NET REGISTER
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NEN in the past, present and future

Somatostatin analogues: Upfront or „second-line“ after watch and wait?

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Characteristic Features of NE Tumours

- rare – increasing incidence
- Tumour Biology: between benign und malignant. Some tumours grow very slowly
- even very small intestinal NENs have malignant potential
- frequently delayed diagnosis or accidental finding (during colonoscopy)
- functionally active or inactive
- to predict response to treatment is difficult

Treatment of NENs: What is important to know

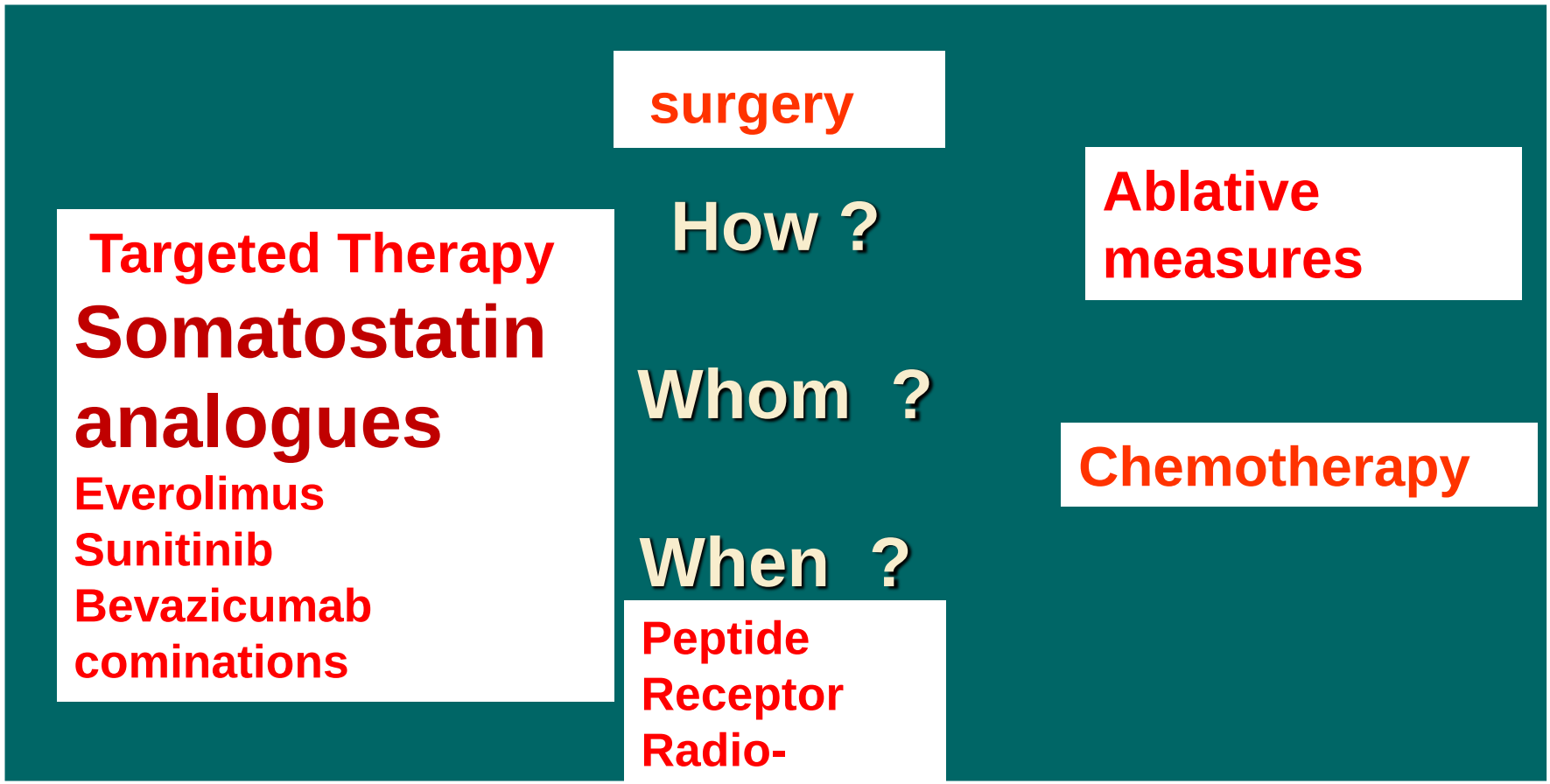
- Extent of disease — localized and resectable / low vs high tumour burden
- Grade of proliferation — stable vs progressive tumour growth
- Histology — NET vs NEC
- Grading — G1 vs G2 vs G3 vs NEC
- Primary tumour — pancreatic vs intestinal
- Functionality — active vs inactive
- Side effects of treatment — mild vs severe

notice: life quality is high in many patients

none of available drugs heals the disease

Treatment strategies in patients with malignant Neuroendocrine Tumors

Which options do we have?



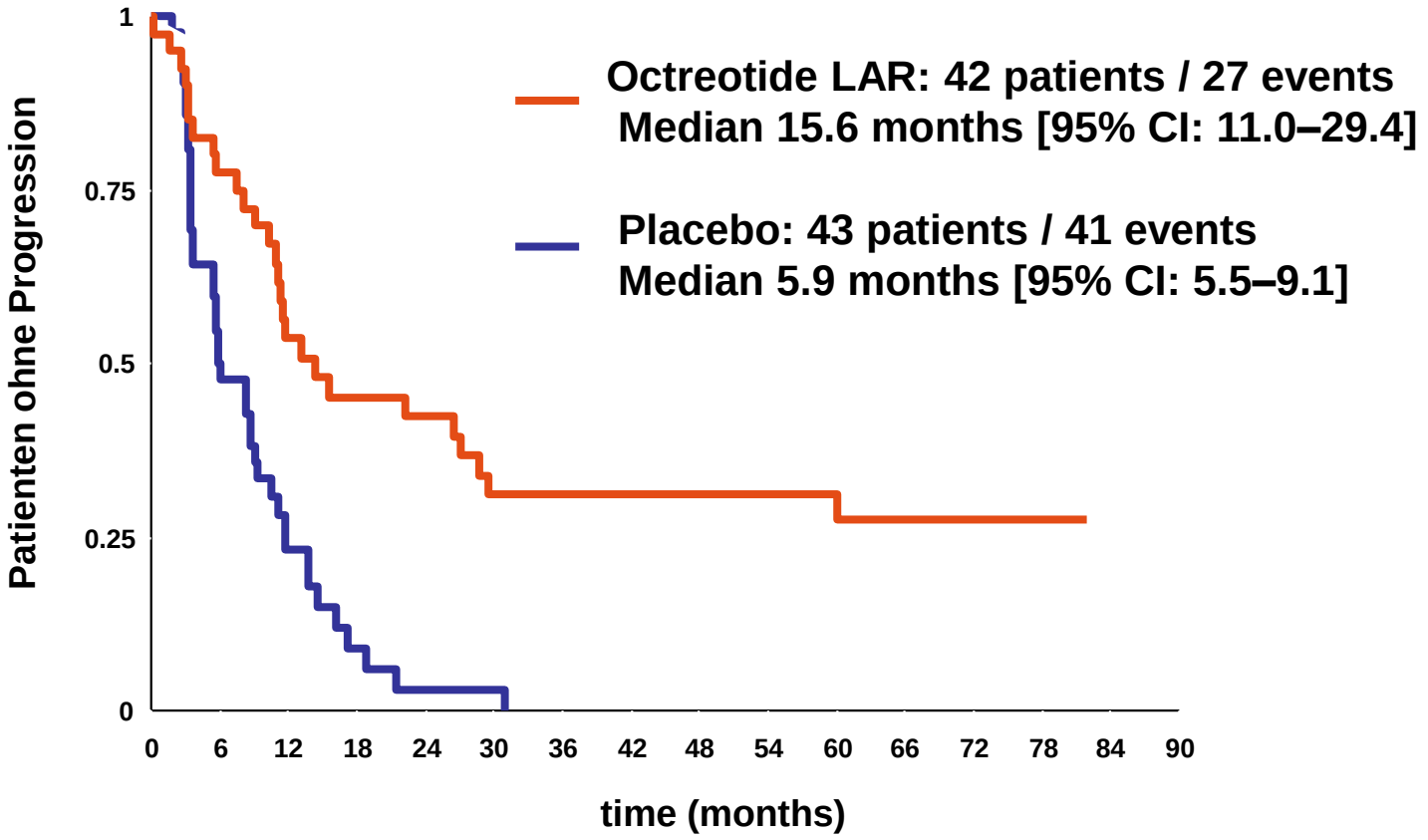
Somatostatin analogues: Upfront or „second-line“ after watch and wait?

Important randomized and published clinical Trials in NE Tumours of the GI Tract

Study	Reference	Study-arms	Nr Patients	TTP or PFS Months
•Promid	Rinke 2009	Octr/Plac	43/43	14.3 vs 6.0
•CLARINET	Caplin 2014	Lanre/Plac	101/103	not reached vs 18.0
Radiant 4	Yao 2016	Everol/Plac	113/65	11.0 vs 3.9
Netter 1	Strosberg 2017	177Lu-DOTATATE +Octreotide 30mg vs Octreotide LAR 60mg	116/113	not reached vs 8.4

PROMID: Octreotide LAR 30mg prolongs time to tumor progression in metastatic midgut NETs

