New treatment options for NET

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Disclosure slide

- I have nothing to disclose.

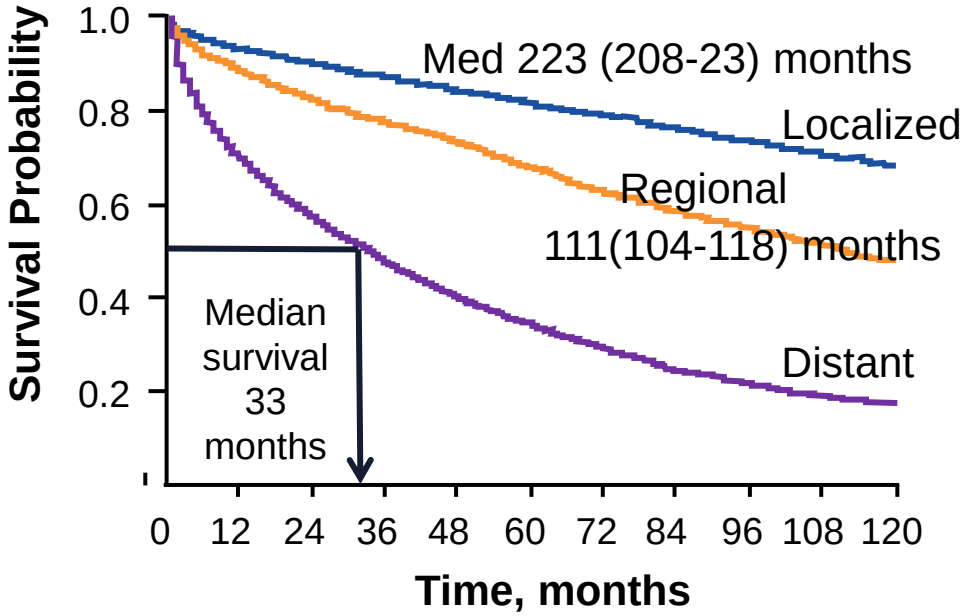
Neuroendocrine Tumors (NET)

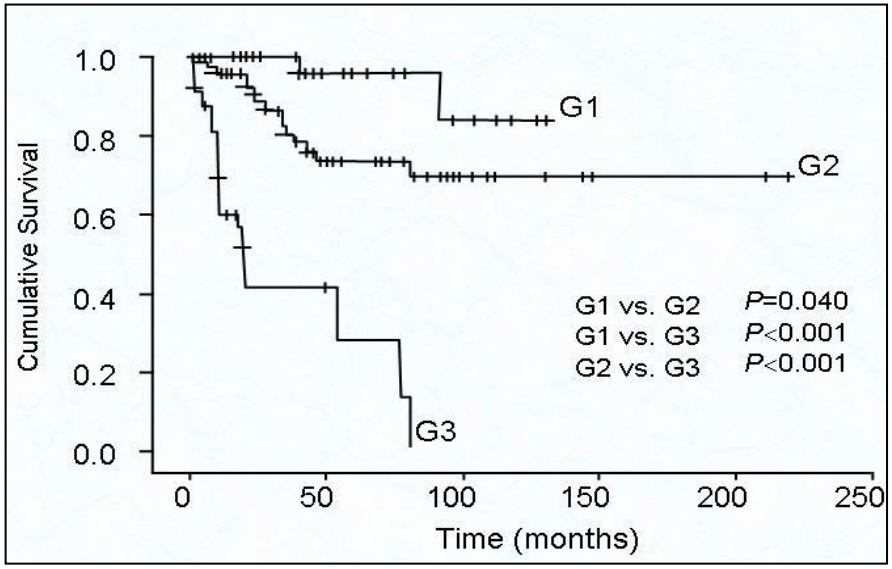
- Heterogenous disease
- Different biology by primary site
- Uncommon disease
- Limited numbers of phase III study
- Treatment mainly based on consensus recommendations of experts

Prognostic factors for treatment decision

- Funtional vs non-functional
- G1/G2 vs G3
- Primary tumor site (pancreatic vs non-pancreatic)
- Localized vs metastatic
- Somatostatin receptor status
- Indolent vs Aggressive

