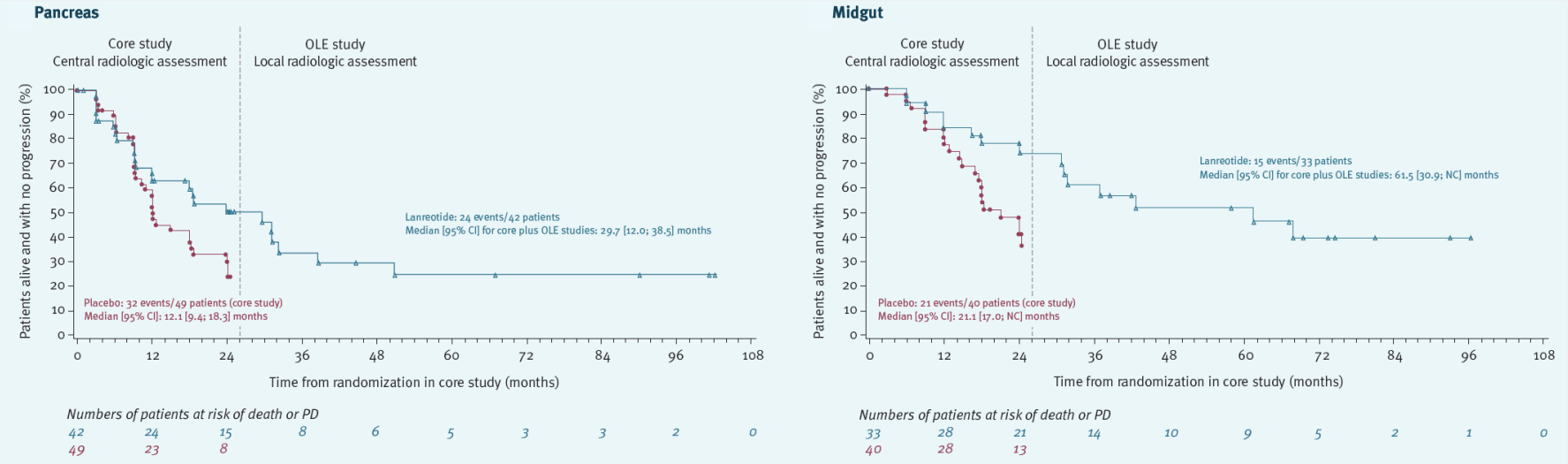
Data are presented in months approximated to 4 weeks. The data from the OLE study (n=41) were appended to data from the core study (n=101) for lanreotide autogel.

CI, confidence interval; OLE, open-label extension; PD, progressive disease.

1. Wolin EM, et al. Poster P81. Presented at the ASCO Annual Meeting, Chicago, IL, USA, June 2–6, 2017.

CLARINET OLE: Median PFS was longer in patients with a NET of midgut origin[1]

Progression-free survival (intention-to-treat population) according to tumour origin



Median PFS [95% CI] (no. of patients)

- Hindgut
  - Lanreotide (core study and OLE): 55.0 [2.9, NC] (n=11)
  - Placebo (core study): 24.4 [12.0, 24.4] (n=3)
- Other/unknown
  - Lanreotide (core study and OLE): 59.4 [32.8, 74.8] (n=15)
  - Placebo (core study): 15.0 [6.3, NC] (n=11)

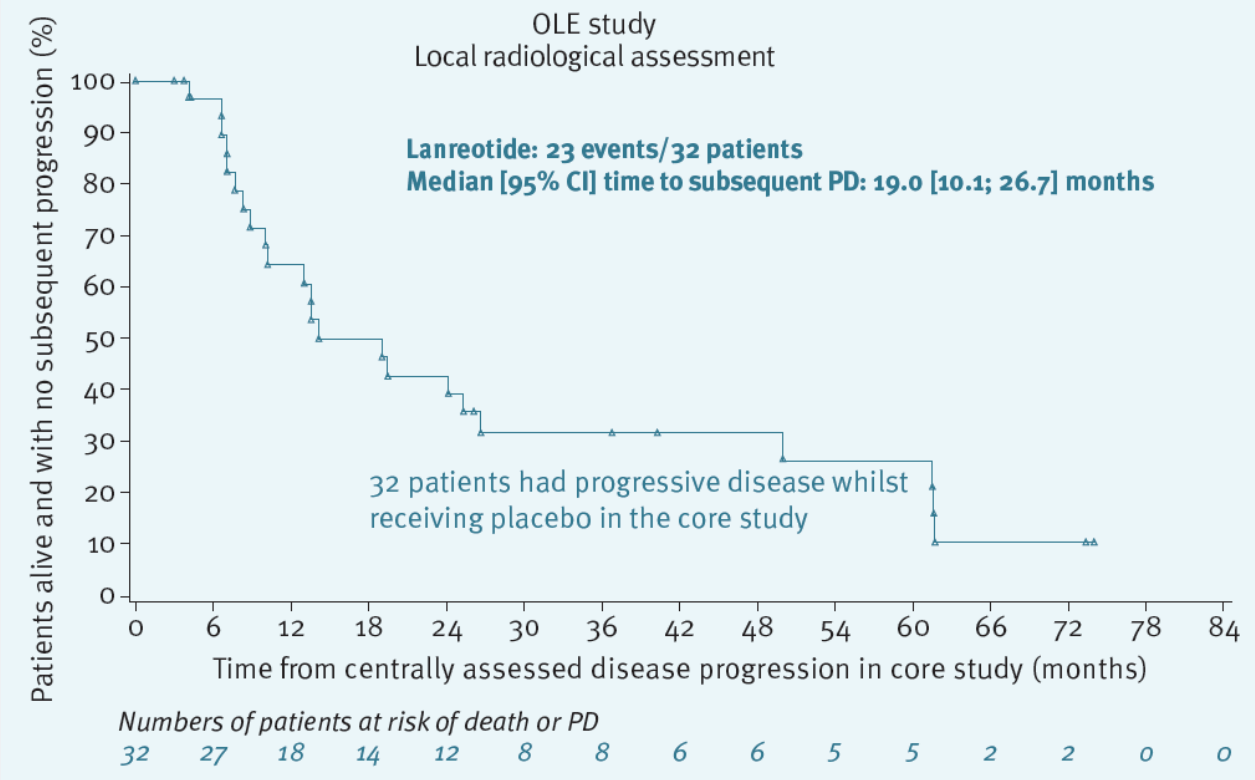
Data are presented in months approximated to 4 weeks. The data from the OLE study were appended to data from the core study for lanreotide autogel.

CI, confidence interval; NC, not calculable; NET, neuroendocrine tumour; OLE, open-label extension; PD, progressive disease; PFS, progression-free survival.

1. Wolin EM, et al. Poster P81. Presented at the ASCO Annual Meeting, Chicago, IL, USA, June 2–6, 2017.

CLARINET OLE: Lanreotide 120 mg has an anti-tumour effect in patients with PD[1]

Time to death or subsequent PD



Data are presented in months approximated to 4 weeks.

CI, confidence interval; OLE, open-label extension; PD, progressive disease.

1. Ćwikła JB, et al. Presented at the ESMO annual congress, Madrid, Spain, September 8–12, 2017.