67% risk reduction of tumor progression
HR=0.33; 95% CI: 0.19–0.55; *P*=0.000017

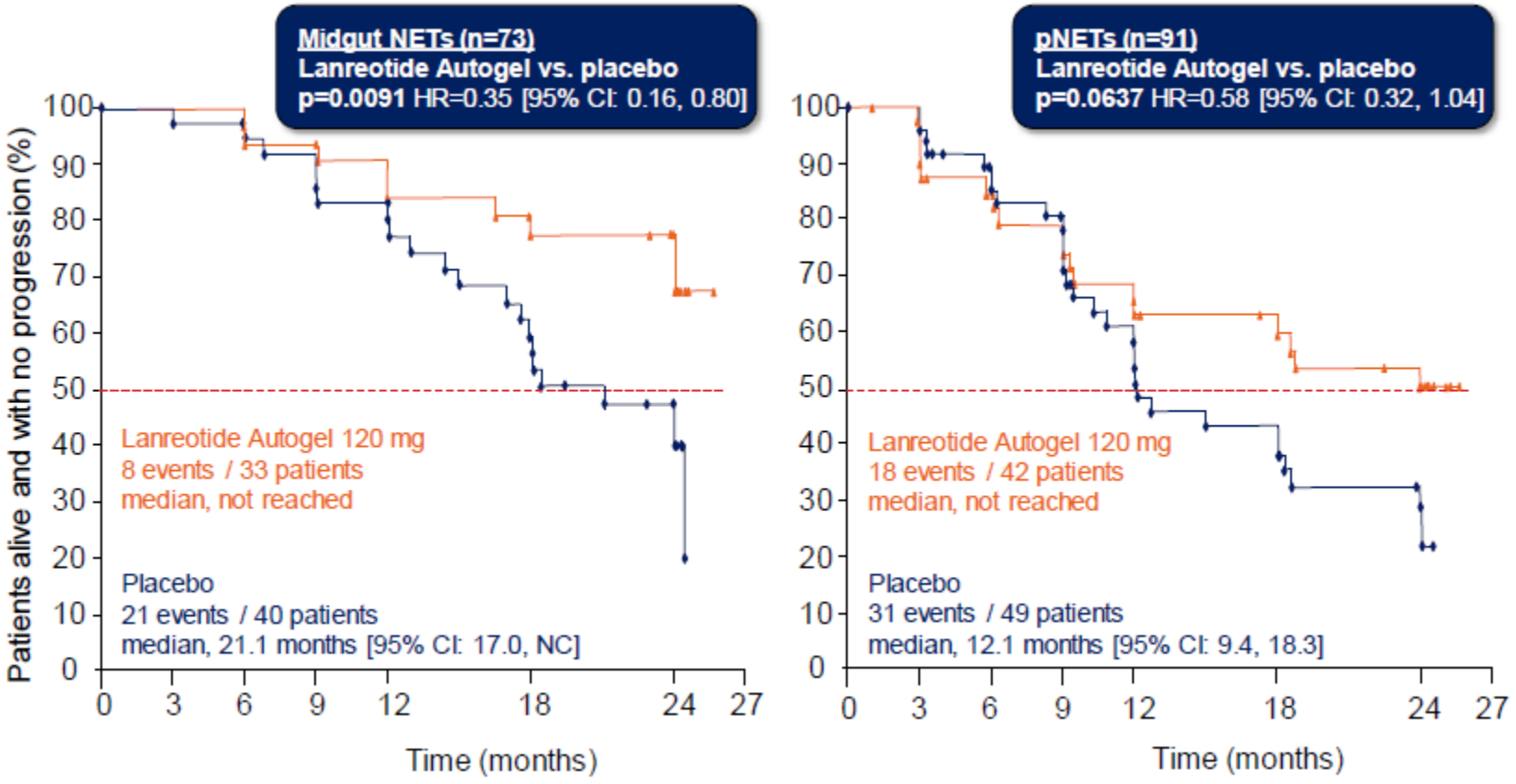


ITT analysis

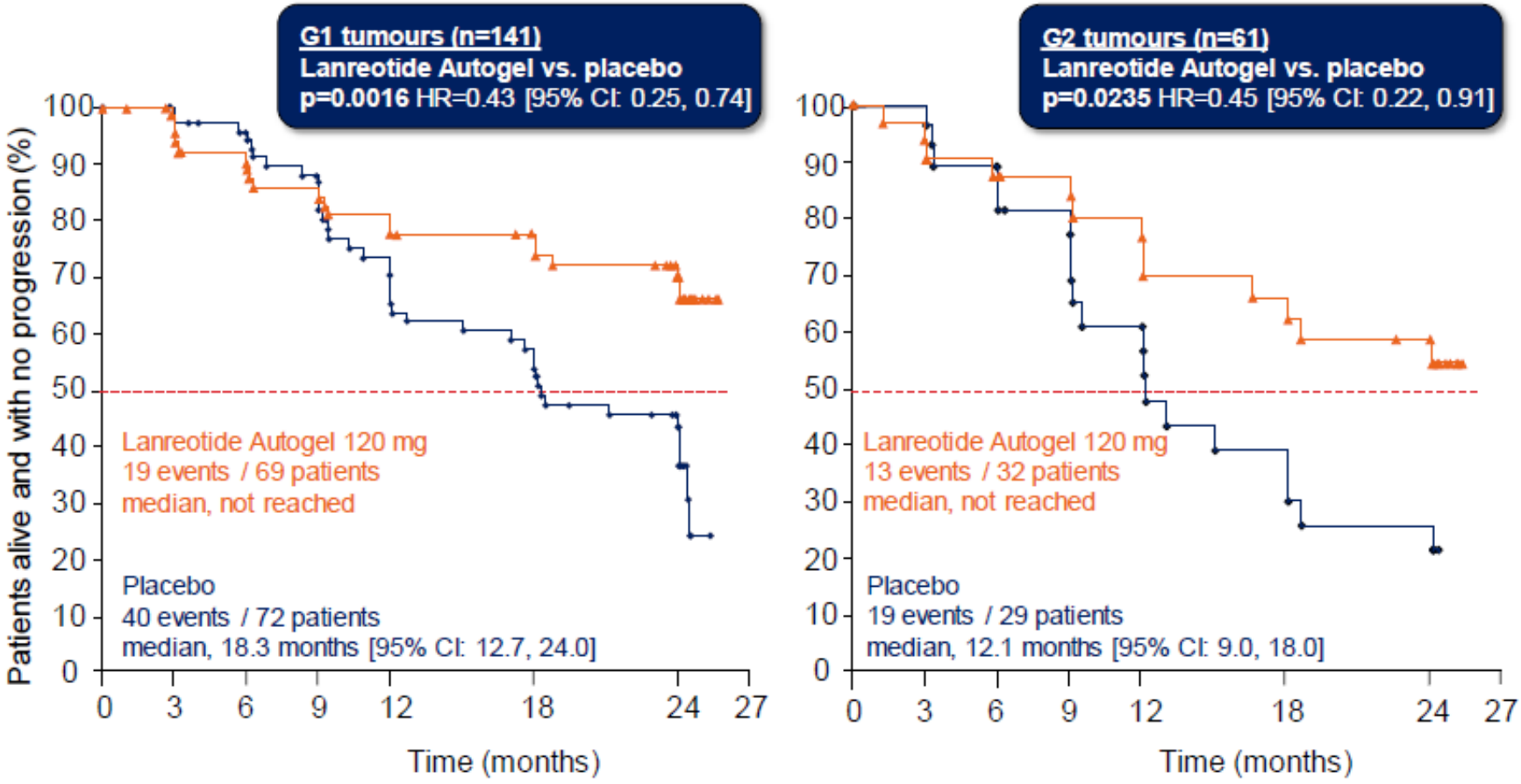
Arnold R. Abst # 4508 presented at ASCO 2009, Orlando FL
Rinke A *et al. J Clin Oncol.* 2009;27(28):4656-4663

CLARINET

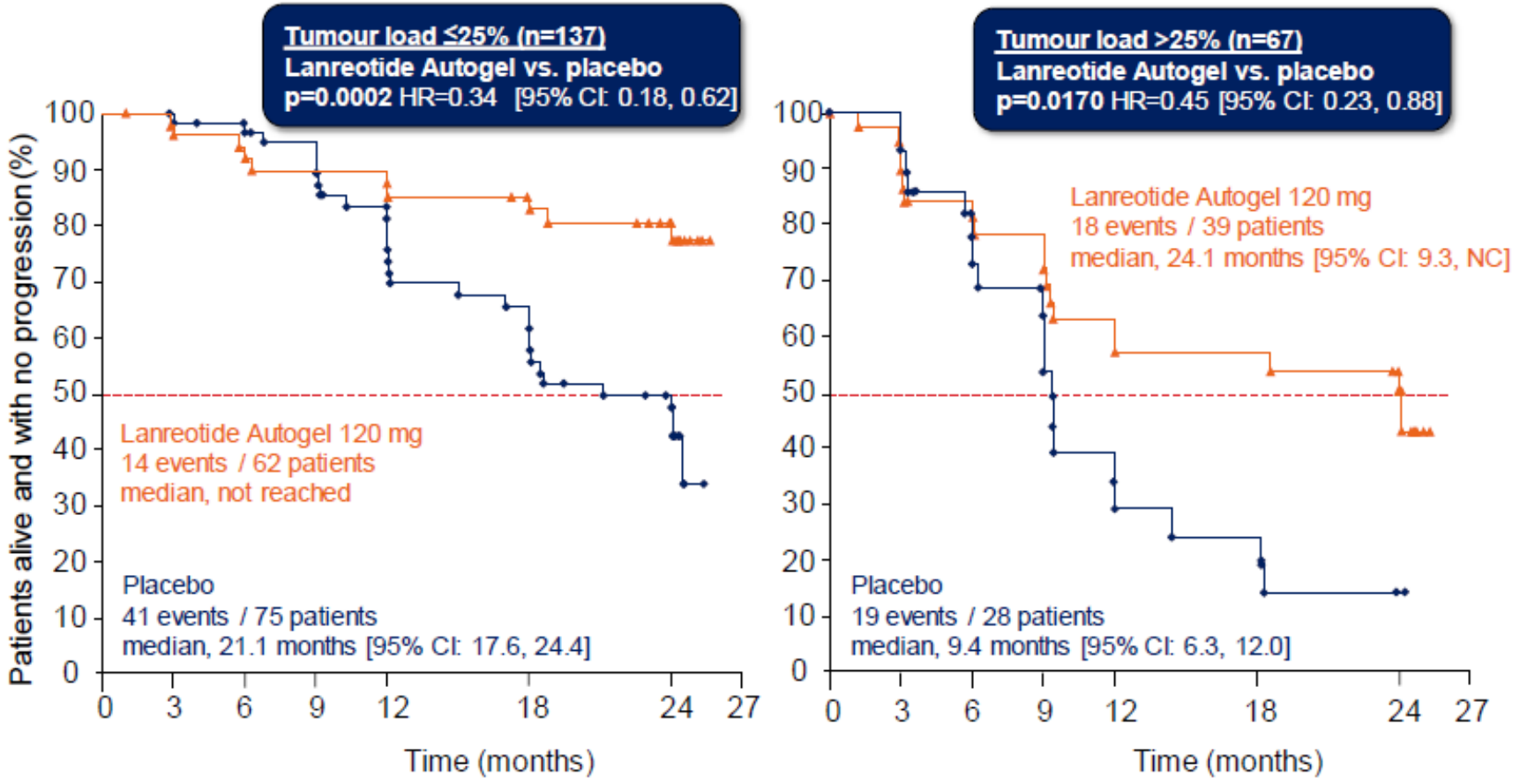
Lanreotide Autogel prolongs PFS in patients with pancreatic und midgut NETS



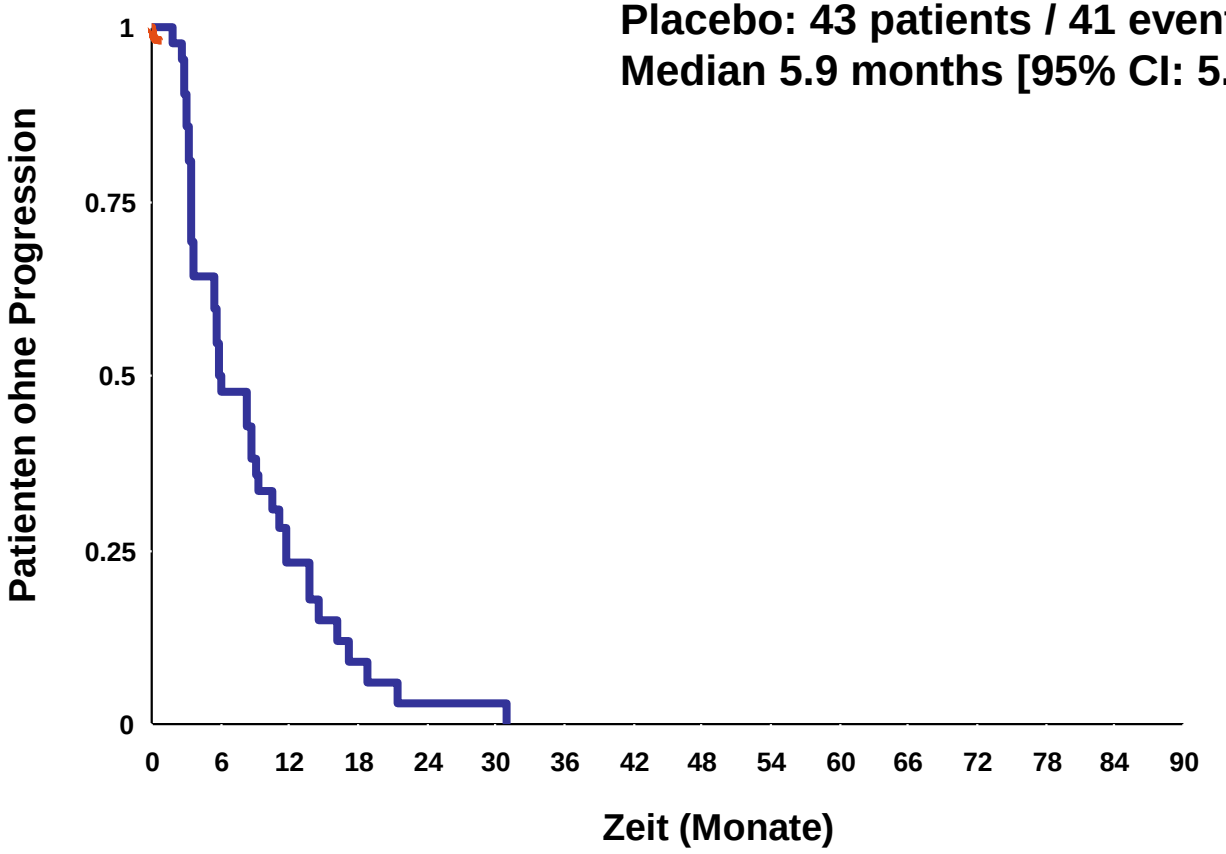
CLARINET: Lanreotide Autogel prolongs progression free survival in patients with G1 and G2 tumors



CLARINET: Lanreotide Autogel prolongs progression free survival in patients with high and low tumor burden



PROMID: very slow progression in the placebo arm:
in ~ 25% no growth during 1-2 years
Should we treat these patients?