Survival based on stage and grade





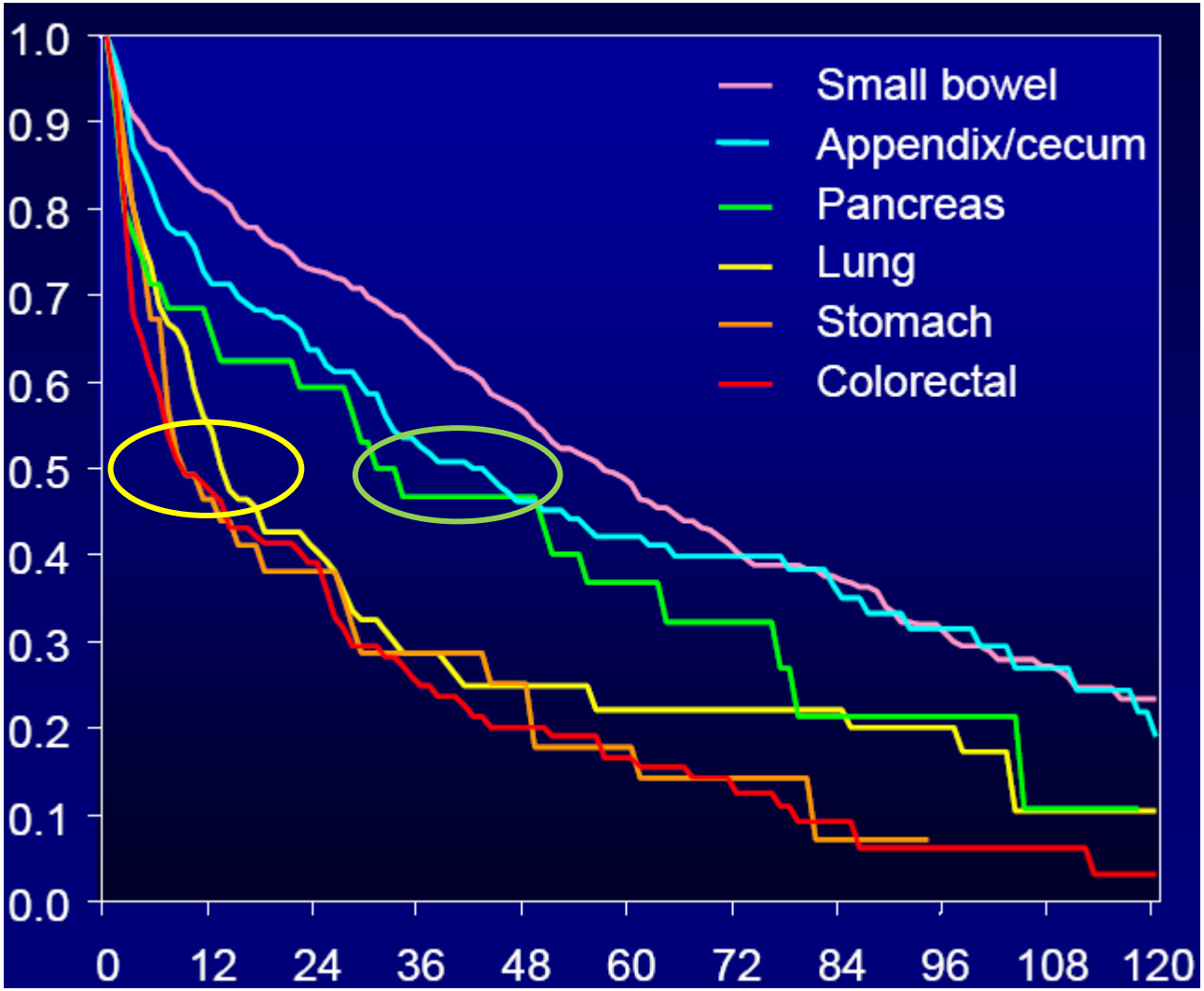
Median Survival (Months)			
Site	Localized	Regional	Distant
Lung	~227	151	**17**

Analysis of 35,825 cases of NET identified in the SEER registries (1988-2004)

Yao JC et al. *J Clin Oncol.* 2008;26:3063-3072

Pape UF et al. Cancer 2008:113:256-265

Survival by primary site

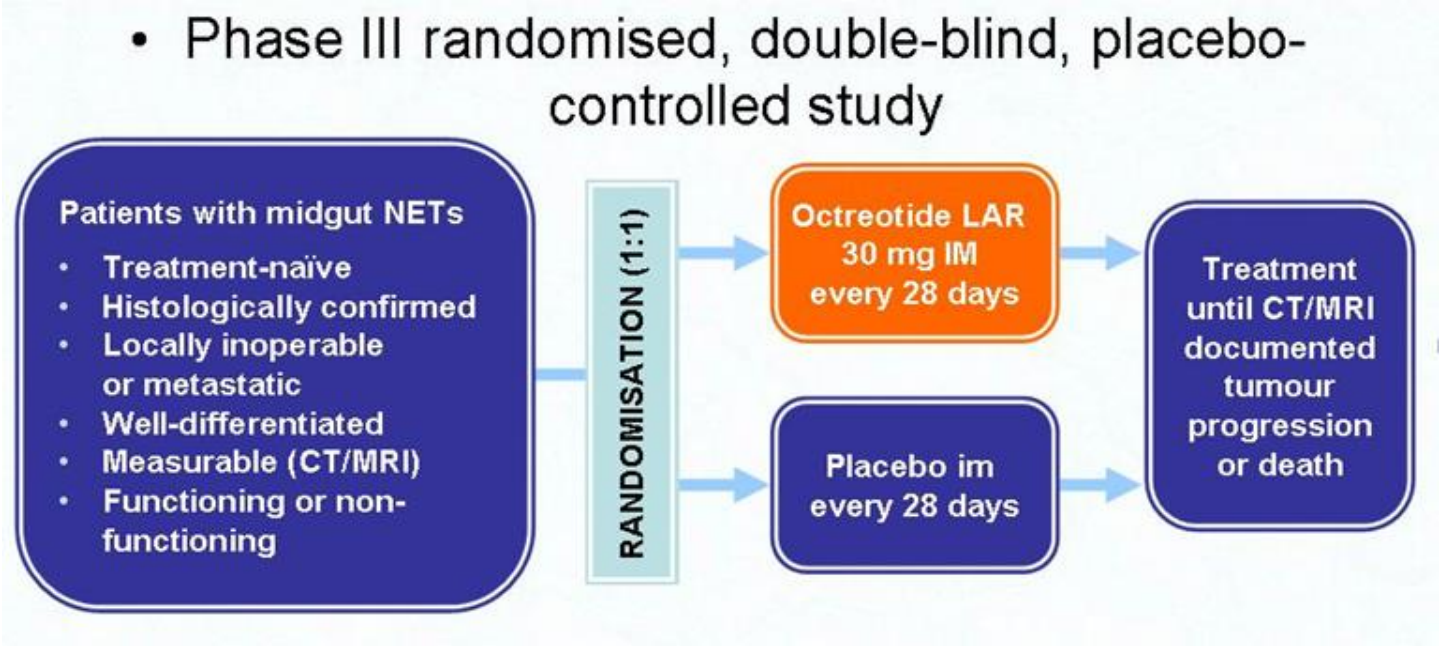


Yao JC et al. *J Clin Oncol*. 2008;26:3063-3072.