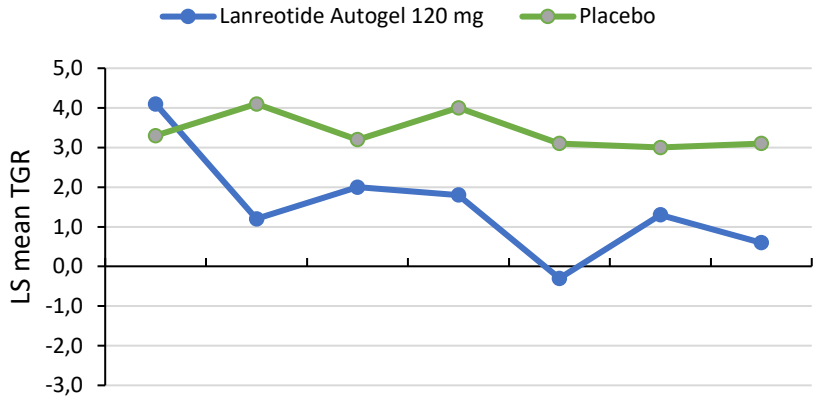
Post-hoc analysis of CLARINET showed that a reduction in TGR following lanreotide treatment was sustained up to 96 weeks[1–3]

Exploratory analysis of TGR in NET patients in CLARINET:

- Target lesions assessed by central radiologic review based on RECIST v1.0
- TGR calculated from sum-of-longest-diameters (SLD) of original target lesions on two CT scans during defined periods
- TGR pre- and post-treatment compared between treatment groups

Results:

- 12 weeks after treatment initiation a significant decrease in TGR following Somatuline® Autogel® treatment vs. placebo was observed
- Trend in TGR between groups was sustained up to 96 weeks
- **TGR at baseline was predictive of the risk of PD/death**
  - TGR at baseline >4%/month was associated with a 4-fold greater risk of PD/death compared with a baseline TGR ≤4%/month (HR 4.1; 95% CI 2.5–6.5; p<0.001; n=187)



Study visit (weeks)	Pre-treatment*	12	24	36	48	72	96
n	200	196	174	154	132	106	90
p value	0.462	0.008	0.277	0.027	0.003	0.009	0.007

- *Pre-treatment TGR is calculated from the second imaging test during the screening period (performed 12–24 weeks after the first screening period).
- CI, confidence interval; CT, computed tomography, HR, hazard ratio; LS, least squares; NET, neuroendocrine tumour; RECIST, response evaluation criteria in solid tumours; TGR, tumour growth rate.
- 1. Caplin ME, et al. *J Clin Oncol* 2016;34(suppl 15):4096; 2. Dromain C, et al. *BMC Cancer* 2019;19:66; 3. Supplement to Dromain C, et al. *BMC Cancer* 2019;19:66.

KEY DATA FROM THE CLARINET AND PROMID STUDIES[1,2]

	PROMID	CLARINET and CLARINET OLE
Patients	• Patients with locally inoperable or metastatic midgut NETs[1] • n=73/85, liver metastasis (most with hepatic tumour load ≤10%)[1] • n=81/85, Ki-67 0–2%[1]	• Patients with non-functioning NETs in the pancreas, midgut and hindgut[2] • n=141/204, Ki-67 0–2%[2] • n=61/204, Ki-67 3–10%[2] • n=67/204 hepatic tumour load >25% • n=89 continued onto the OLE (n=42 continued lanreotide autogel and n=47 switched from placebo to lanreotide autogel)[3]
Recruitment site	N=85 from 18 academic centres in Germany[1]	N=204 patients from 48 secondary or tertiary care centres in 12 counties (12 in Europe, the USA and India)[2]
Intervention	Octreotide LAR 30 mg IM vs placebo[1]	CLARINET: lanreotide autogel 120 mg SC vs placebo[2] OLE: all patients received lanreotide autogel 120 mg SC[3]
Time to progression	TTP: 14.3 vs 6 months (WHO criteria) (HR 0.34)[1]	–
Tumour response	SD: n=28/42 vs n=16/43[1]	–
Survival	OS: Median could not be estimated, HR 0.81 (95% CI: 0.30–2.18)[1]	CLARINET median PFS*: NR vs 18.0 months (RECIST)[2] OLE median PFS (95% CI) : 38.5 months (30.9–59.4)[4] OLE median OS : Not reached >9 years, HR 0.92 (95% CI: 0.5–1.71)[5]

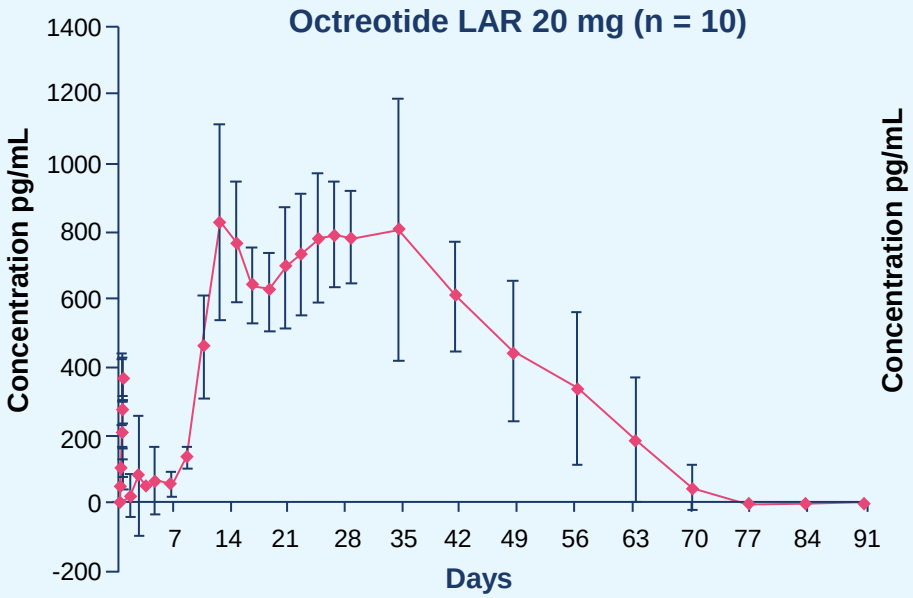
*30 events in the lanreotide group and 58 events in the placebo group; The median PFS for lanreotide 120 mg is calculated for patients in both the core plus the open-label extension trials, this is compared with the 18.0-month median PFS for placebo reported in the core study.