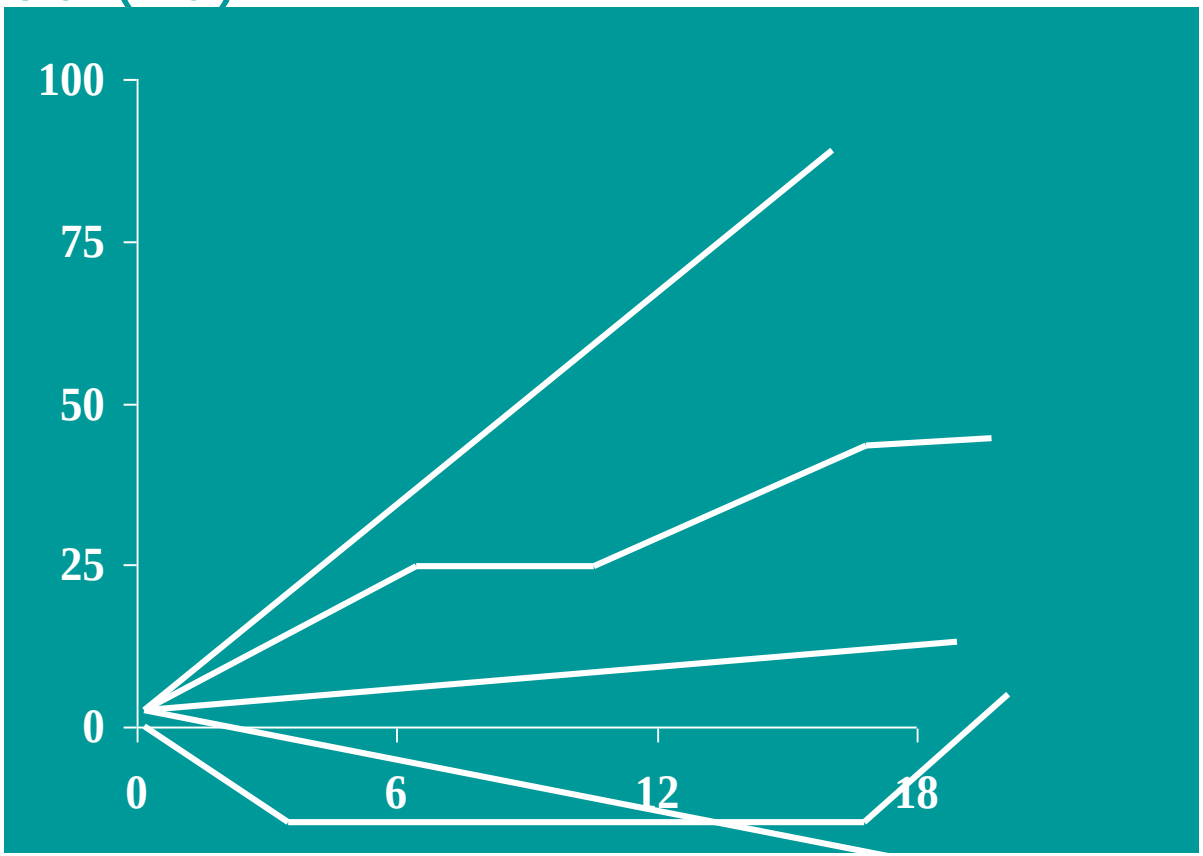
Placebo: 43 patients / 41 events
Median 5.9 months [95% CI: 5.5–9.1]

ITT analyse

Arnold R. Abst # 4508 presented at ASCO 2009, Orlando FL
Rinke A *et al. J Clin Oncol.* 2009;27(28):4656-4663

Spontaneous Growth of NETs

Increase of tumor-load (%)



Time (months)

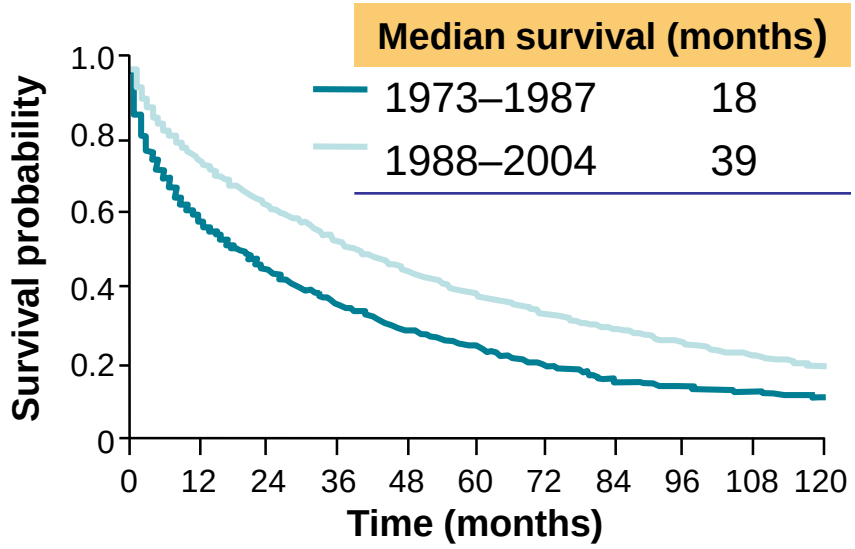
Treatment of NET patients with somatostatin analogues

Open Questions

- **How long do NET patients live if treated with somatostatin analoues at diagnosis and do somatostatin analogues prolog life?**
- How long do NET patients live if treated later, i.e. after documented progression?
- First line therapy: are there equally matched alternatives to somatostatin analogues?
- What should we offer patients not responding to treatment with somatostatin analogues?

Longer survival of NET patients after introduction of somatostatin analogues

Survival in patients with GEP NET and distant metastases was significantly longer in 1988–2004 (post-octreotide) compared to 1973–1987 (pre-octreotide)

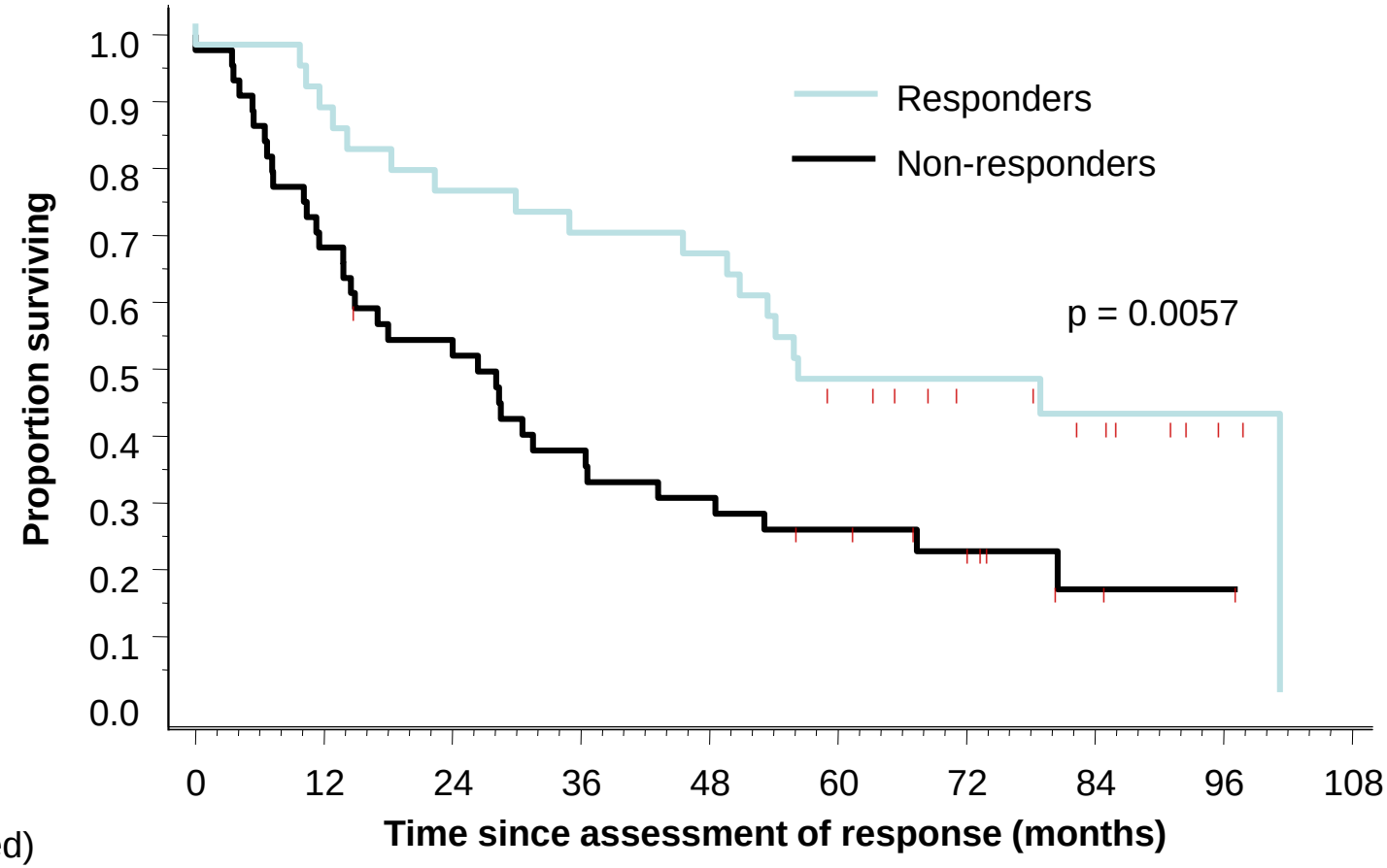


From an analysis of 35,825 cases of GEP NET identified in the SEER registries

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

Responders to biotherapy live longer

Patients treated with octreotide or octreotide + interferon-α



Patients at risk (censored)										
After 6 months of treatment										
Stable disease/partial regression	31	28	24	22	21	14	10	7	2	0
progression	44	30	23	16	13	10	7	2	1	0

Arnold R, et al. Clin Gastroenterol Hepatol. 2005;3:761-71.

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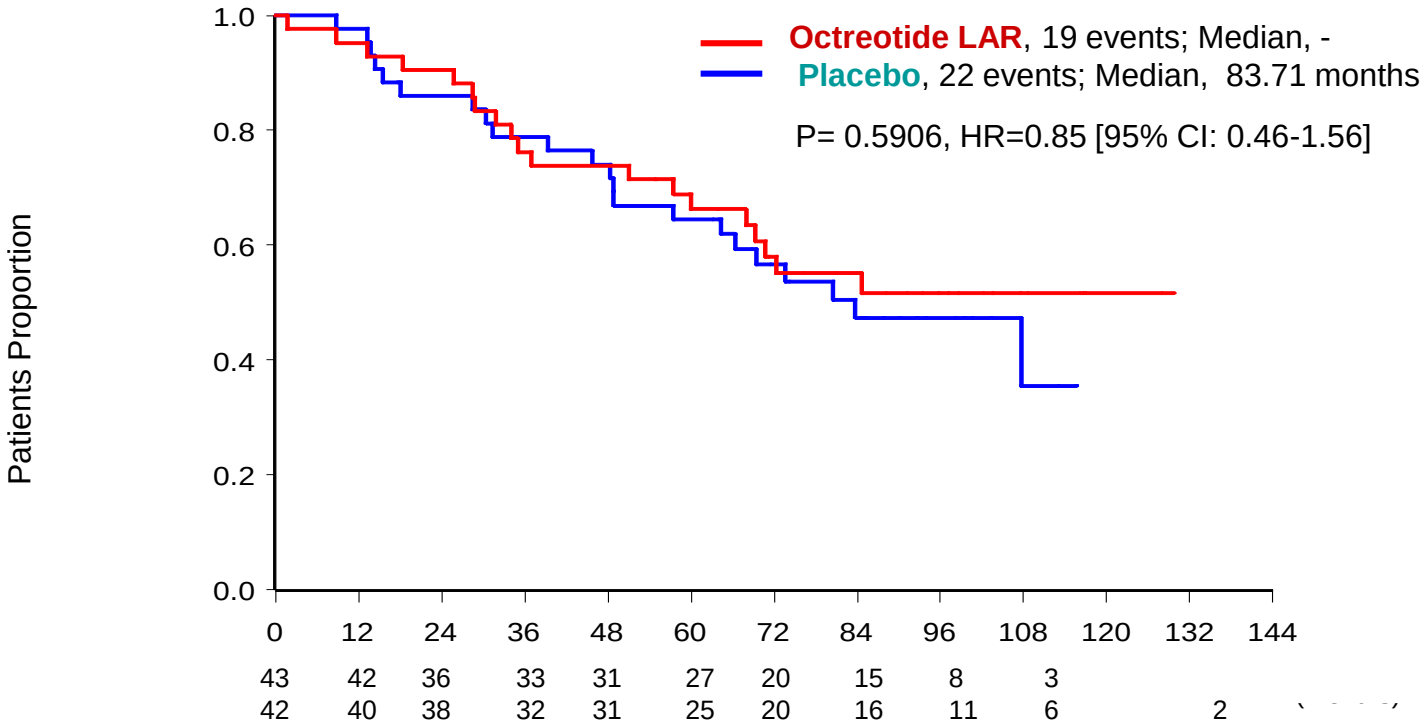
PROMID