Phase III trials for non-functional, non-pancreatic NET

- Somatostatin analogs
  - PROMID study
  - CLARINET study
- Peptide receptor Radionuclide Therapy (PRRT)
  - NETTER-1 study
- Targeted agents
  - SWOG S0518 study
  - RADIANT-4 study

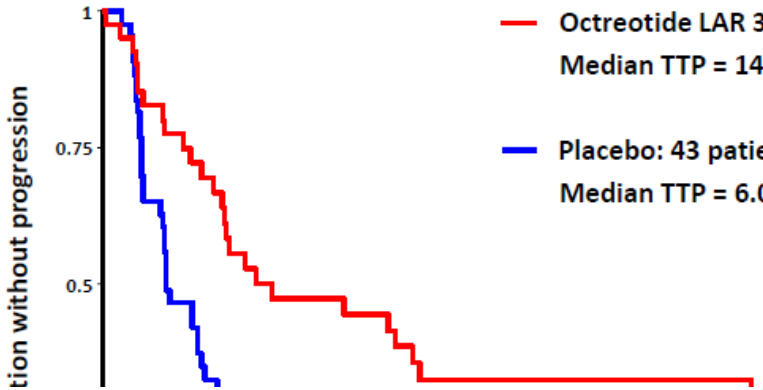
PROMID: Evaluation of the anti-proliferative effect of octreotide LAR



Primary endpoint: time to progression
Secondary endpoint: Objective response rate, OS, QOL, Safety

Rinke A et al. JCO 2009:27:4656

66% reduction in the risk of tumor progression
HR=0.34; 95% CI: 0.20–0.59; *P*=0.000072

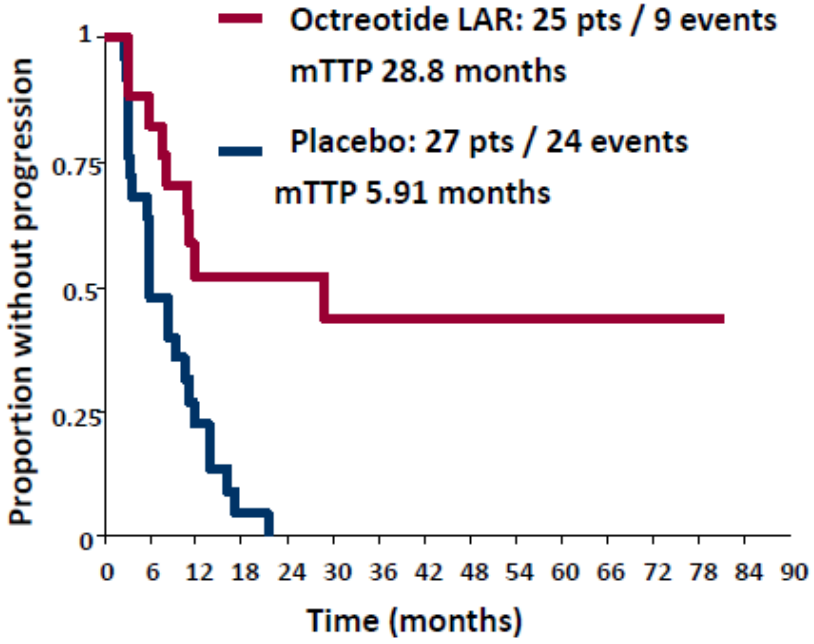


Octreotide LAR 30 mg: 42 patients / 26 events
Median TTP = 14.3 months [95% CI: 11.0–28.8]

Placebo: 43 patients / 40 events
Median TTP = 6.0 months [95% CI: 3.7–9.4]