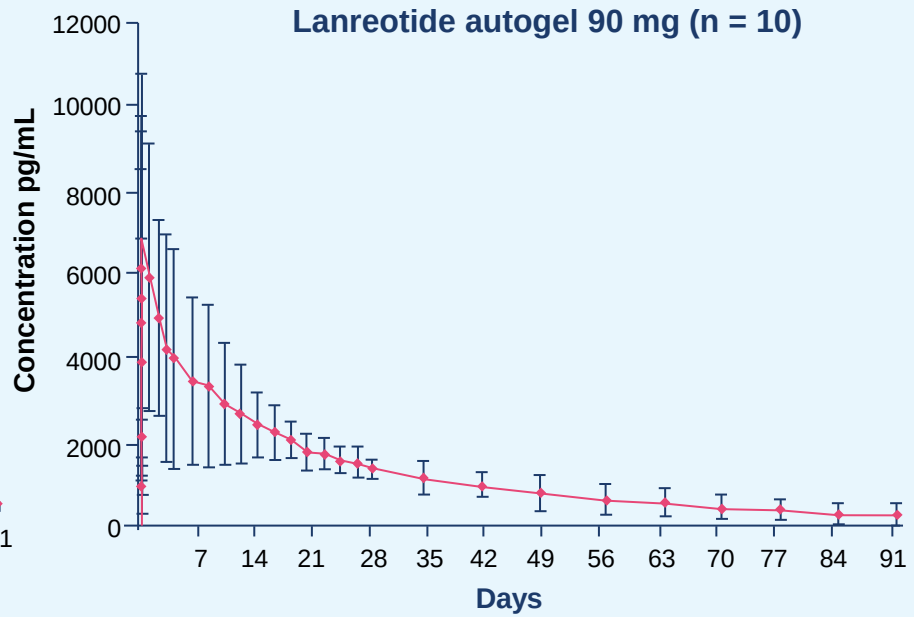
CI, confidence interval; HR, hazard ratio; IM, intramuscular; LAR, long-acting release; NET, neuroendocrine tumour; NR, not reached; OLE, open-label extension; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours; SC, subcutaneous; SD, stable disease; WHO, World Health Organization.

1. Rinke A, et al. *J Clin Oncol* 2009;27:4656–4663; 2. Caplin ME, et al. *N Engl J Med* 2014;371:224–233; 3. Ćwikła JB, et al. Presented at ESMO 2017; 4. Wolin EM, et al. Poster P81. Presented at ASCO 2017; 5. Phan AT, et al. Presented at ENETS 2017.

The single-dose PK profiles of octreotide LAR and lanreotide autogel are different[1]

Pharmacokinetic profiles (mean drug concentrations ± SD) after single application





- The mean time taken for octreotide LAR 20 mg to reach maximum concentration (t_{max}) was 22 days
- The mean time taken for lanreotide autogel 90 mg to reach maximum concentration (t_{max}) was 2.4 days

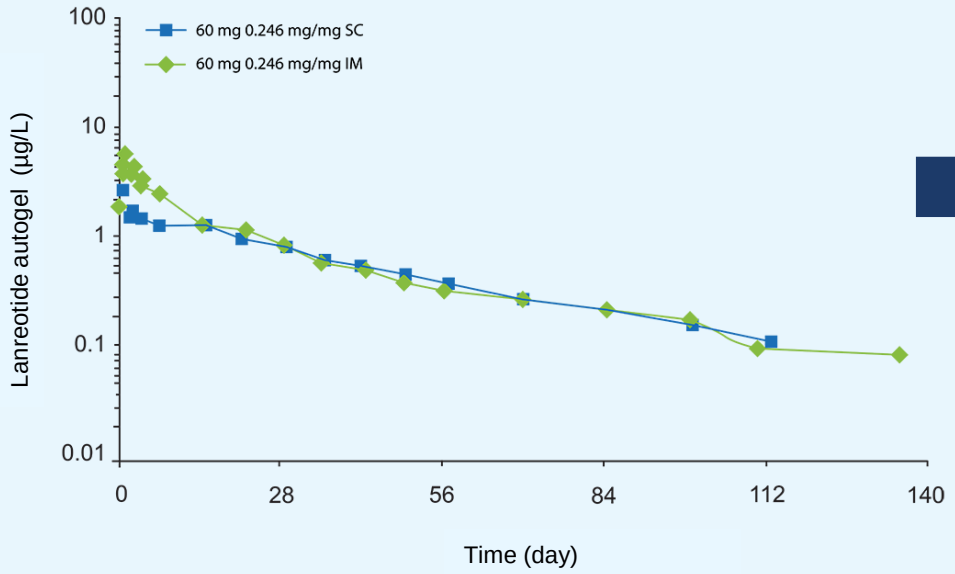
Following an initial peak in concentration on day 1, **octreotide** remained **at sub-therapeutic levels** until it reaches a plateau therapeutic concentration **from day 14–42**[2]
Lanreotide autogel reached therapeutic concentration from day 1 and for at least 28 days, thus there is no need for rescue medication at onset[3]

LAR, long-acting release; PK, pharmacokinetic; SD, standard deviation.

1. Astruc B, et al. *J Clin Pharmacol* 2005;45:836–844; 2. Sandostatin LAR® 30 mg summary of product characteristics. Available at: www.medicines.org.uk/emc/product/7828/smpc. Accessed September 2019; 3. Somatuline® Autogel® Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/8257/smpc. Accessed September 2019.

Lanreotide autogel concentration is maintained whether injected SC or IM[1]

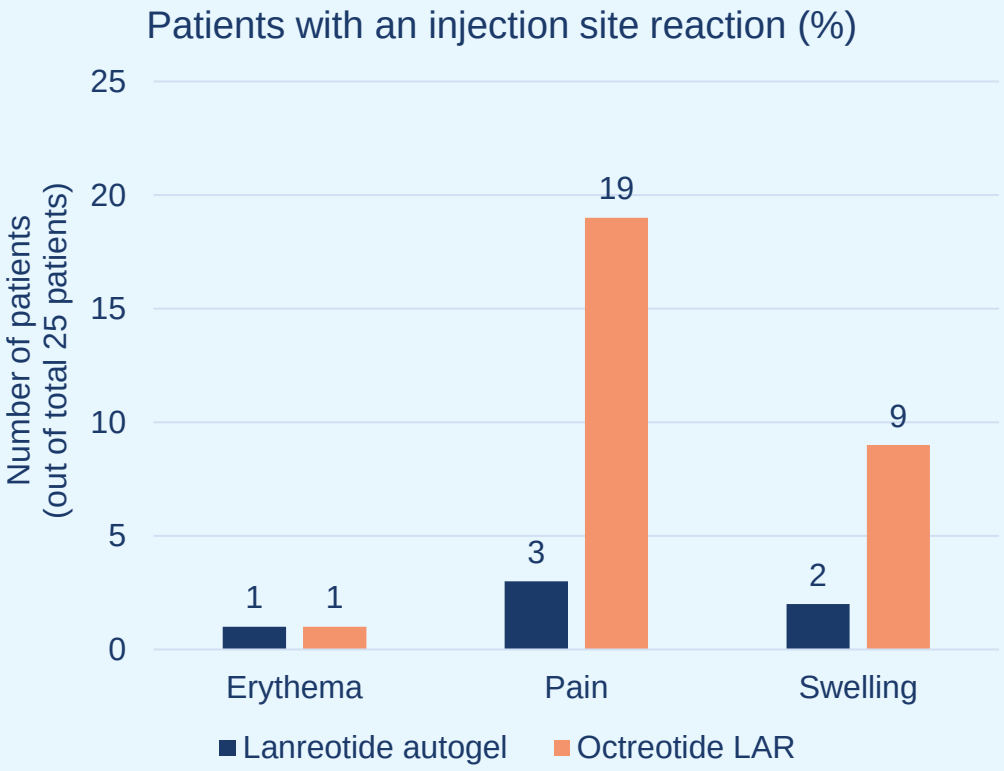
Mean concentration-time profiles of lanreotide autogel after IM and SC* administration of lanreotide autogel 60 mg 0.246 mg/kg to healthy volunteers**,[1]



- No difference in PK between IM and SC injection of lanreotide autogel[1]

*Lanreotide autogel is indicated for subcutaneous administration. **Randomised, parallel, double-blind Phase I trial and included 7 treatment groups of 6 patients. Each group received a single IM or SC of lanreotide autogel at a predetermined dose.
IM, intramuscular; PK, pharmacokinetics; SC, subcutaneous.
1. Manon A, et al. Poster presented at NANETS symposium, 2016.