Survival (OS) in patients treated with Octreotide LAR or Placebo at diagnosis is not different

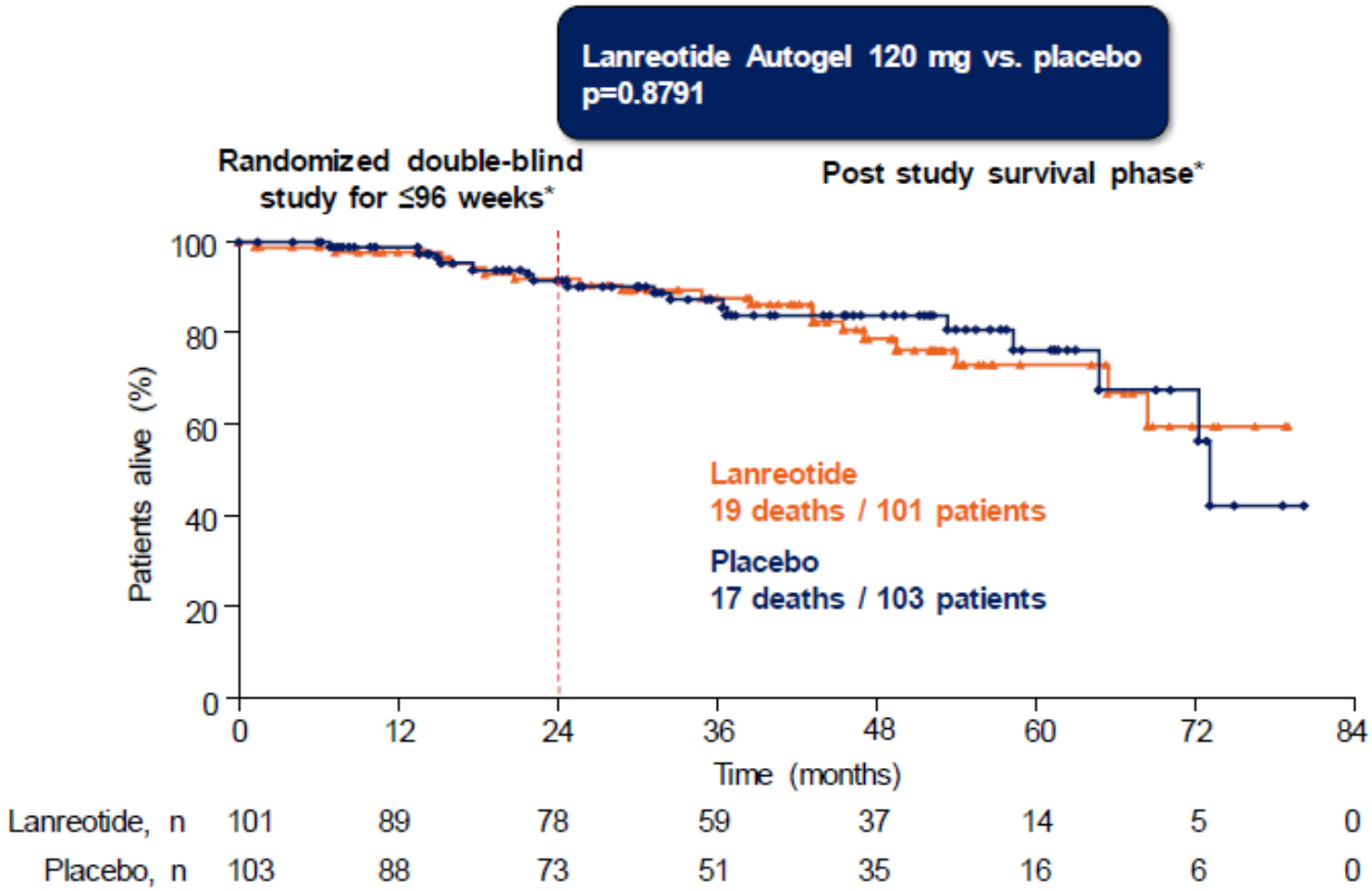


No survival benefit

Notice, > 90% of patients in the Placebo group at diagnosis received octreotide LAR after documented progression

CLARINET

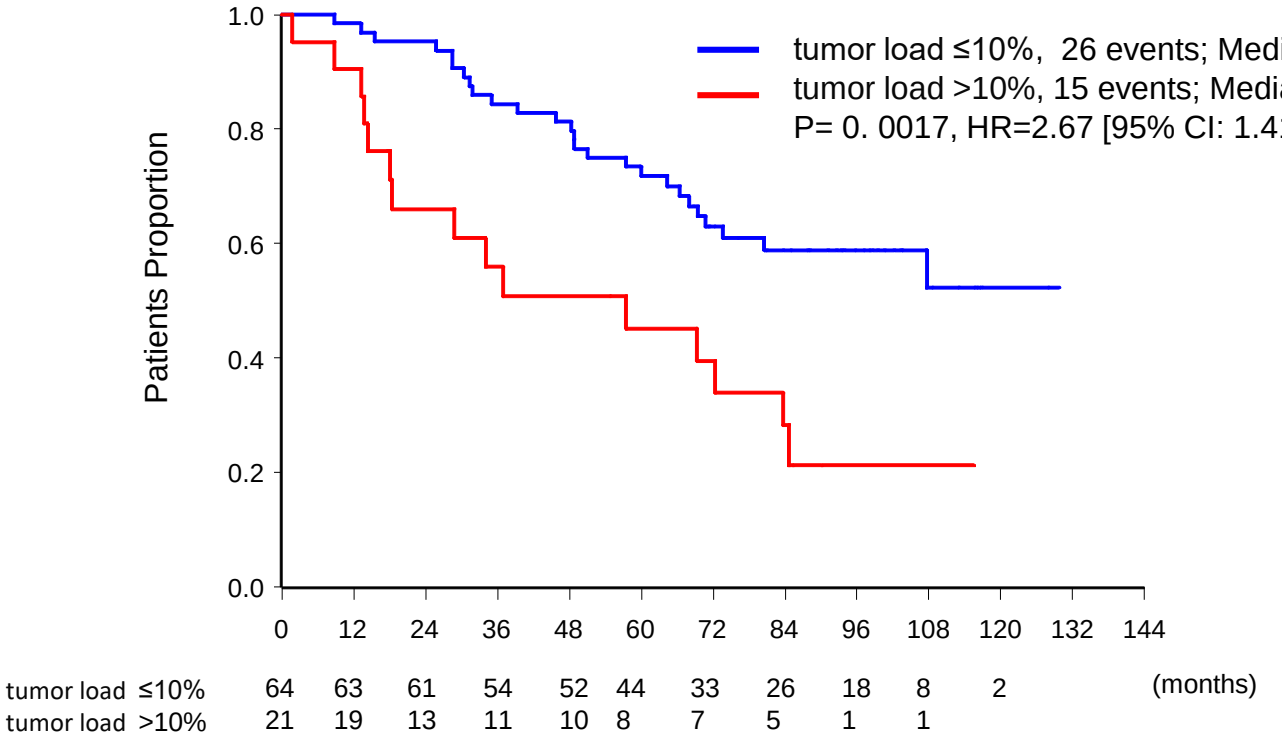
Survival (OS) in patients treated with Lanreotide autogel or Placebo at diagnosis is not fifferent



PROMID

Overall Survival in all Promid patients according their initial hepatic tumour burden

Importance of tumour load



Somatostatin analogues: Upfront or „second-line“ after watch and wait

Reasons for a „Watch and Wait Strategy“

- Both in the Promid- and Clarinet trial **overall survival was not dependent** on the time of onset of treatment with somatostatin analogues,i.e. immediately after diagnosis or after documented tumour progression (G1 and G2)

- A „watch and wait“ strategy is, therefore, justified in **patients with low tumour burden and very slow spontaneous tumour growth i.e. in those patients with no spontaneous tumour growth for 1 – 2 years**

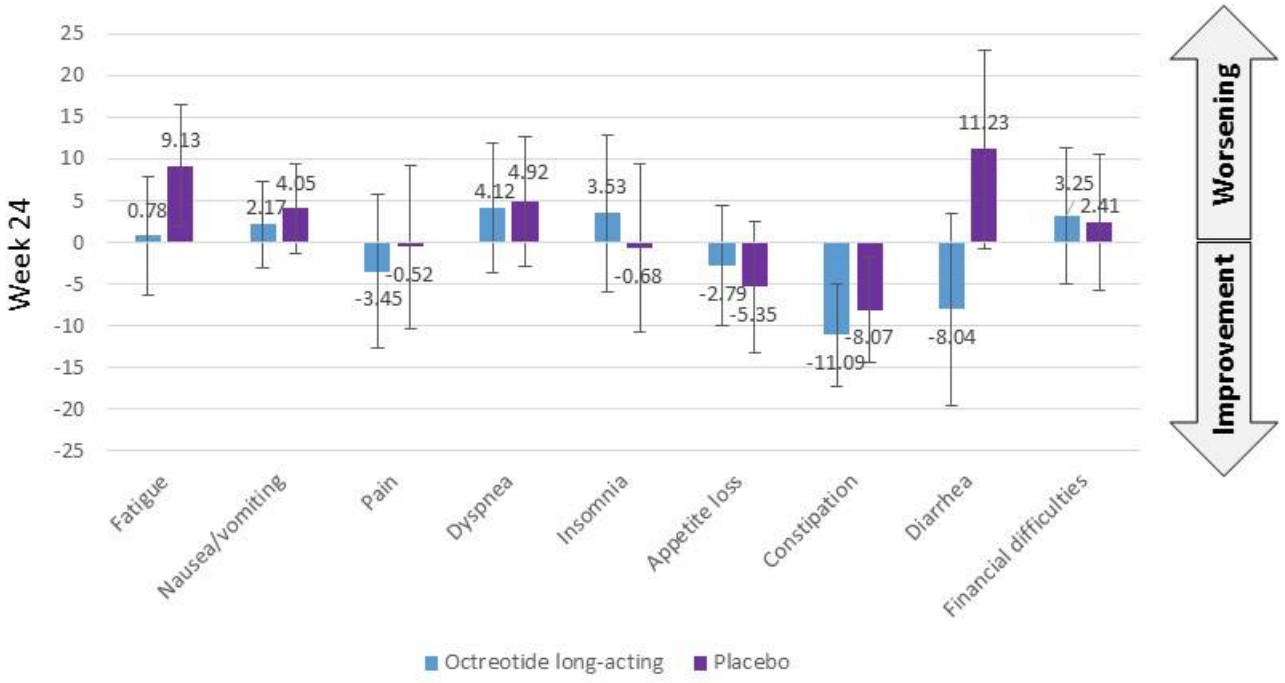
- **„watch and wait“ = tumour growth control every 3 months and start of treatment after documented progression**

Somatostatin analogues
Reasons for upfront treatment with somatostatin analogues

- Patients wish treatment because they have a malignant disease and do not agree to a „watch and wait“ strategy
- Doctors have a bad feeling if experts recommend a „wait and watch“ strategy
- Life quality is superior in patients receiving somatostatin analogues.This could be a valid argument for early treatment