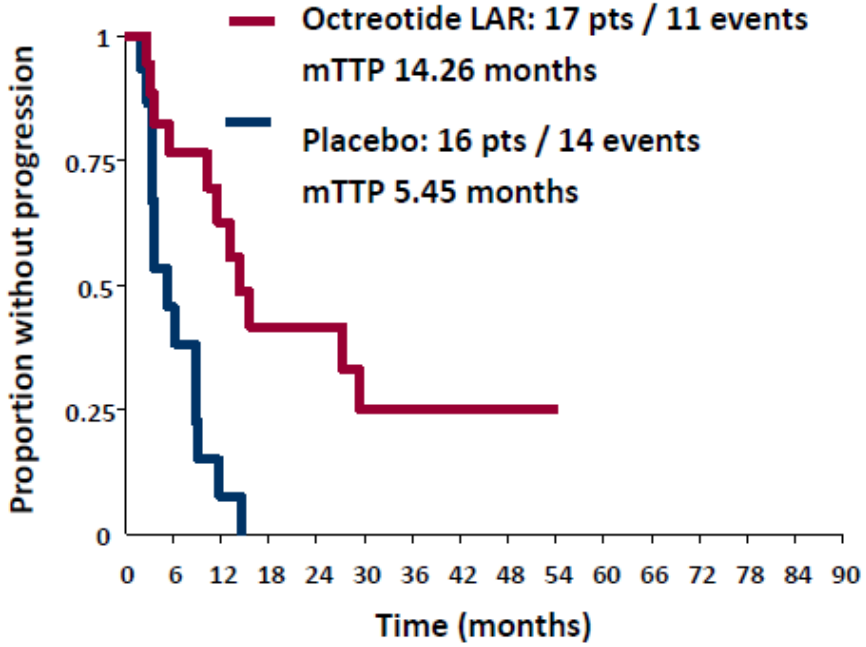
60% Patient

Pts without carcinoid syndrome



HR=0.25 [IC 95%: 0.10–0.59]
P=0.0008

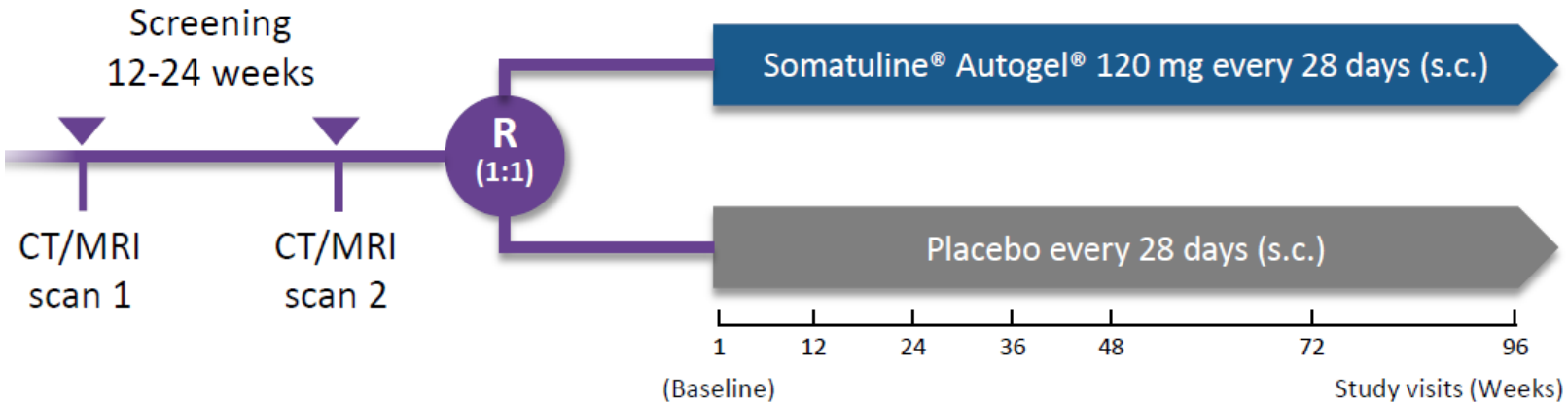
Pts with carcinoid syndrome



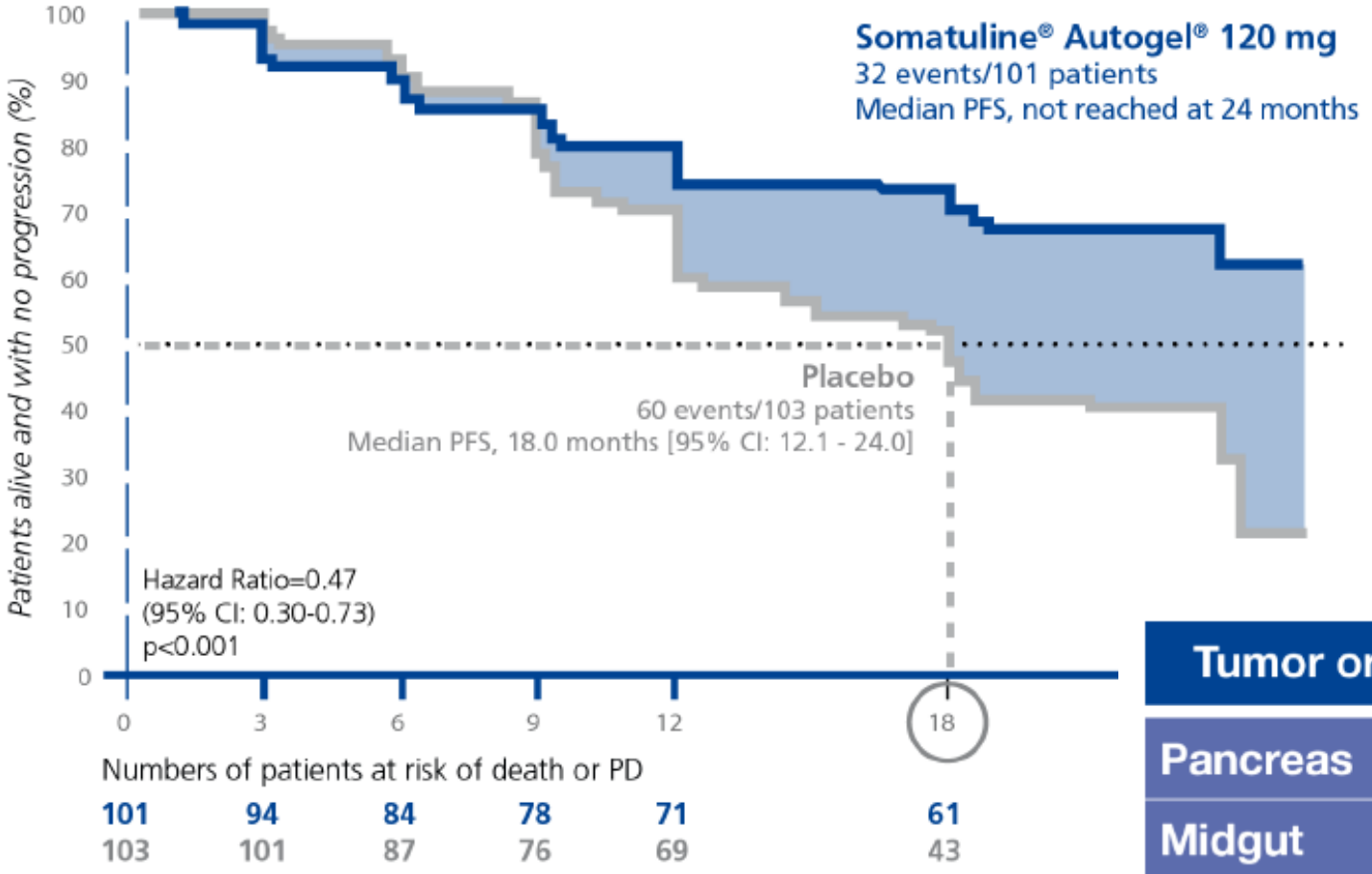
HR=0.23 [IC 95%: 0.09–0.57]
P=0.0007

CLARINET: Controlled study of Lentreotide Antiproliferative Response in NET

Aim	To compare effect of Somatuline® Autogel® 120 mg *vs.* placebo on PFS in non-functioning enteropancreatic NETs
Design	International, randomized, double-blind, placebo controlled, phase III study