Injection site reactions are reported less frequently in patients receiving lanreotide autogel compared with octreotide LAR[1]



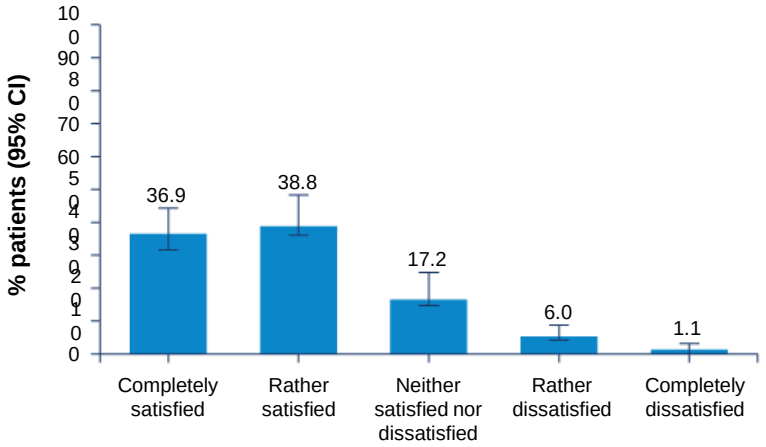
- p<0.001 for lanreotide autogel compared with octreotide LAR for all injection site reactions[1]

*Prospective, open-label multicentre, within-subject controlled study.
LAR, long-acting release.
1. Alexopoulou O, et al. *Eur J Endocrin* 2004;151:317–324.

SYMNET - RWD FOR LANREOTIDE[1]

LARGE STUDY (N = 273) REPORTING PATIENT SATISFACTION WITH SYMPTOM CONTROL DURING LANREOTIDE TREATMENT FOR CS-RELATED DIARRHOEA

- 79% reported improved diarrhoea control with lanreotide depot, and 76% were completely or rather satisfied with this effect
- The satisfaction regarding the control of flushing was similarly high (73%)
- Compared with baseline, a clinically significant decrease in median daily stool frequency (from 4.7 to 2.6) was observed



Patient satisfaction with diarrhoea control associated with lanreotide treatment

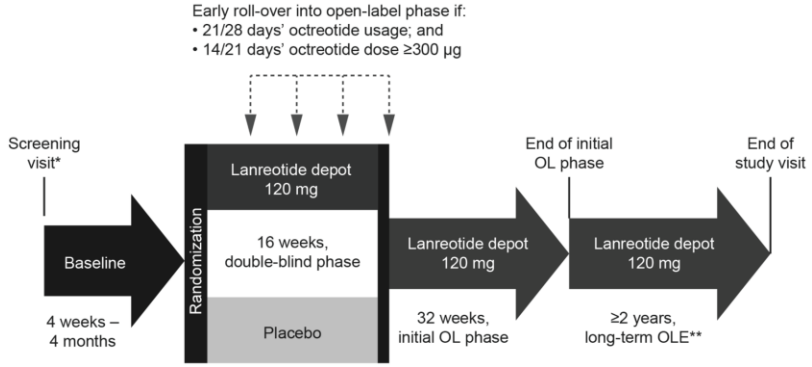
CI, confidence interval; CS, carcinoid syndrome; RWD, real-world data.

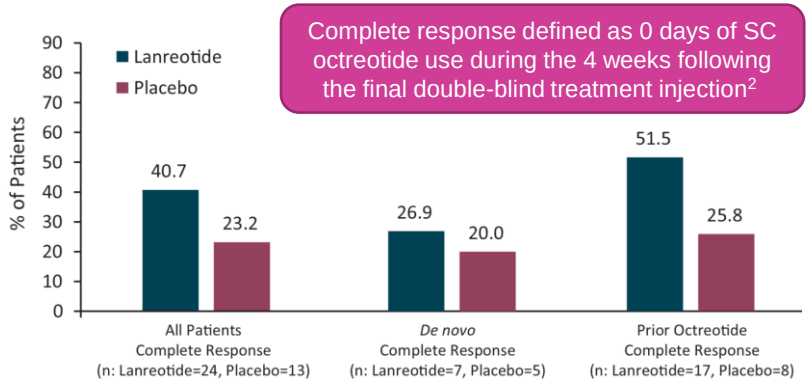
1. Ruszniewski P, et al. *Dig Liver Dis* 2016;48:552–558.

ELECT – RCT FOR LANREOTIDE[1,2]

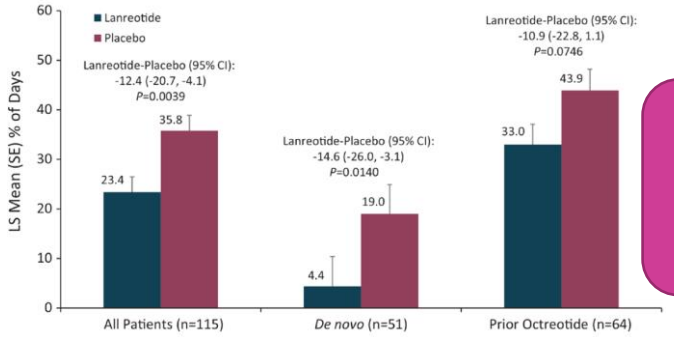
ELECT WAS A DOUBLE-BLINDED, RANDOMISED, PHASE III TRIAL OF LANREOTIDE VS PLACEBO IN PATIENTS WITH CARCINOID SYNDROME (CS)

- Primary endpoint: The percentage of days where rescue short-acting octreotide was used
- Small trial, 115 enrolled patients with CS: SSA naïve patients and patients previously responsive to octreotide LAR or short-acting octreotide





Complete response defined as 0 days of SC octreotide use during the 4 weeks following the final double-blind treatment injection[2]



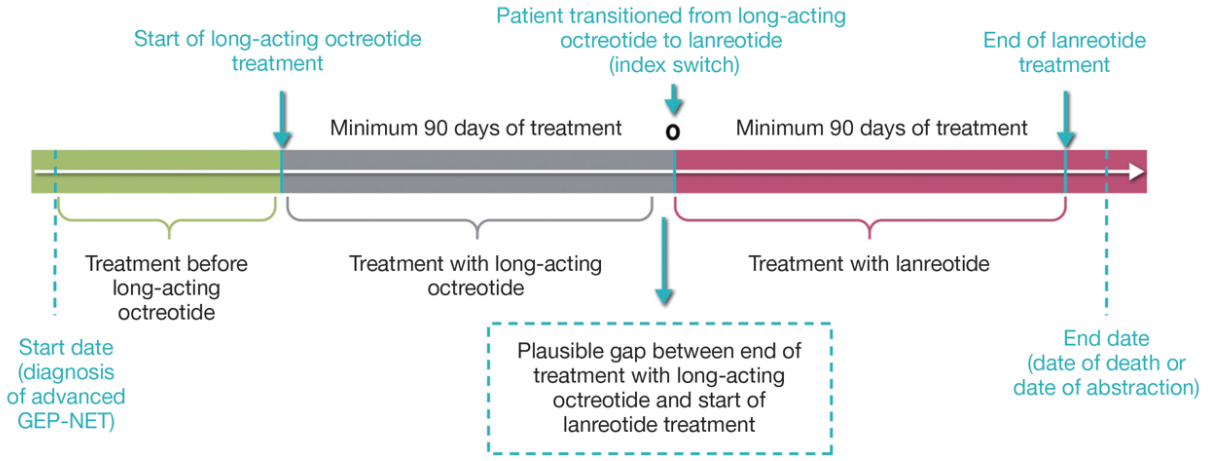
Least square mean (SE) percentage of days with moderate/severe diarrhoea and/or flushing[2]