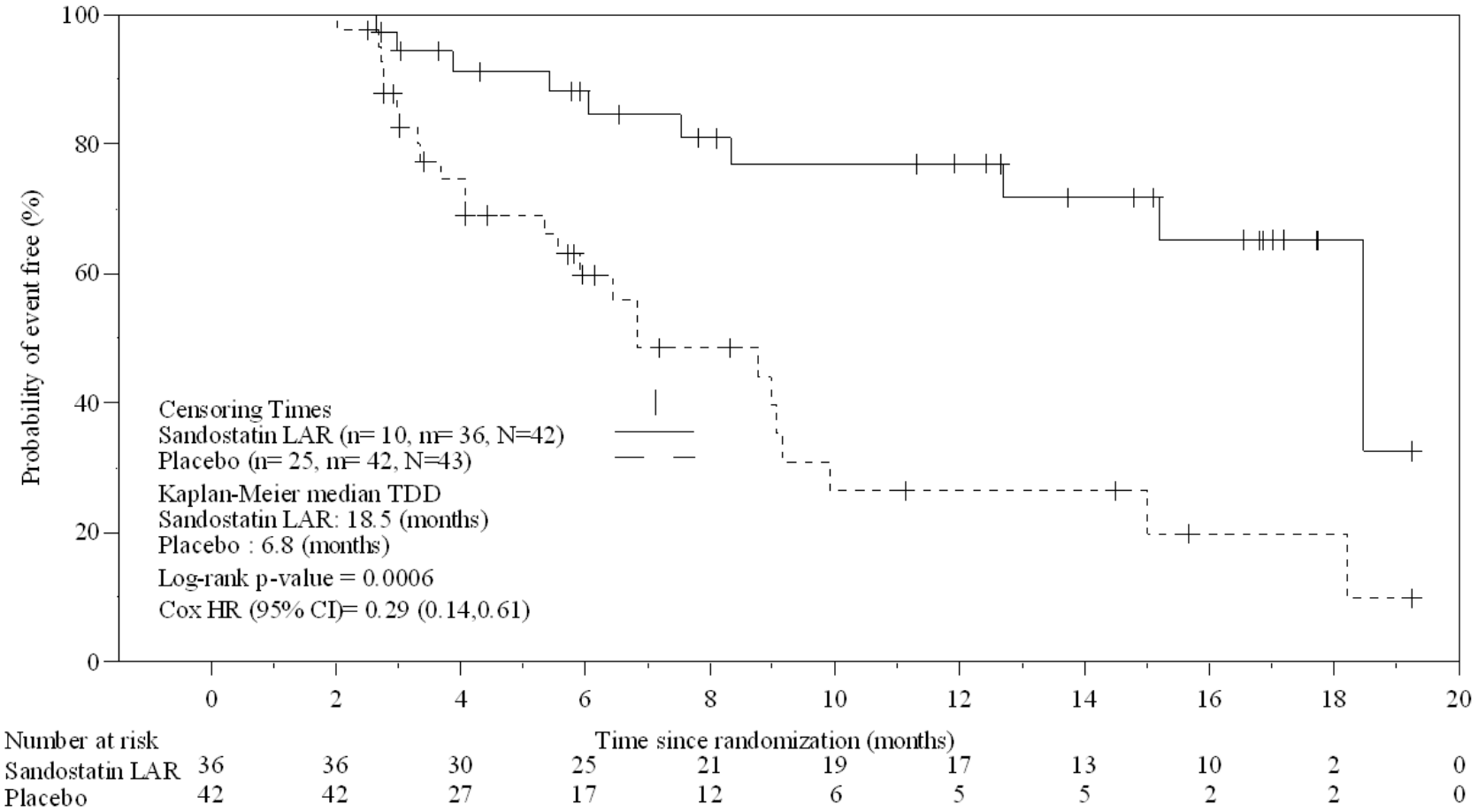
Mean Change from Baseline to Week 24 in QLQ-C30 Symptom Scales (PROMID STUDY)

Rinke et al. 2018, submitted



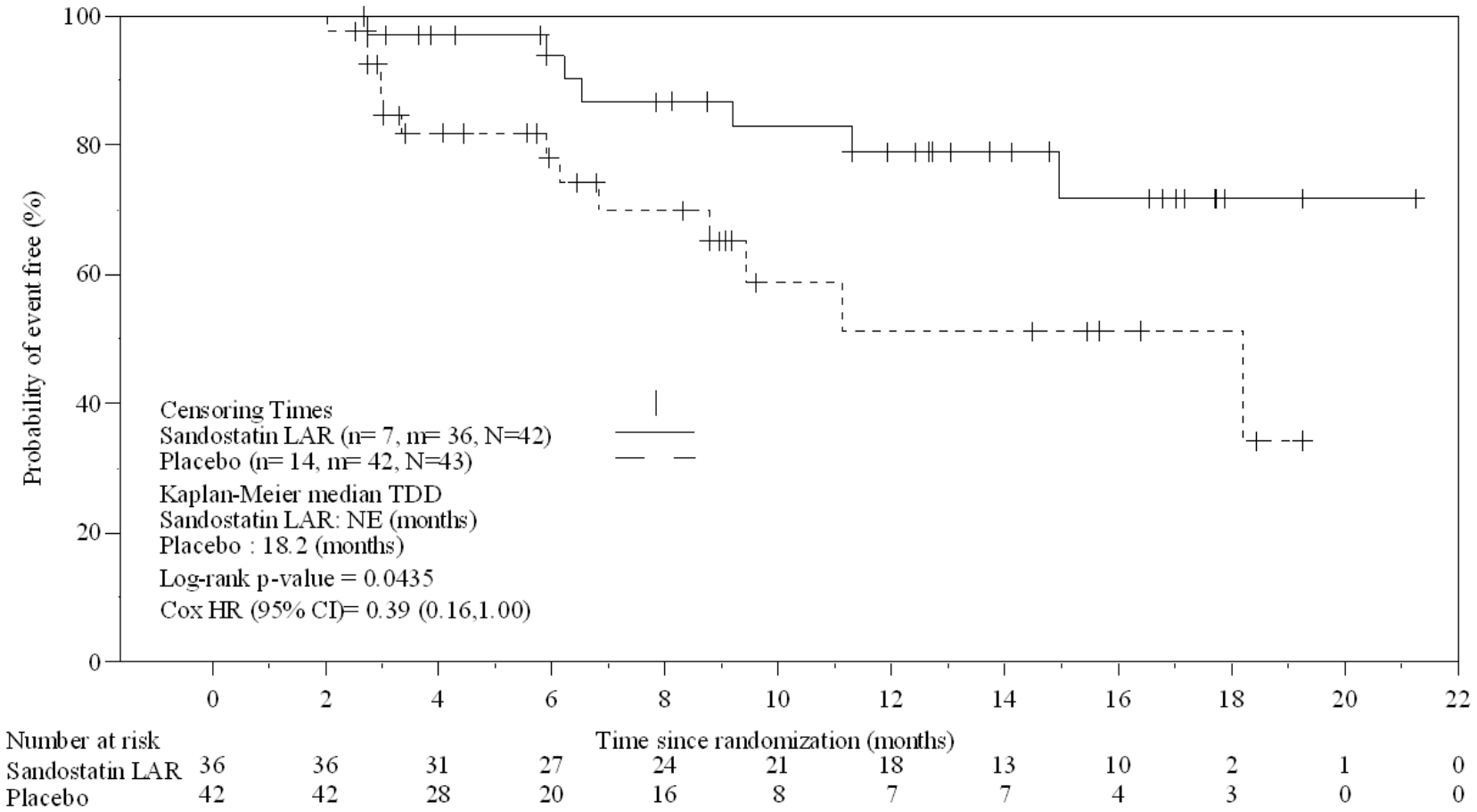
Kaplan Meier Analysis of Time to Definitive Deterioration of QLQ-C30 **Fatigue** Symptom Scale (PROMID STUDY)

Rinke et al. 2018, submitted

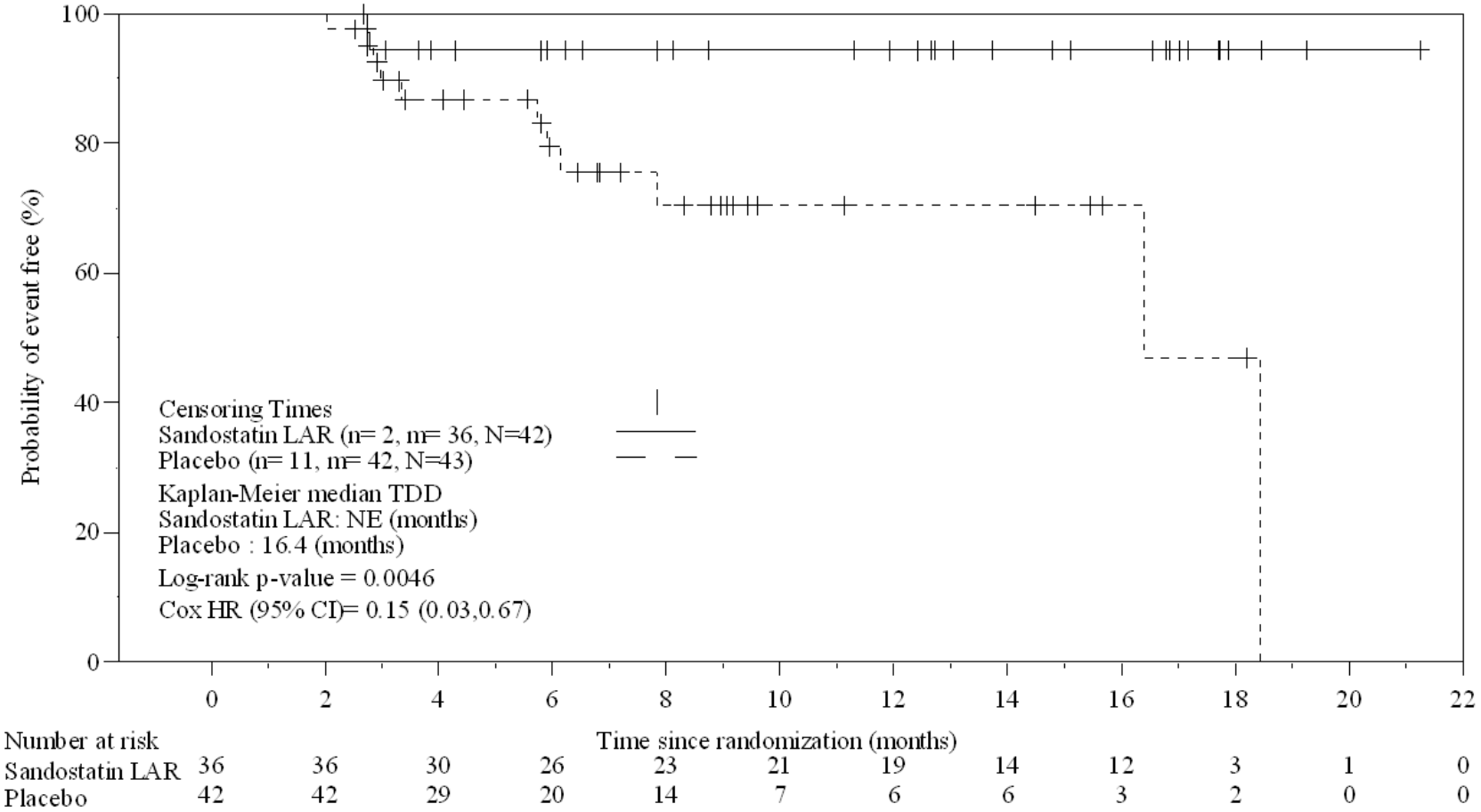


Kaplan Meier Analysis of Time to Definitive Deterioration of QLQ-C30 **Pain** Symptom Scale (PROMID STUDY)

Rinke et al. 2018, submitted



Kaplan Meier Analysis of Time to Definitive Deterioration of QLQ-C30 **Insomnia** Symptom Scale (PROMID STUDY)



Somatostatin analogues
Reasons for upfront treatment with somatostatin analogues

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- Life quality is superior in patients receiving somatostatin analogues.This is a valid argument for early treatment

NEN in the past, present and future Somatostatin analogues: Upfront or „second-line“ after watch and wait?

Summary and Conclusion (I)

- **For both strategies there are valid arguments from prospective trials**
- **„Watch and Wait“ is justified in expert centers for well informed patients with low tumour burden**

NEN in the past, present and future Somatostatin analogues: Upfront or „second-line“ after watch and wait?