Caplin ME et al. NEJM 2014:371:224



Tumor origin (%)	
Pancreas	**45%**
Midgut	**36%**
Hindgut	7%
Unknown /other	13%

Chemotherapy in Lung NET

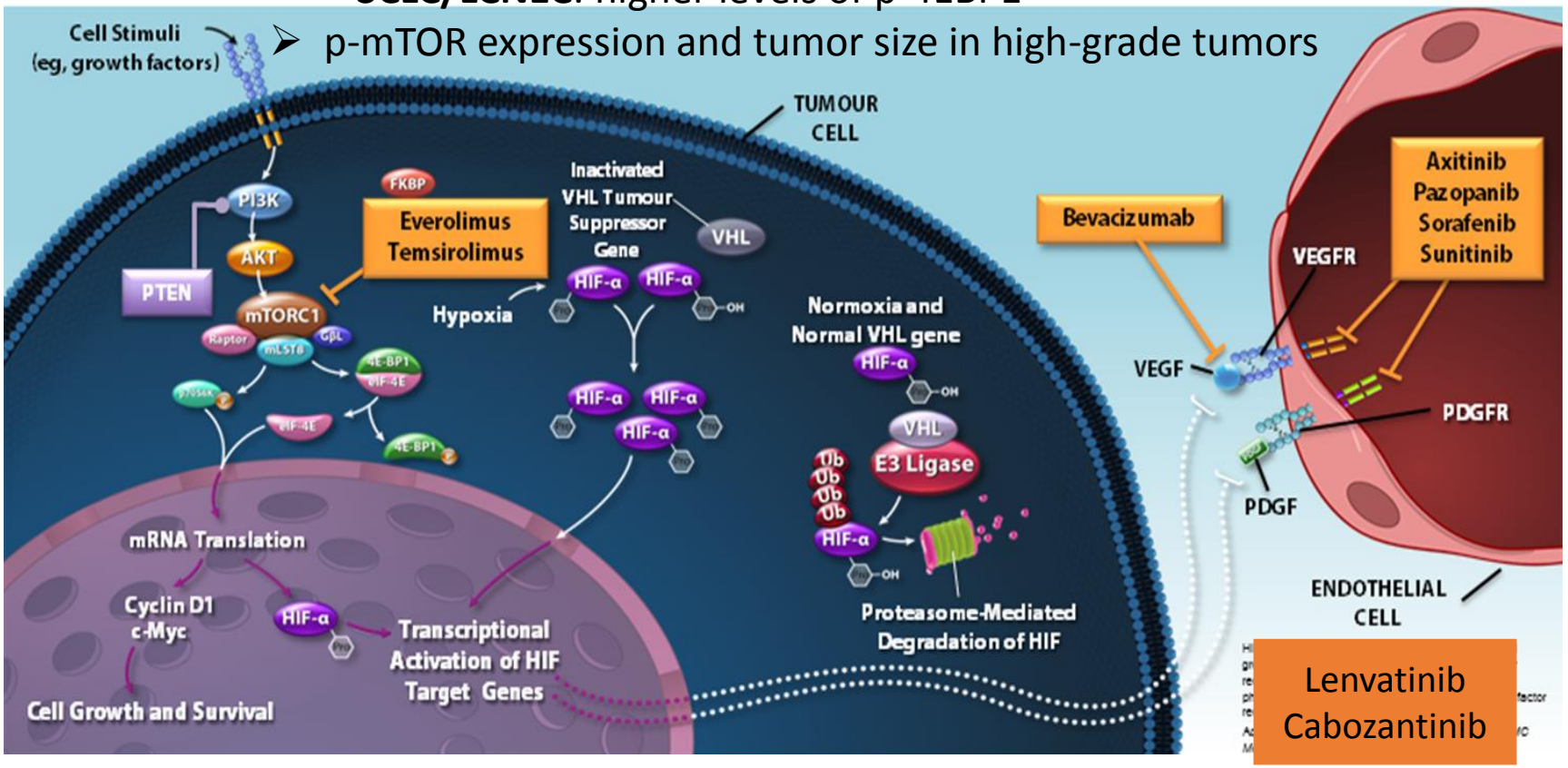
- No standard chemotherapy regimen for lung NET[1]
  - Data from small studies and retrospective series[1,2]
  - Primarily cisplatin- or streptozocin-based regimens[2]
    - Heterogeneous methods used to measure response[3]
  - Overall, response rates are discouraging: ~14% to 30%[4-6]
    - Advanced lung NET generally resistant to streptozocin-based therapies[1,3]

- Several chemotherapeutic agents with moderate efficacy
  - Temozolomide, cisplatin, etoposide, capecitabine, and oxaliplatin[1]
  - Cisplatin + etoposide effective in high proliferating lung NET tumors[3,7,8]
  - Capecitabine + temozolomide under evaluation in a phase II study in patients with metastatic NET, including lung NET (NCT00869050)

1. Horsch D et al. *Oncol Res Treat.* 2014;37:266-276; 2. Kosmidis PA. *Curr Opin Oncol.* 2004;16:146-149; 3. Granberg D et al. *Ann Oncol.* 2001;12:1383-1391; 4. Gustafsson BI et al. *Cancer*. 2008;113:5-21; 5. Ekeblad S et al. *Clin Cancer Res*. 2007;13:2986-2991; 6. Crona J et al. *Neuroendocrinology*. 2013;98:151-155; 7. Oberg K et al. *Ann Oncol.* 2012;23(suppl 7):vii120-vii123;
8. Fjajllskog ML et al. *Cancer.* 2001;92:1101-1107.