CI, confidence interval; CS, carcinoid syndrome; LAR, long-acting release; LS, least squares; OL, open-label; OLE, open-label extension; RCT, randomised controlled trial; SC, subcutaneous; SSA, somatostatin analogue.

1. Vinik AI, et al. *Endocr Pract* 2016;22:1068–1680; 2. Fisher GA, et al. *Endocr Pract* 2018;24:243–255.

Octreotide to lanreotide switch – RWE

- Most patients who start therapy with octreotide LAR will experience progression of disease and/or progression of symptoms within 2 years of starting therapy
- The role of switching from one long-acting somatostatin analogue to another is not well established (no randomised trials)
- A retrospective study of 91 patients at 6 different US institutions looked at the switch from octreotide LAR to lanreotide in patients with advanced or metastatic GEP NETs



- LAR, long-acting release; mPFS, median progressive-free survival; NE, not estimable; PRRT, peptide receptor radionuclide therapy; RWE, real-world evidence.
- 1. Saif WM, et al. *J Gastrointest Oncol* 2019;10:674–687.

Octreotide to lanreotide switch – RWE

- Most common reasons for switching from octreotide to lanreotide:
  >progressive disease (22.0%)
  >formulary change (15.4%)
  >patient preference (9.9%)

- Overall mPFS following the transition to lanreotide was 23.7 months [20.2 months–NE]
  - PFS in patients with non-progressive disease when transitioned to lanreotide: **24.7 months**
  - PFS in patients with progressive disease when transitioned to lanreotide: **15.2 months**

Lanreotide may contribute to stabilisation of disease in a subset of patients with locally advanced or metastatic GEP NETs previously treated with long-acting octreotide

- LAR, long-acting release; mPFS, median progressive-free survival; NE, not estimable; PRRT, peptide receptor radionuclide therapy; RWE, real-world evidence.
- 1. Saif WM, et al. *J Gastrointest Oncol* 2019;10:674–687.

CLARINET FORTE (NCT02651987)

Open label non comparative study

Well Differentiated, Metastatic or Locally Advanced, Unresectable Pancreatic or Midgut Neuroendocrine Tumours Having Progressed Radiologically While Previously Treated With Lanreotide Autogel® 120 mg Administered Every 28 Days

- Histopathologically confirmed, grade 1 or 2, metastatic or locally advanced, unresectable pNET or midgut NET with or without hormone related syndromes, with a proliferation index (Ki67) ≤20%
- Positive somatostatin receptors type 2
- Progression (RECIST 1.0) as assessed by an independent central reviewer

N=100 (midgut cohort = 50; panNET cohort = 50)

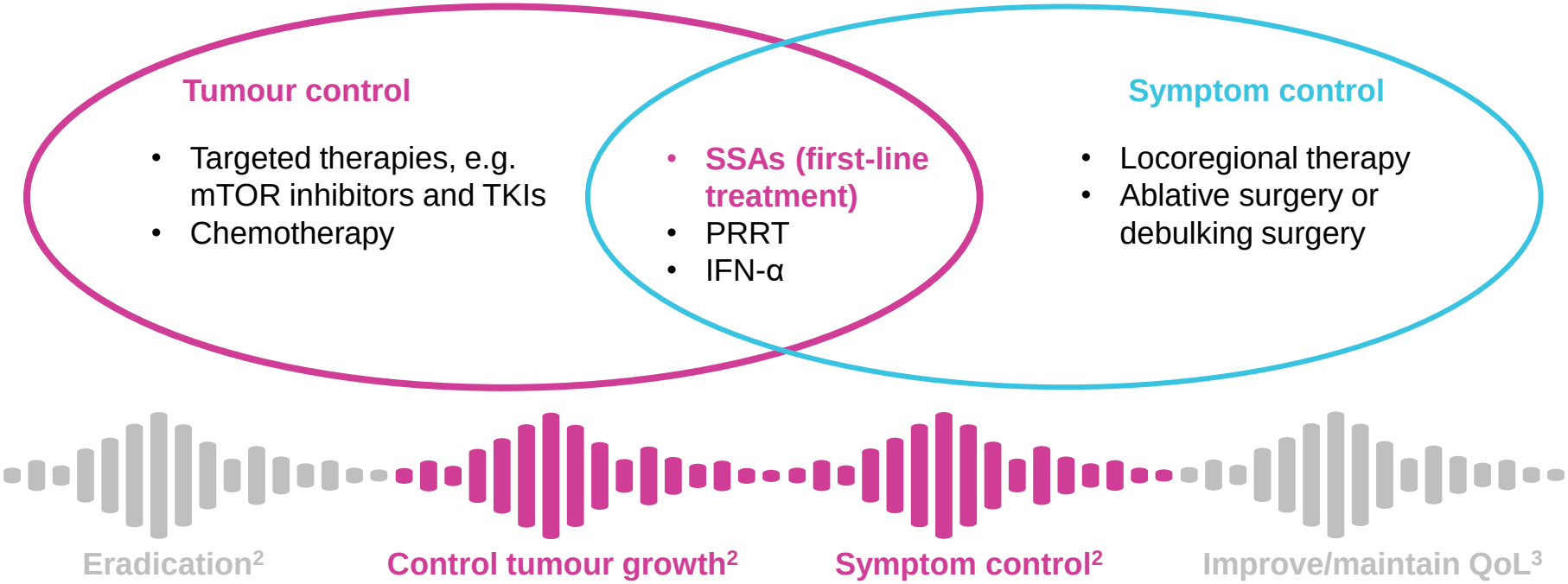
Lanreotide autogel 120 mg/14 days

Primary endpoint:	Median progression free survival
Main secondary endpoints:	Median time to progression, Overall survival, Overall response rate, Disease control rate, symptom control (diarrhea, flushing), Quality of life
Sponsor	Ipsen
Countries	Belgium, Denmark, France, Germany, Republic of Ireland, Italy, Netherlands, Poland, Spain, United Kingdom
Timelines	Study Start Date: November 2015; Study Completion Date: Q3-Q4 2019; 1st draft results: Q2 2020
Recruitment status	Recruiting