Summary and Conclusion (II)

- **Upfront strategy is and will remain the regular setting in daily practice due to**

  the wish of most patients

  the wish of most doctors

  the beneficial effect of somatostatin

  analogues on life quality

Treatment Related Adverse Events

Occurring in >10%	Everolimus n = 204		Placebo n = 203	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Stomatitis*	64	7	17	0
Rash	49	<1	10	0
Diarrhea	34	3	10	0
Fatigue	31	2	14	0
Nausea	20	2	18	0
Infections*	23	2	6	<1
Peripheral Edema	20	<1	3	0
Decreased appetite	20	0	7	1
Headache	19	0	6	0
Dysgeusia	17	0	4	0
Anemia	17	6	3	0
Epistaxis	17	0	0	0
Pulmonary Events*	17	2	0	0
Weight decreased	16	0	4	0
Vomiting	15	0	6	0
Pruritus	15	0	9	0
Hyperglycemia	13	5	4	2
Thrombocytopenia	13	4	<1	0
Asthenia	13	1	8	1
Nail disorder	12	<1	1	0
Cough	11	0	2	0
Pyrexia	11	0	0	0

Yao et al, NEJM 364,6, 2011

***Related toxicities grouped for calculation**

Most Frequent All-Causality Adverse Events (%) with Sunitinib 37.5 mg/day

AE in ≥20 % of patients in either arm, n (%)	Sunitinib		Placebo	
	All Grades (n=83)	Grade 3/4 (n=83)	All Grades (n=82)	Grade 3/4 (n=82)
Diarrhea	59	5	39	2
Nausea	45	1	29	1
Asthenia	34	5	27	4
Vomiting	34		30	2
Fatigue	32	5	27	8
Hair color changes	29	1	1	
Neutropenia	29	12	4	
Abdominal pain	28	5	32	10
Hypertension	26	10	5	1
Hand–foot syndrome	23	6	2	
Anorexia	22	2	21	1
Stomatitis	22	4	2	
Dysgeusia	20		5	
Epistaxis	20	1	5	

Raymond et al, ASCO GI 2010 Raymond et al NEJM 2011, 364, 6

Therapie Neuroendokriner Tumoren

Offene Fragen

- **Gibt es Alternativen zur Erstlinientherapie mit Somatostatinanaloga?**
- **Wie entscheide ich mich bei mehreren therapeutischen Alternativen?**
- **Was folgt bei Versagen der Erstlinientherapie?**
- **Welche Bedeutung hat die Tumorlast für meine Therapieentscheidung?**

Gibt es Alternativen zur Erstlinientherapie mit Somatostatinanalog bei G1 und GS NE Tumoren?

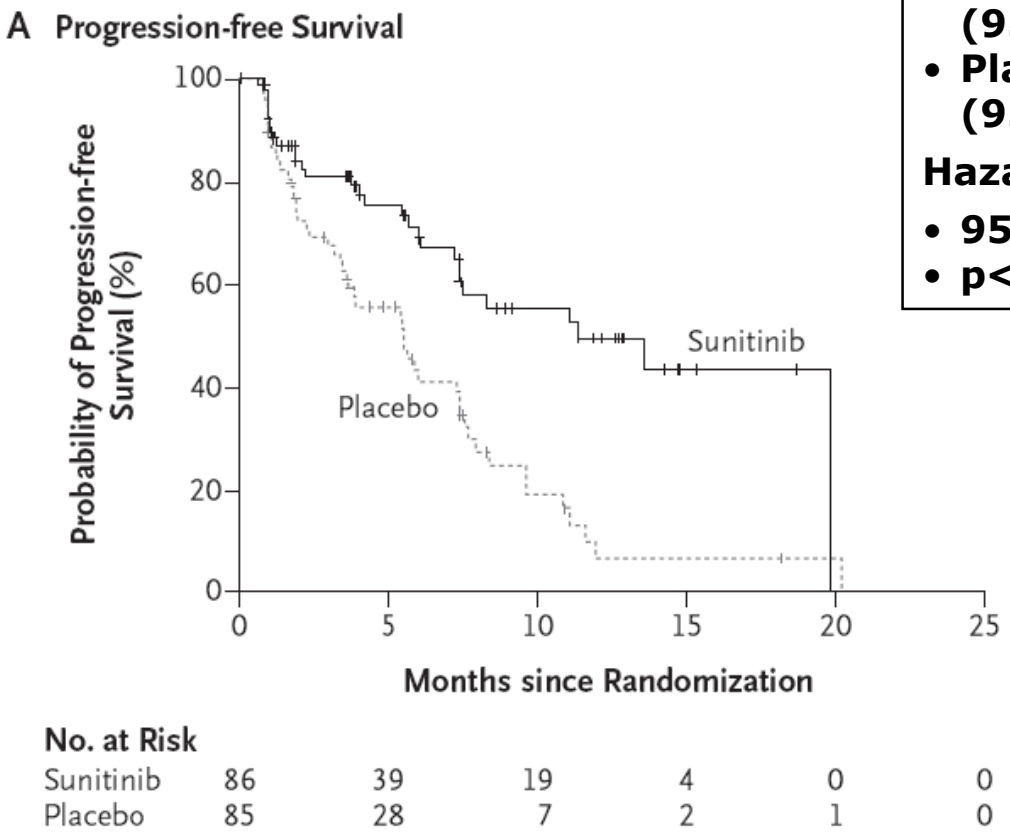
ja

- Sunitinib bei pankreatischen NETs
- Chemotherapie bei pankreatischen NETs
- Everolimus bei pankreatischen und intestinalen NETs
- PRRT
- Lokoregionale Therapieverfahren

Problem

Nebenwirkungen

Progression free survival
Sunitinib vs. Placebo in pancreatic NET



Estimate of median PFS:
- **Sunitinib, 11.4 months (95% CI: 7.4, 19.8)**
- **Placebo, 5.5 months (95% CI: 3.6, 7.4)**

Hazard ratio 0.42
- **95% CI: 0.26, 0.66**
- **p<0.001**

Study stopped early
- 171/340 pts. recruited

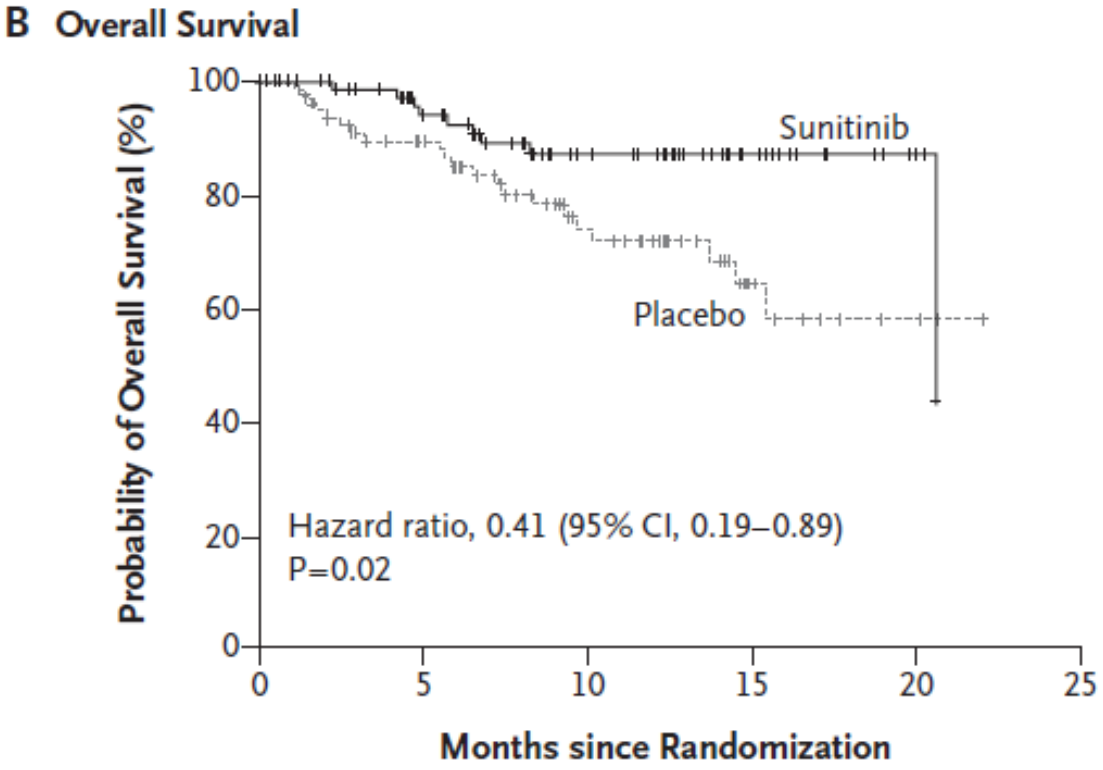
Low patient number at risk from month 15

No central radiology

Prior systemic therapy: 66.3/ 71.8% (SUN/ PLB)

Raymond et al NEJM 2011, 364, 6

Sunitinib: Overall Survival



Baseline Features Sunitinib vs Placebo

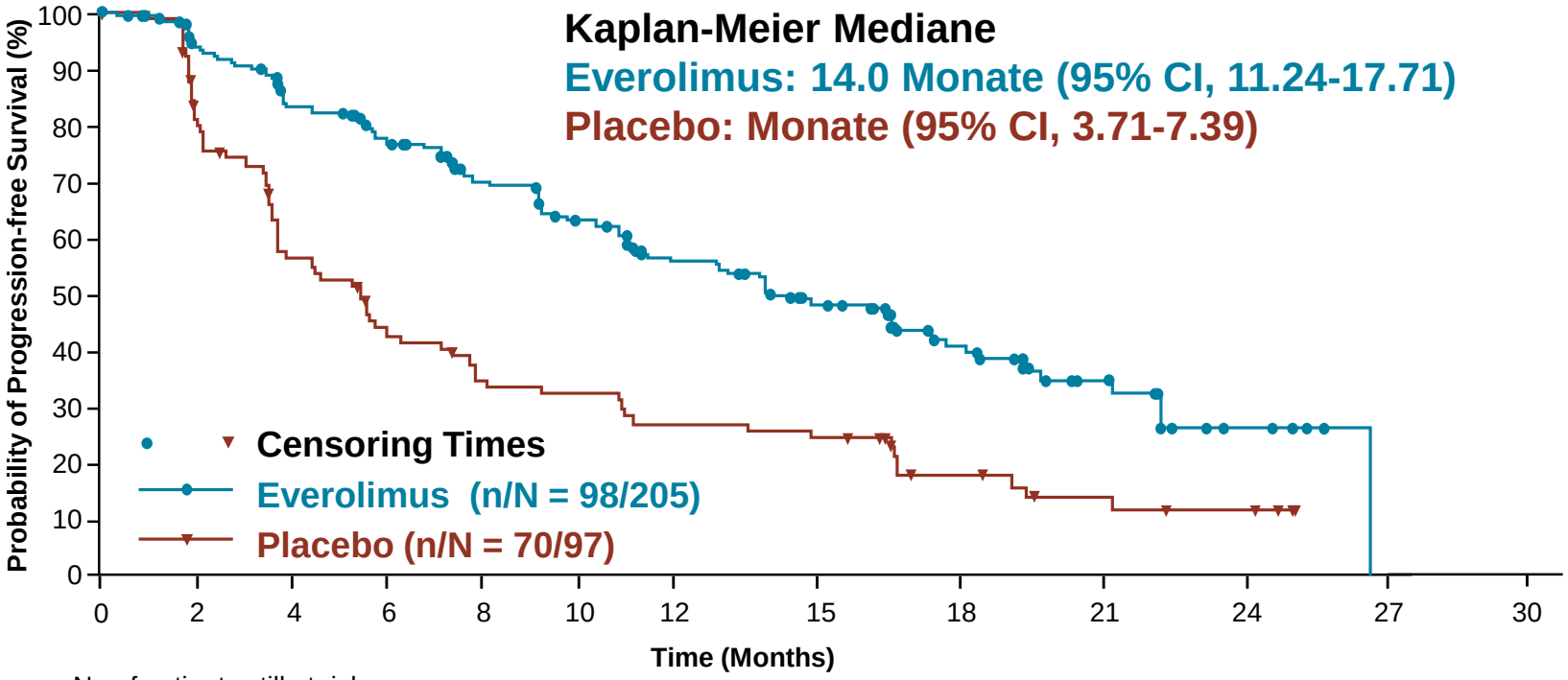
- Median time since Dx 2.4 < 3.2 yrs
- Extrahepatic disease 24<40%
- ECOG PS > 0 38<52%

Updated survival analysis – no significant survival benefit

Raymond E, Dahan L, Raoul J, et al. *N Engl J Med*. 2011;364:501-513.
Raymond et al ASCO Meeting Proceedings 2011

Radiant-4: Primärer Endpunkt: PFS (Untersucher basierte Auswertung)