Targeted Therapies in NET

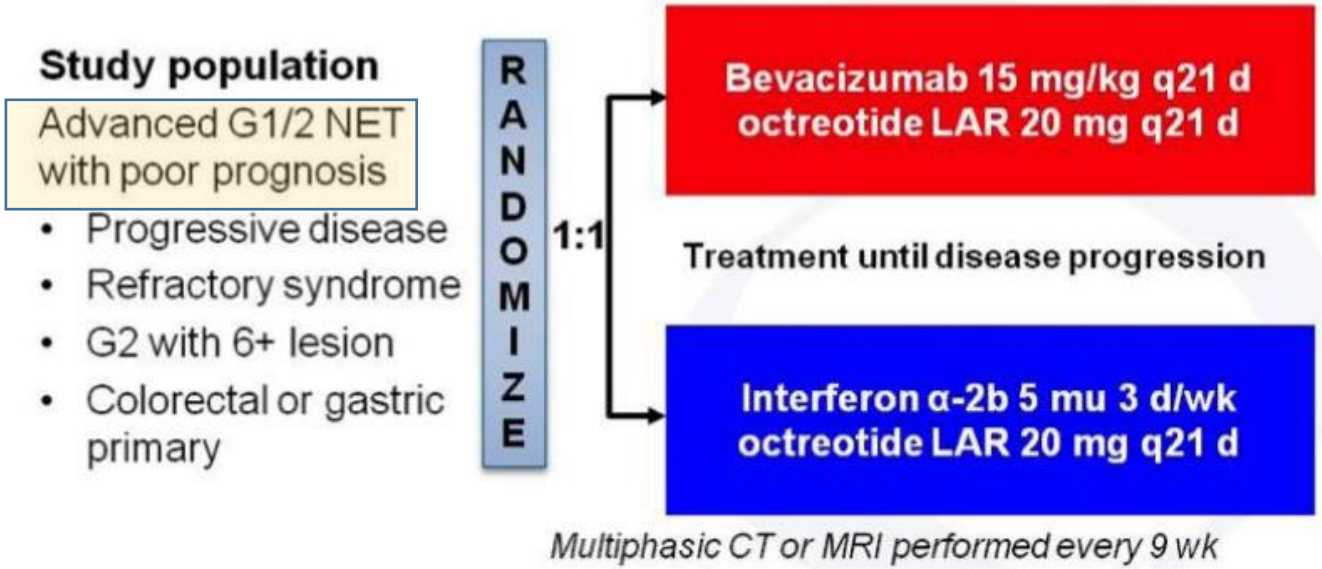
- Distinct mTOR signaling patterns across lung NET subtypes
  - **TC/AC**: higher levels of p-mTOR, p-Akt, and p-SK6
  - **SCLC/LCNEC**: higher levels of p-4EBP1
- p-mTOR expression and tumor size in high-grade tumors



- mTOR pathway activation is observed with genetic cancer syndromes associated with pNET: TSC2, NF1, VHL

- AC, atypical carcinoid; LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell lung carcinoma;TC, typical carcinoid.
- 1. Righi L, et al. *Endocr Relat Cancer* 2010;17:977–987; 2. Ali G, et al. *Exp Ther Med* 2011;2:787–792.

SWOG S0518 : Phase III prospective randomized comparison of depot octreotide plus interferon alpha-2b versus depot octreotide plus bevacizumab in advanced, poor prognosis carcinoid patients.



Primary endpoint:
- PFS (Central radiology review)

Stratification factors:
- Primary site: Midgut vs others
- RECIST PD since diagnosis
- Histologic grade: G1 vs G2
- Octreotide 2 months prior to registration