Aim	**To aim of the CLARINET FORTE study is to assess the efficacy and safety of increasing the frequency of lanreotide 120 mg dosing to every 14 days in patients with progressive pancreatic of midgut NETs who have been receiving the standard regimen of lanreotide 120mg for 28 days. This analysis reports the baseline quality of life and characteristics of patients enrolled.**
Methods	• Prospective, single-arm, open-label, exploratory, international, phase 2 study • Patients will receive lanreotide 120 mg every 14 days for a core treatment period of 48 weeks for panNETs and 96 weeks for midgut NETs • Primary endpoint is median PFS, centrally assessed using RECIST v1.0 • Adults patients with an ECOG PS ≤2; well-differentiated, SSTR2+, metastatic or locally advanced, unresectable, grade 1/2 panNET or midgut with Ki67 ≤20%; and centrally assessed radiological progression within the last 2 years while on a standard lanreotide regimen for ≥24 weeks • Patients were excluded if they had received prior treatment with chemotherapy, interferon, PRRT or molecular targeted therapy
Results	• 99 patients were enrolled from 10 countries; 48 in the panNET cohort and 51 in the midgut NET cohort • Mean age: was 63.3 in the panNET cohort and 67.1 in the midgut NET cohort; 41.7% of patients in the panNET cohort were males vs 56.9% in the midgut NET cohort • Overall the mean QLQ-C30 patient global health status score was 68.0 • 16.7% patients in the panNET cohort had diarrhoea vs 41.7% in the midgut NET cohort; flushing was experienced in 8.3% of patients in the panNET cohort vs 28.0% in the midgut NET cohort • Overall 60% had a grade 2 tumour, most patients had a grade 3 or 4 Krenning score and nearly half of patients tumours were SSTR2+ heterogeneous
Authors' conclusions	The CLARINET FORTE study will provide efficacy and safety data on the use of lanreotide 120 mg at an increased dosing frequency in patients with progressive panNET or midgut NET.

ECOG PS, Eastern Cooperative Oncology Group performance status; NET, neuroendocrine tumour; panNET, pancreatic NET; RECIST, response evaluation criteria in solid tumours; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; SSTR, somatostatin receptor.

TREATMENT OPTIONS AVAILABLE



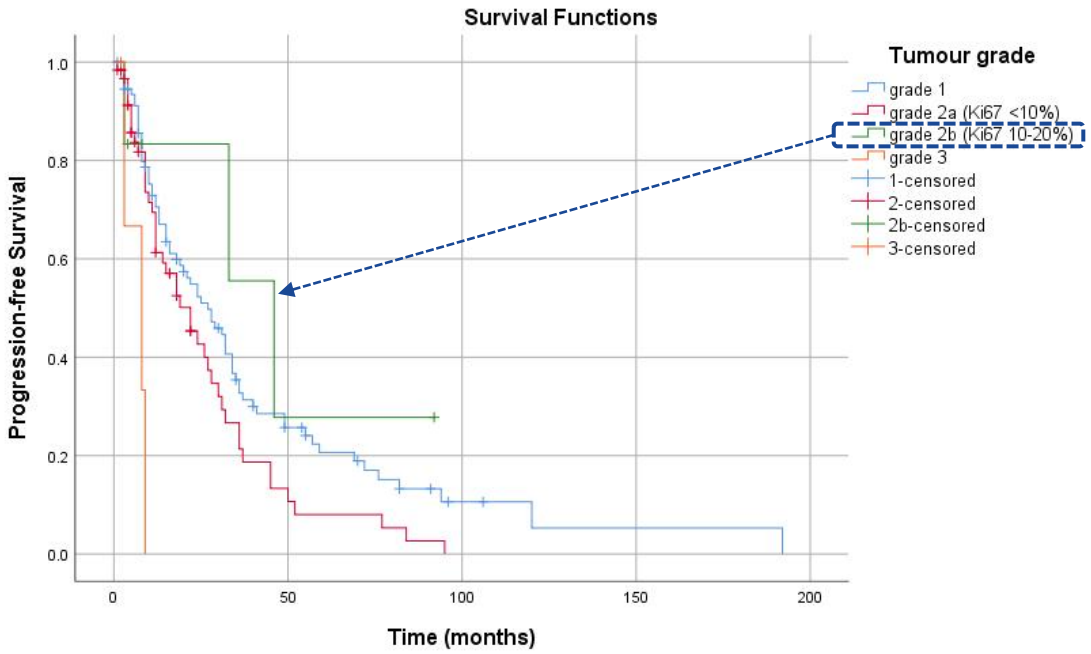
WHAT IS THE EFFECT OF LANREOTIDE AUTOGEL WHEN COMBINED WITH OTHER TREATMENTS?

Reference	Study description	Concomitant therapy	No of pts	Results
Marconcini et al 2014[1]	Retrospective Progressive EP and lung NENs	Capecitabine	30	Disease stabilization in 54% PFS: 4.9 months
Capdevila et al 2015[2]	Retrospective Progressive EP and lung NENs	Molecular Targeted Therapies (everolimus, sunitinib)	133	Median-Time to Progression With everolimus: 25.8 months With sunitinib: not reached
Pavel et al 2018 (SONNET study)[3]	Prospective Progressive EP NENs	Temozolomide	57	Best overall response at 12 months was SD in 73.0%, PR in 10.8%, PD in 16.2%. Median PFS (ITT pts) was 11.1 months
Pusceddu et al 2018[4]	Retrospective Diabetic patients with Pancreatic NENs	Metformin	44 (including pts with Octreotide LAR)	PFS without Metformin: 24 months PFS with Metformin: 45.9 months

EP, enteropancreatic; NEN, neuroendocrine neoplasm; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

1. Marconcini R, et al, Presented at ENETS 2014; 2. Capdevila J, et al, *BMC Cancer* 2015;15:495; 3. Pavel M, et al, Presented ay ENETS 2018; 4, Pusceddu S, et al, *Gastroenterology* 2018;155:479–489.

WHAT IS THE EFFECT OF LANREOTIDE AUTOGEL IN GRADE 2 NETs WITH KI-67 10–20%?