Everolimus vs Placebo
HR = 0.39 (95% CI, 0.28-0.54); *P* < 0.00001

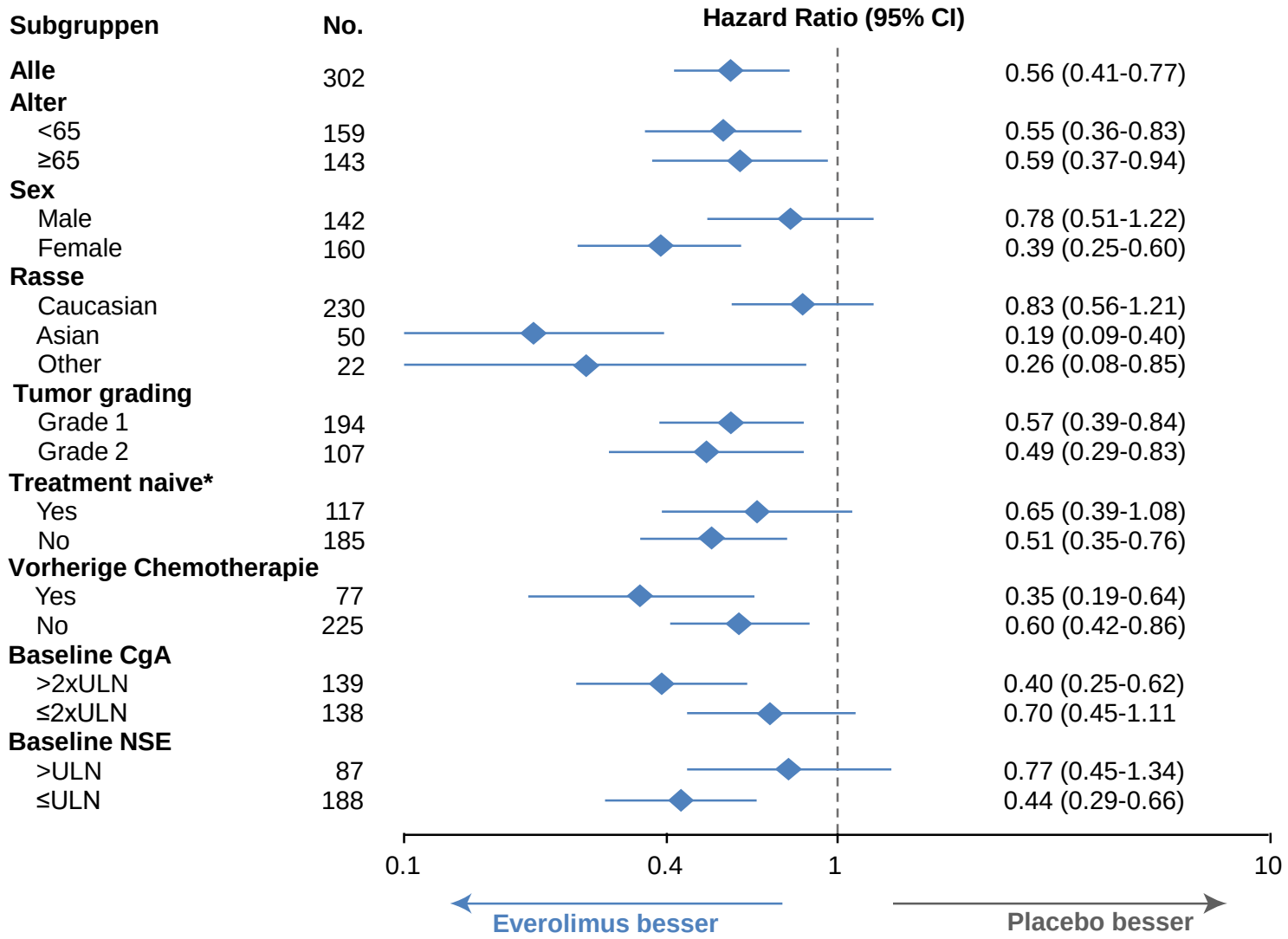


No.of patients still at risk

Everolimus	205	171	148	132	108	93	75	59	33	15	5	0	0
Placebo	97	70	47	35	27	25	21	19	10	6	4	0	0

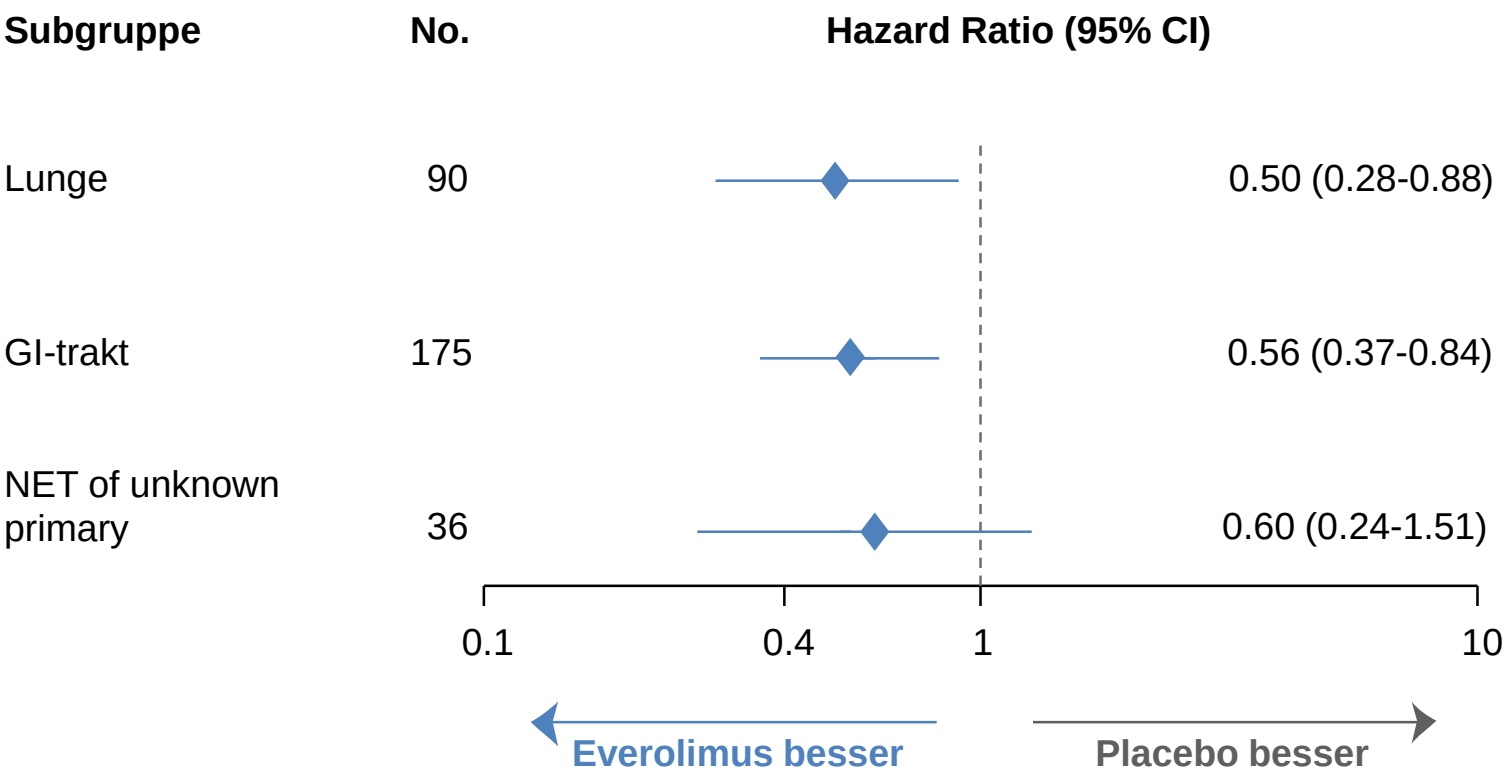
P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.

Radiant-4: PFS nach Subgruppen



*Defined as no prior chemotherapy or no SSA therapy continuously for ≥12 weeks any time before study.
Hazard ratio is obtained from unstratified Cox model.
CgA, chromogranin A; NSE, neuron-specific enolase; ULN, upper limit of normal.

Radiant-4: PFS nach Primärtumorsitz

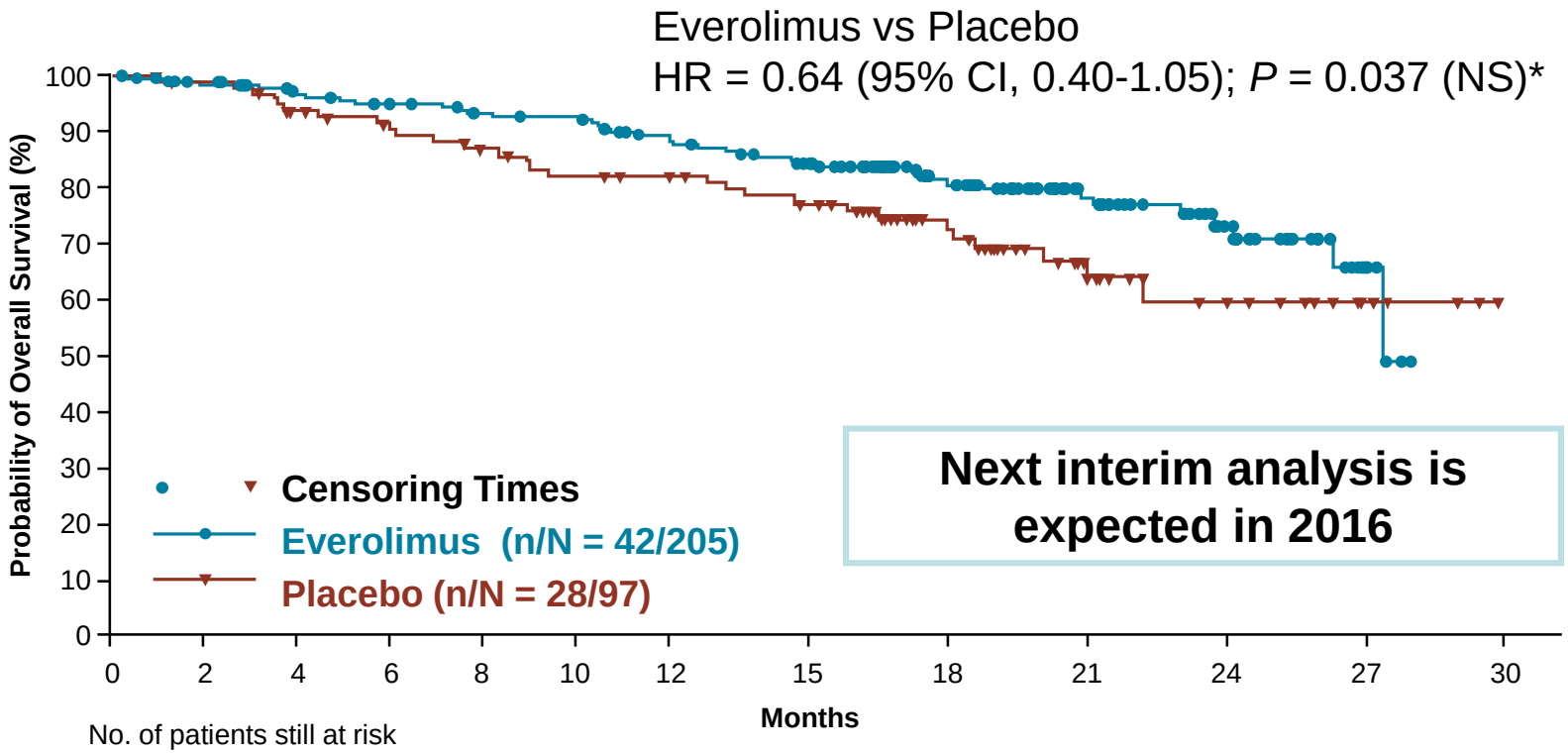


*One patient with thymus as primary tumor origin was not included.
†Stomach, colon, rectum, appendix, cecum, ileum, duodenum, and jejunum are grouped under GI.

Hazard ratio obtained from unstratified Cox model.
GI, gastrointestinal; NET, neuroendocrine tumors.

Interim Overall Survival Analysis

First interim OS analysis performed with 37% of information fraction favored the everolimus arm



Next interim analysis is expected in 2016

No. of patients still 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

*_P_-value boundary for significance = 0.0002.
_P_-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.
NS, not significant.