- Changing statistical assumption

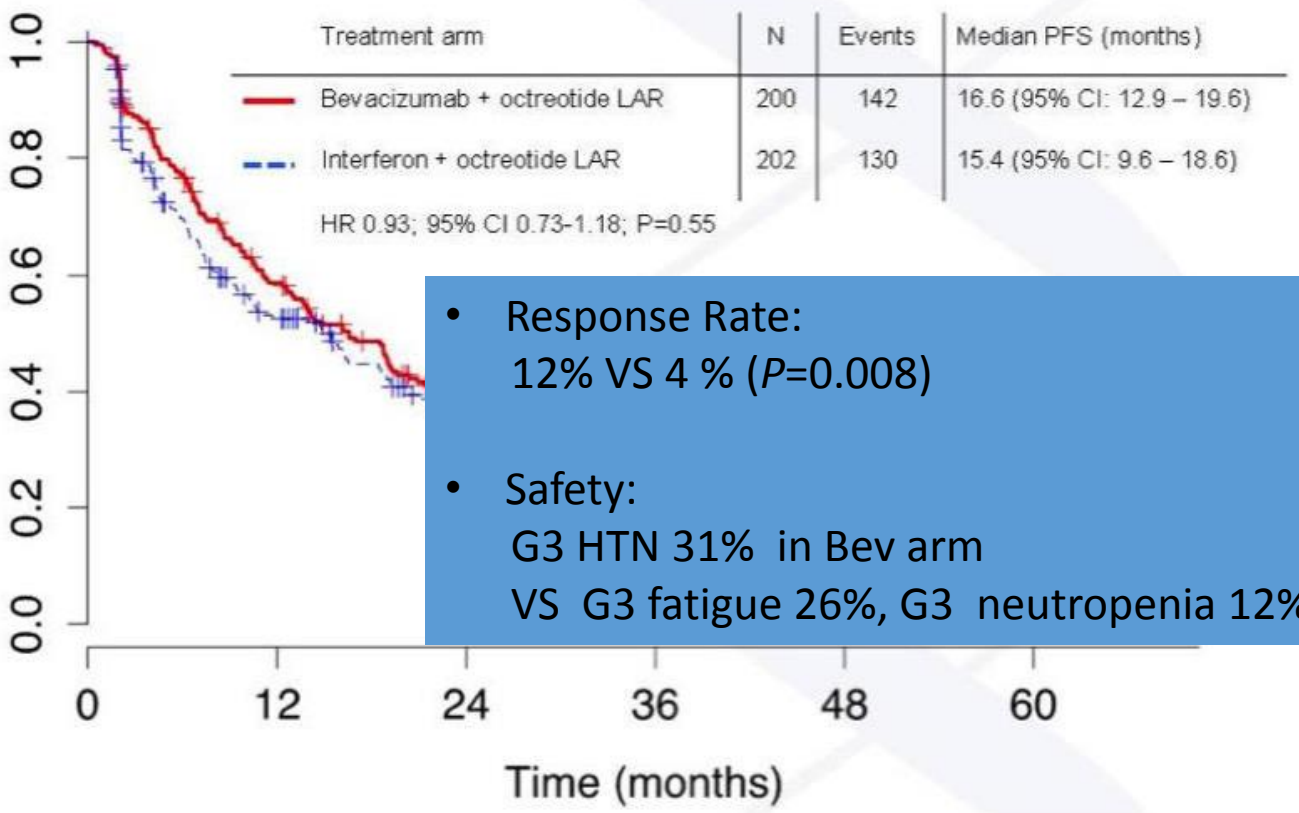
PFS :6m-> 9m to PFS' : 15 m-> 21m

- Good prognostic group?

Presented by Yao JC at 2015 ASCO Annual Meeting

- IFN –a as a control arm?

SWOG S0518 : PFS by central review



- Response Rate:
  12% VS 4 % (*P*=0.008)
- Safety:
  G3 HTN 31% in Bev arm
  VS G3 fatigue 26%, G3 neutropenia 12% in IFN arm

ICR, independent central review

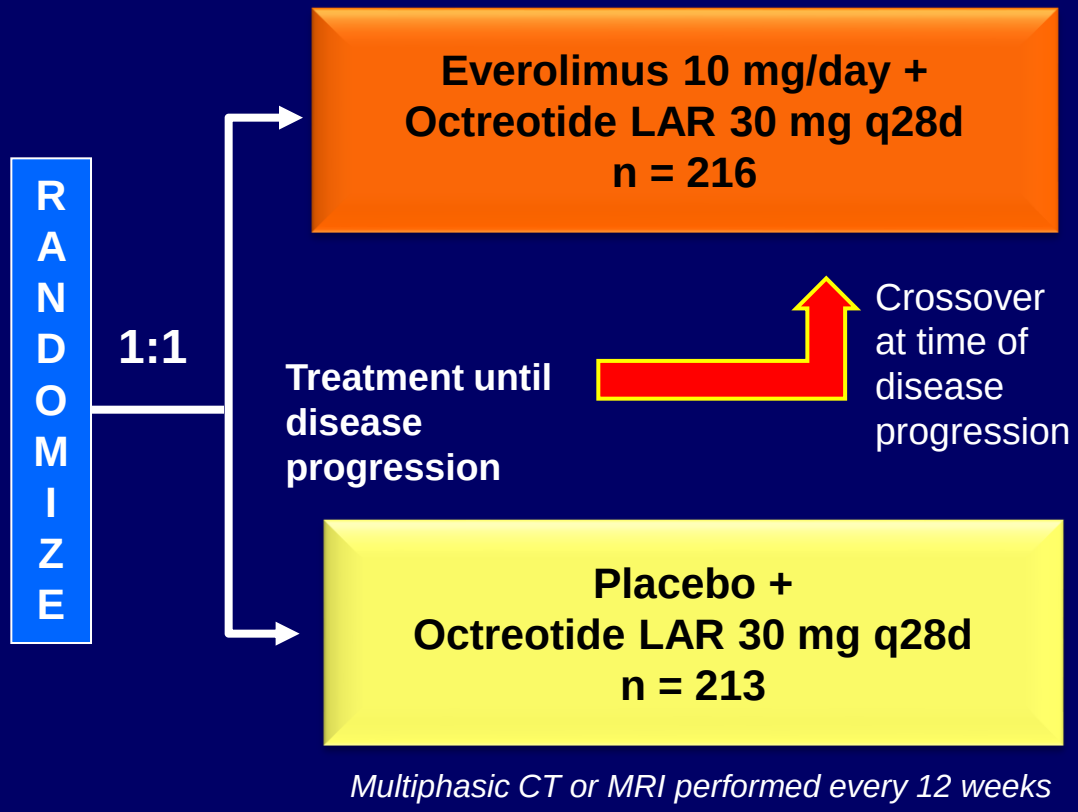
Presented by Yao JC at 2015 ASCO Annual Meeting

RADIANT-2 Study Design

Phase III Double-blind Placebo-Controlled Trial

Patients with advanced NET and a history of secretory symptoms (N = 429)

- Advanced low- or intermediate-grade NET
- Radiologic progression within 12 months
- History of secretory symptoms (flushing, diarrhea)
- Prior antitumor therapy allowed
- WHO PS ≤2