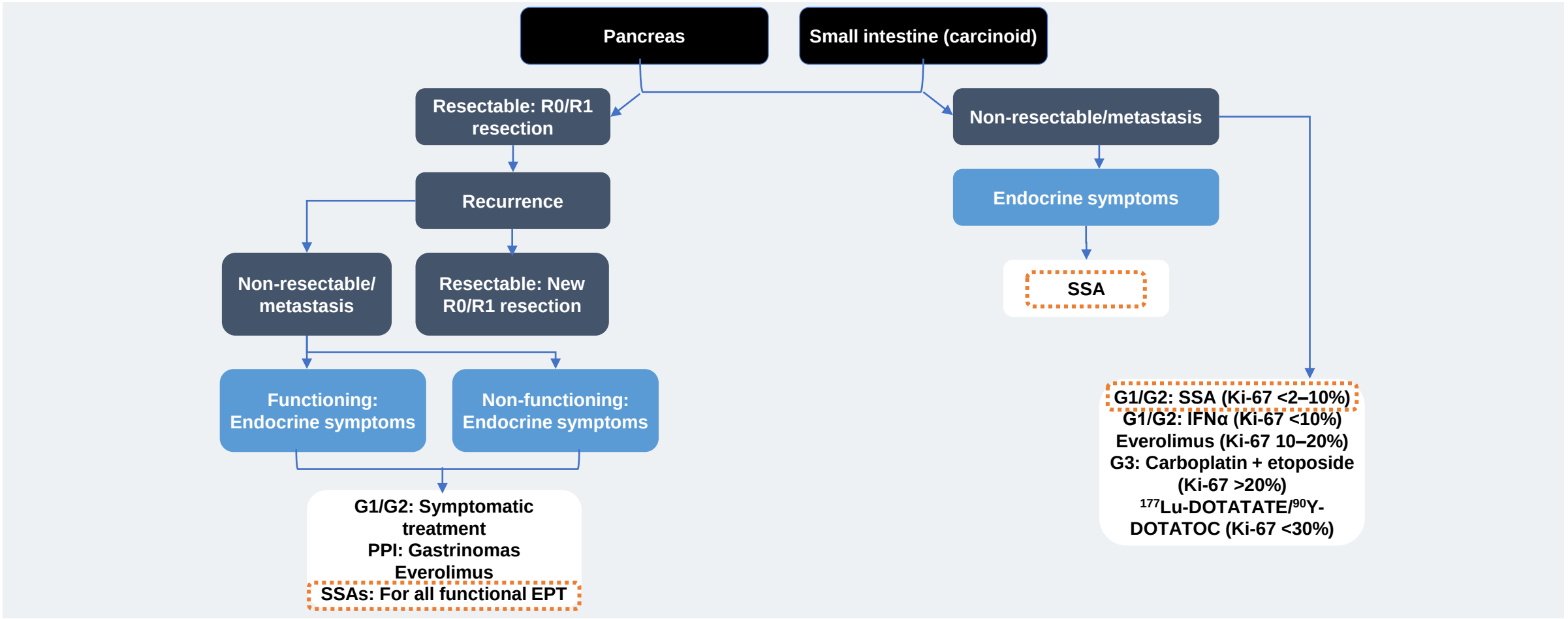


- DATA FROM ONLY 6 OUT OF 191 PATIENTS
- PFS IN GRADE 2, STABLE DISEASE AT TREATMENT COMMENCEMENT: 46 MONTHS

PFS, progression-free survival.

Laskaratos F, et al, Royal Free NET Unit, Presented at ENETS 2018.

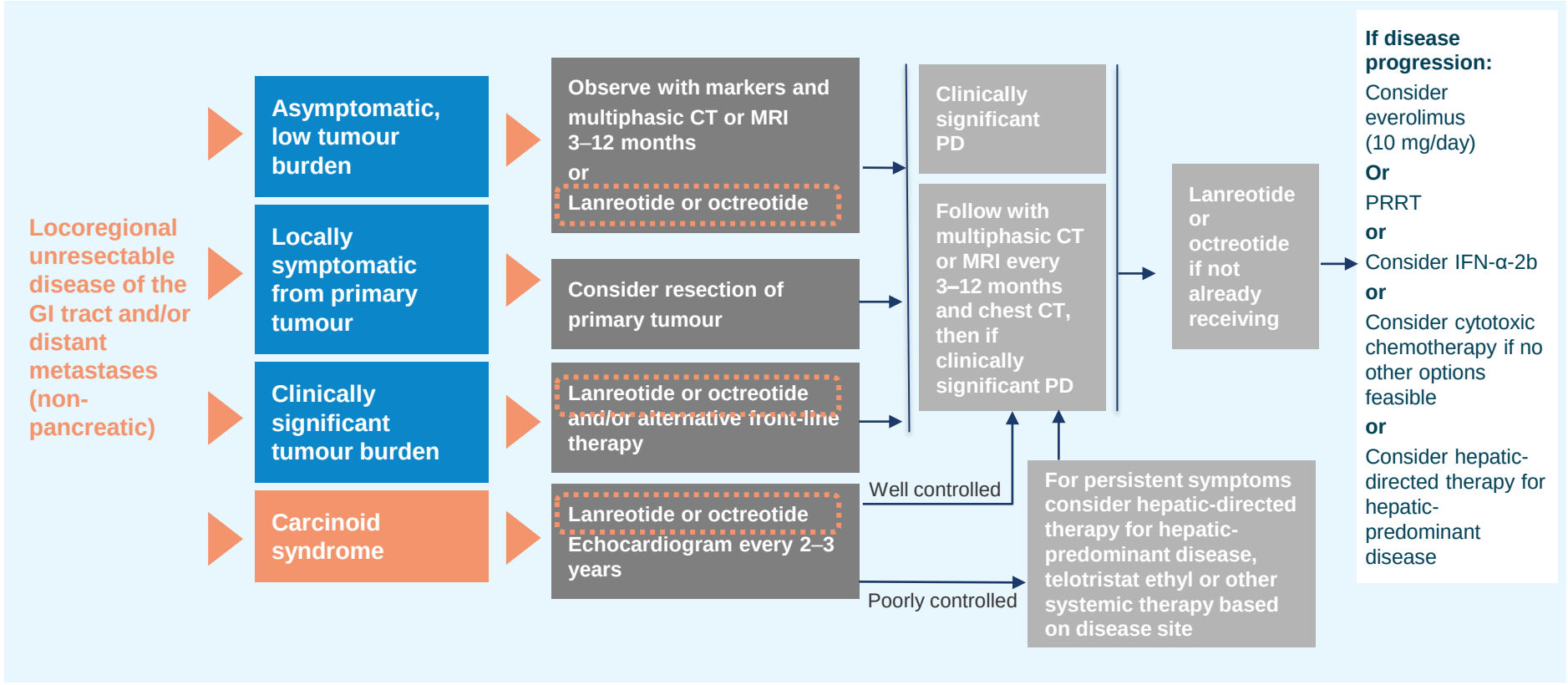
ESMO guidelines recommend SSAs for the management of pancreatic and small intestinal NETs[1]



EPT, endocrine pancreatic tumour; ESMO, European society for medical oncology; FU, fluorouracil; G, grade; IFN, interferon; NET, neuroendocrine tumour; PPI, protein pump inhibitor; R0, complete resection with negative margins; R1, incomplete resection with microscopic residual tumour; SSA, somatostatin analogue.