Therapie Neuroendokriner Tumoren
Alternativen zu Octreotid

- Sutent: ja
- Everolimus: ja
- PRRT: ja
- Interferon:?
- Chemotherapie: ja, Pankreas NEN

Chemotherapie bei gut differenzierten G1/G2 metastatischen NETs

Ja — **Metastatische NETS des Pancreas:**

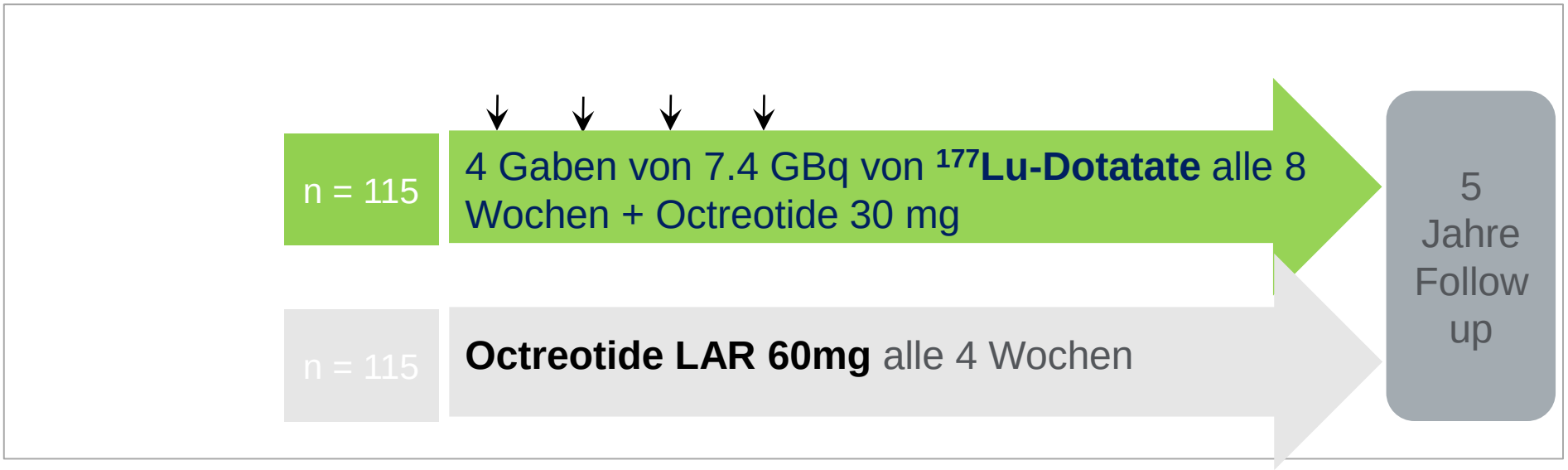
- **Streptozotocin plus 5-FU** (CG Moertel et al. NEJM 1992)
- **Streptozotocin plus Doxorubicin**
- **Dacarbazin** (Ramanathan et al. 2001)
- **Temozolomid** (Ekeblad et al. 2007)
- **Temozolomid plus Thalidomid or Bevacizumab or Capecitabin** (Kulke et al 2006, Strosberg et al 2008)

Nein — **Midgut Tumore**

Nein — **Fore- and Hindgut Tumore**

Untersucht wurde das Tumorwachstum (Recist) im Abstand von 12 Wochen

Ziel	Wirksamkeit und Sicherheit von ^{177}Lu-Dotatate plus Octreotide30 mg verglichen mit Octreotide LAR 60mg bei Patienten mit inoperablen, somatostatin rezeptor positiven, midgut NET, die unter Octreotide LAR 30mg progredient waren
Design	International, multicenter, randomisiert, placebo-kontrolliert



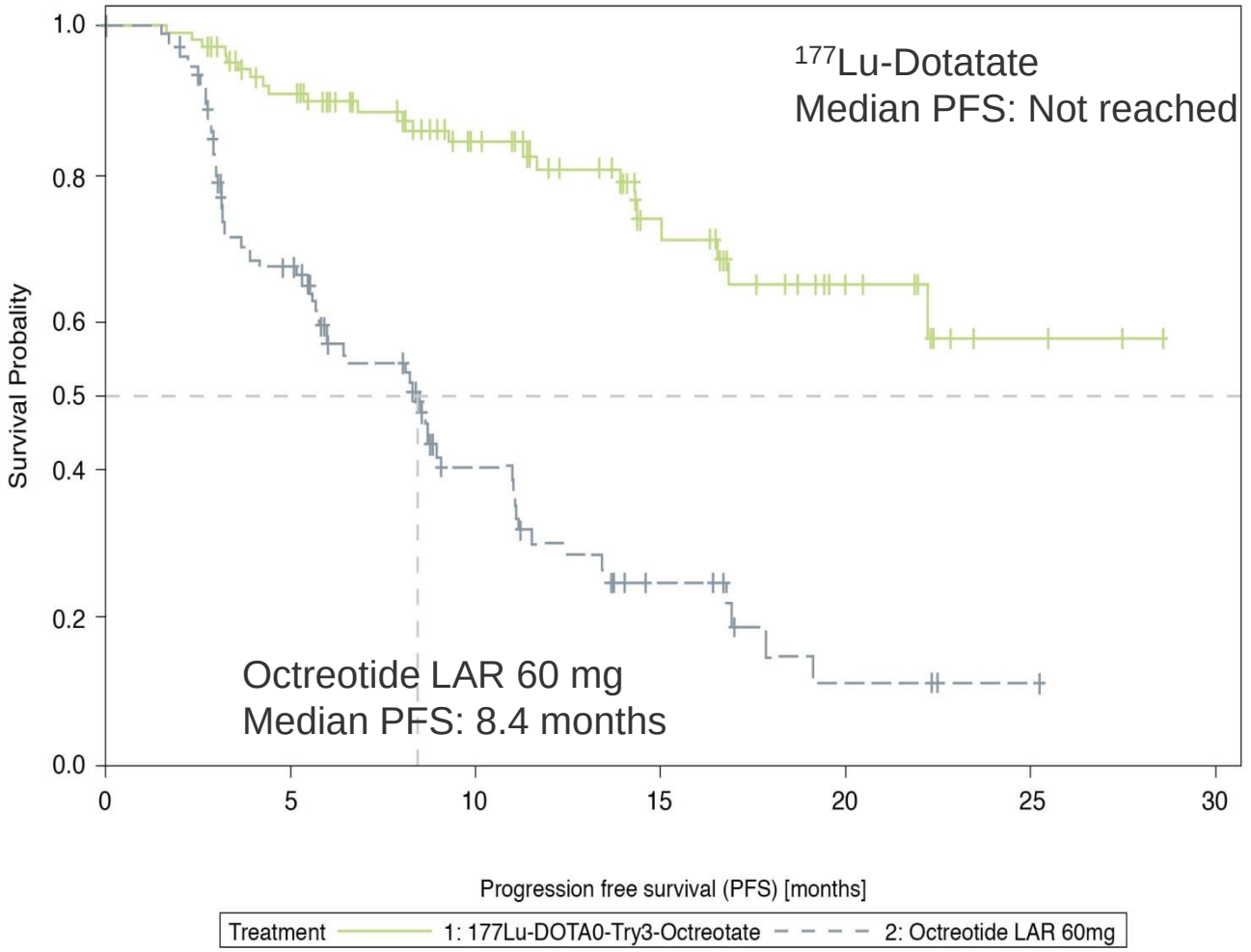
Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

Progressions Freies Überleben

N = 229 (ITT)
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard Ratio [95%
0.209 [0.129 – 0.33
p < 0.0001



All progressions centrally confirmed and independently reviewed for eligibility (SAP)

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Tumour Response Rate (currently evaluable patients)

	^{177}Lu-Dotatate (n=101)	Octreotide LAR 60mg (n=100)
Complete Response (n)	1	0
Partial Response (n)	18	3
Objective Response Rate (CI 95%)	19 (11-26) %	3 (0-6) % *
Progressive Disease (n, %)	5 (4%)	27 (24%)
Stable Disease (n, %)	77 (66%)	70 (62%)

***P<0.0004**

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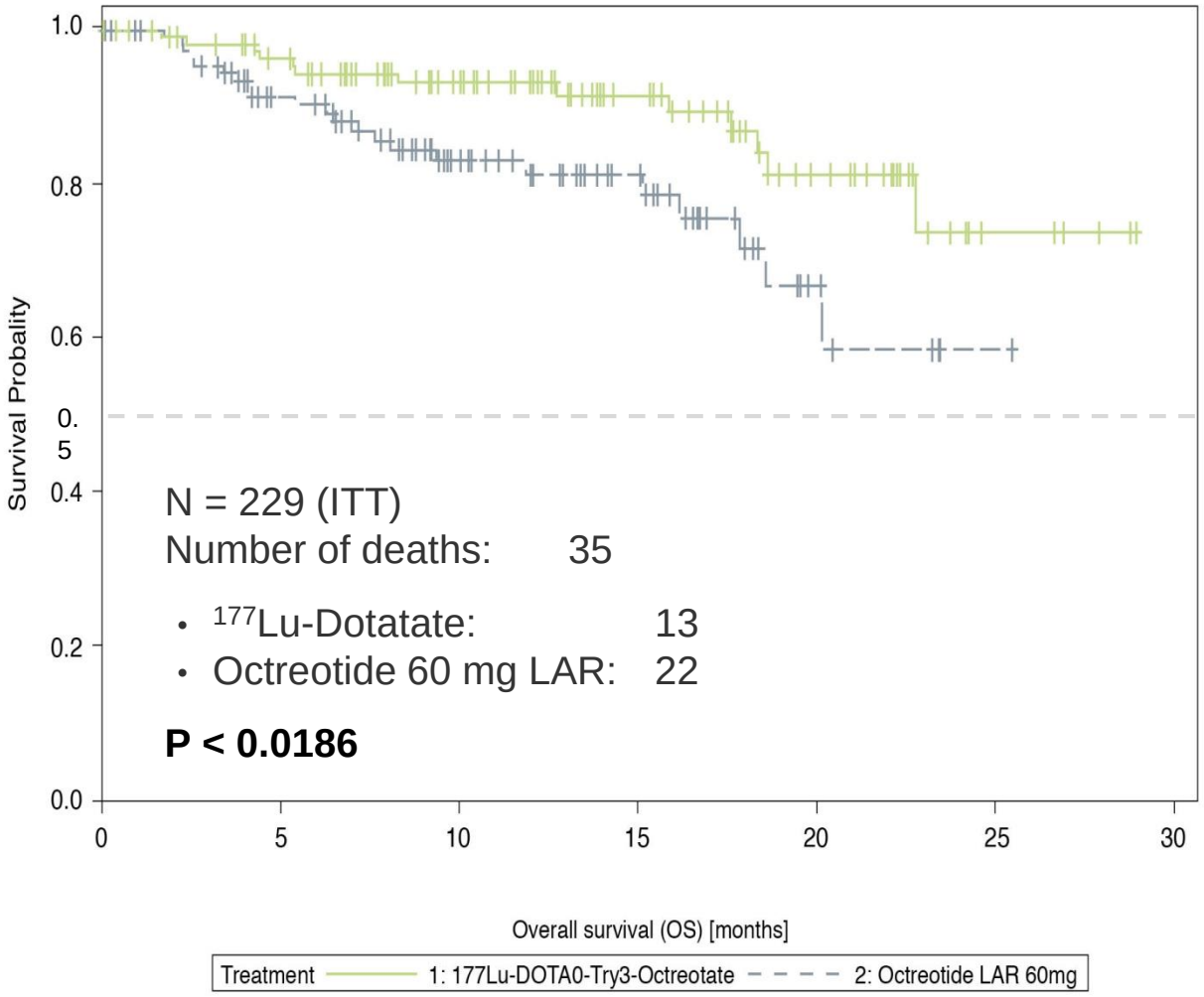
Overall Survival (interim analysis)



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Safety and Tolerability
(Nb of patients (%), Safety Set; n=221)

	177-Lu-Dotatate (n=111)	Octreotide LAR 60mg (n=110)
Any adverse event	106 (96%)	95 (86%)
Related to treatment	95 (86%)	34 (31%)
Serious adverse events	29 (26%)	26 (24%)
Related to treatment	10 (9%)	1 (1%)
Withdrawals due to adverse events	7 (6%)	10 (9%)
Related to treatment	5 (5%)	0 (0%)

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Therapie Neuroendokriner Neoplasien

Welche Antworten haben wir durch die neuen prospektive Studien für die Therapie metastasierter intestinaler NEN erhalten?

- **Bei Intestinalen NENs muß der Primärtumor entfernt werden Auch ein Tumordebulking verlängert das Leben**
- **Für jede Therapie ist grundsätzlich die Kenntnis des Gradings (Ki-67) von entscheidender Bedeutung: G1, G2, G3**
- **Somatostatinanaloga (Octreotide LAR[1], Lanreotide Autogel[2]) hemmen das Tumorwachstum bei allen GEP-NETs (PROMID, CLARINET) mit einem Grading G1 oder G2**

[1] **Zulassung Octreotid LAR: Midgut NET**
[2] **Zulassung Lanreotid Autogel: GEP-NET G1, G2 (Ki67<10%)**