1. ESMO guidelines for neuroendocrine gastroenteropancreatic tumours. *Annals Oncol* 2019;in press.

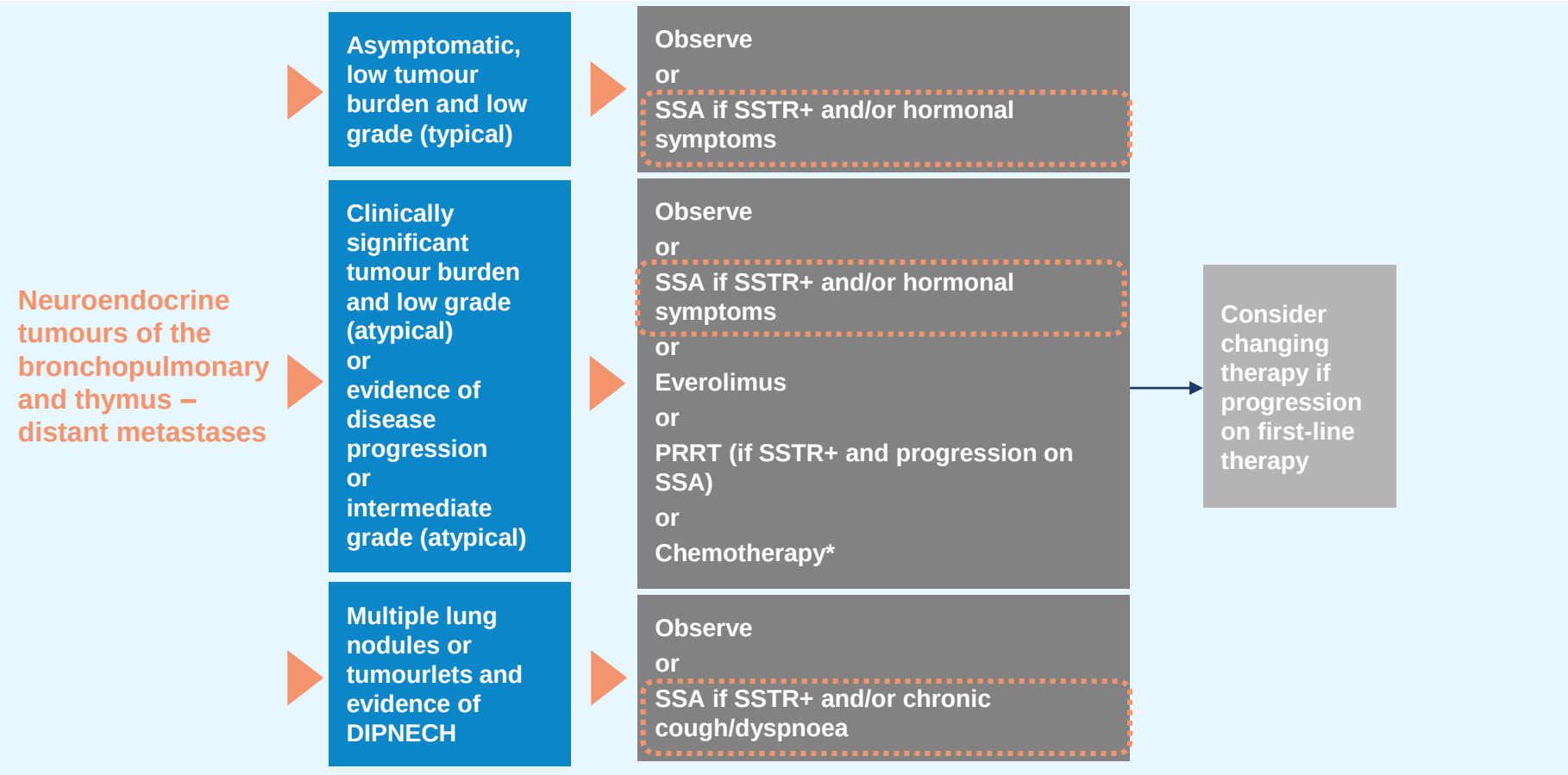
NCCN guidelines recommend SSAs for the management of advanced GI NETs[1]



Note: All recommendations are category 2A unless otherwise indicated.
CT, computed tomography; GI, gastrointestinal; IFN, interferon; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NET, neuroendocrine tumour; PD, progressive disease; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue.

1. NCCN clinical practical guidelines in oncology: Neuroendocrine and adrenal tumors. Version 1. 2019.

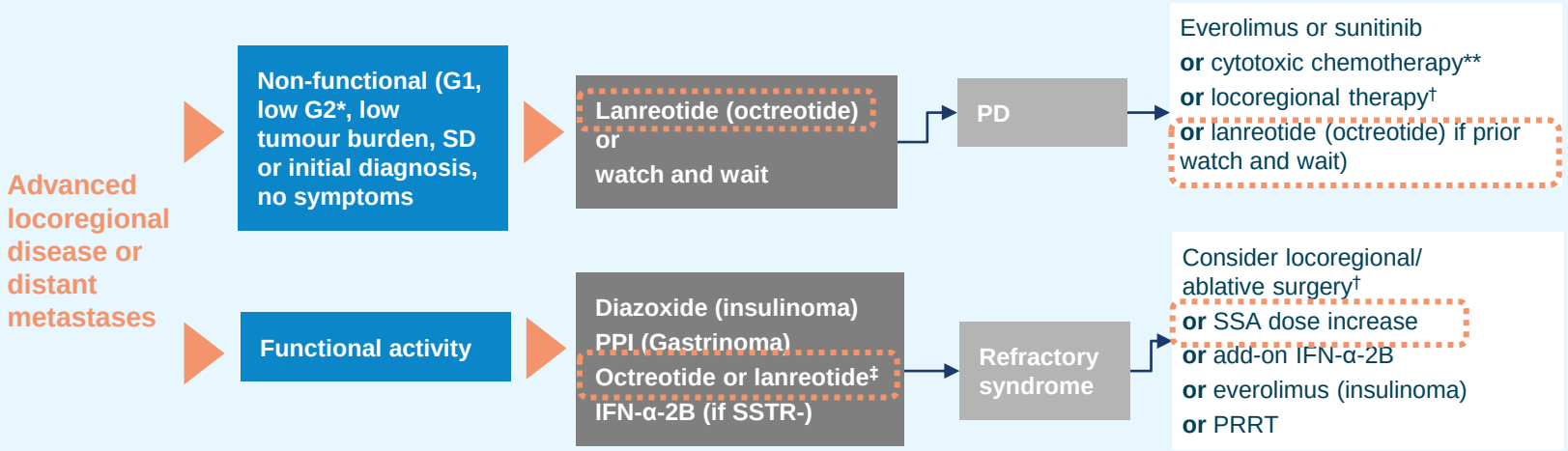
NCCN guidelines recommend SSAs for the management of distant metastasis bronchopulmonary and thymus NETs[1]



Note: All recommendations are category 2A unless otherwise indicated.
*Cisplatin/etoposide, carboplatin/etoposide or temozolomide with/without capecitabine.
CT, computed tomography; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SSTR, somatostatin receptor.

1. NCCN clinical practical guidelines in oncology: Neuroendocrine and adrenal tumors. Version 1. 2019.

ENETS guidelines recommend SSAs for the management of pancreatic NENs with locoregional and/or distant metastases[1]



*"There is consensus that SSA can be used as first-line systemic therapy in pancreatic NET (Ki-67 <10%) in view of lack of toxicity, and although the antiproliferative effects of SSA are considered a drug class effect, based on the CLARINET study **lanreotide autogel should preferably be used in pancreatic NET since prospective data on the use of octreotide LAR in pancreatic NET are lacking**"*

*Ki-67 <5-10%. **Recommended chemotherapy includes STZ/5-FU or STZ/ doxorubicin; TEM/CAP is an alternative chemotherapy regimen if STZ-based chemotherapy is not available. †Locoregional therapies are contraindicated after Whipple procedure. ‡Patients should be closely monitored for paradoxical reaction (increasing hypoglycaemia).
ENETS, European neuroendocrine tumour society; G, grade; IFN, interferon; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; PD, progressive disease; PPI, proton pump inhibitor; PRRT, peptide receptor radionuclide therapy; SD, stable disease; SSA, somatostatin analogue; SSTR, somatostatin receptor; STZ, streptozotocin; TEM/CAP, temozolomide/capecitabine; 5-FU 5-fluorouracil.

1. Pavel M, et al. *Neuroendocrinology* 2016;103:172–185.