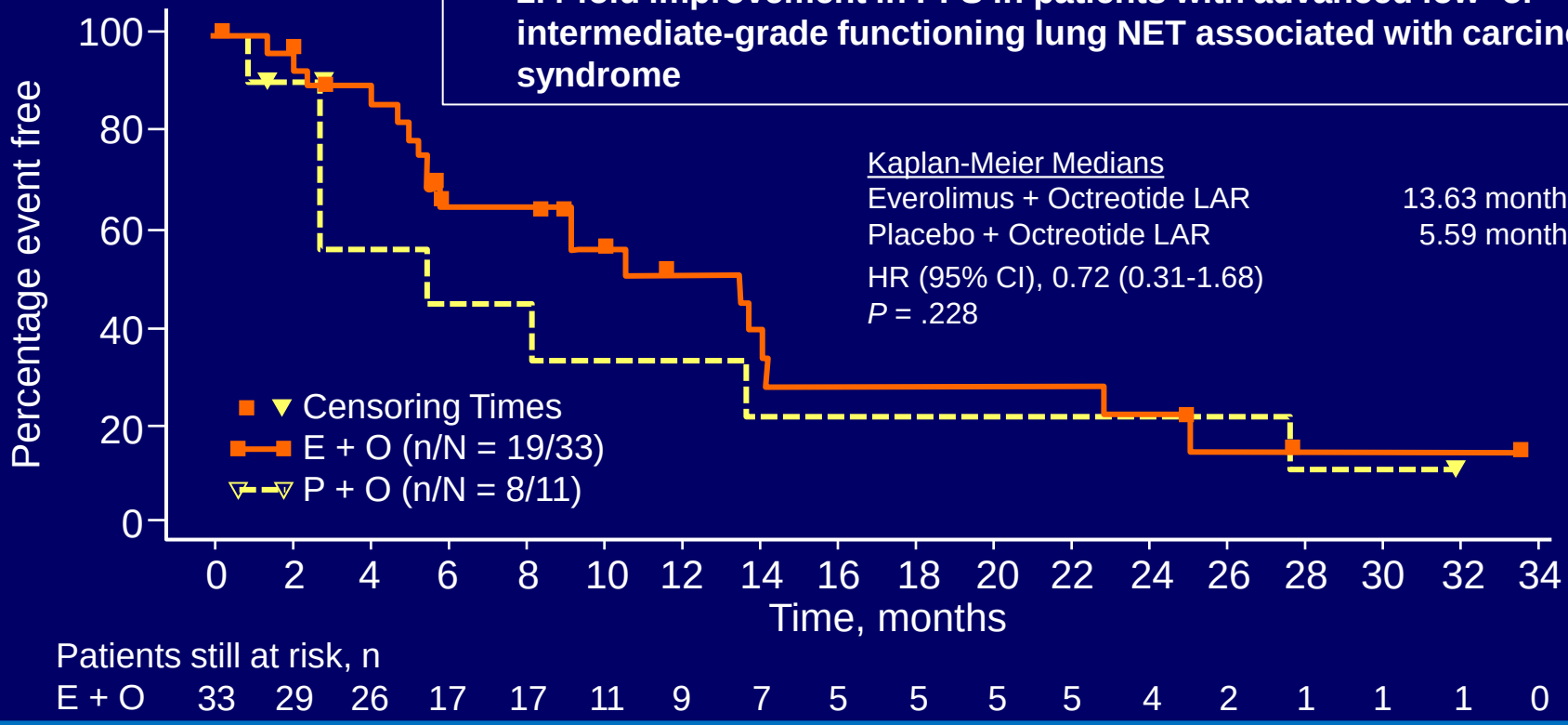
CT = computed tomography; MRI = magnetic resonance imaging; WHO PS = World Health Organization performance status

Pavel M, Hainsworth J, Baudin E, et al. *Lancet.* 2011;378(9808):2005-2012.

Fazio N, et al. *Chest.* 2012.

PFS per Central Radiology Review in Patients with Primary Lung NET

- **2.4-fold improvement in PFS in patients with advanced low- or intermediate-grade functioning lung NET associated with carcinoid syndrome**



"These clinically significant observations support the continued evaluation of everolimus…in this patient population"

E

P value obtained from the 1-sided log-rank test. HR obtained from unadjusted Cox model.

Fazio N, et al. Chest. 2013;143:955-62.

- **Sample size (n = 44)**
- **Imbalance in number of patients (3× more patients treated with everolimus than with placebo)**

RADIANT-4: Efficacy and Safety of Everolimus in Advanced, Nonfunctional Neuroendocrine Tumors (NET) of the Lung or Gastrointestinal (GI) Tract

J.C. Yao,[1] S. Singh,[2] E. Wolin,[3] M. Voi,[4] L.B. Pacaud,[5] J. Lincy,[5] C. Sachs,[5] J. W. Valle,[6] E. van Cutsem,[7] Y. Shimada,[8] **D.-Y. Oh**[9]

[1]University of Texas/MD Anderson Cancer Center, Houston, Texas, USA; [2]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [3]Markey Cancer Center, University of Kentucky, Lexington, Kentucky, USA; [4]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [5]Novartis Pharma AG, Basel, Switzerland; [6]Institute of Cancer Studies, University of Manchester, The Christie Hospital, Manchester, United Kingdom; [7]Digestive Oncology, University Hospitals Gasthuisberg/Leuven and KULeuven, Leuven, Belgium; [8]National Cancer Center Hospital, Tokyo, Japan; [9]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea.

On behalf of the RADIANT-4 Study Investigators

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The Lancet 2015 Dec 15th

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 progression

RANDOMIZE

2:1

Everolimus 10 mg/day
N = 205

Placebo
N = 97

Treated until PD, intolerable AE, or consent withdrawal

Endpoints:

- **Primary:** PFS (central)
- **Key Secondary:** OS
- **Secondary:** ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

Stratified by:

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

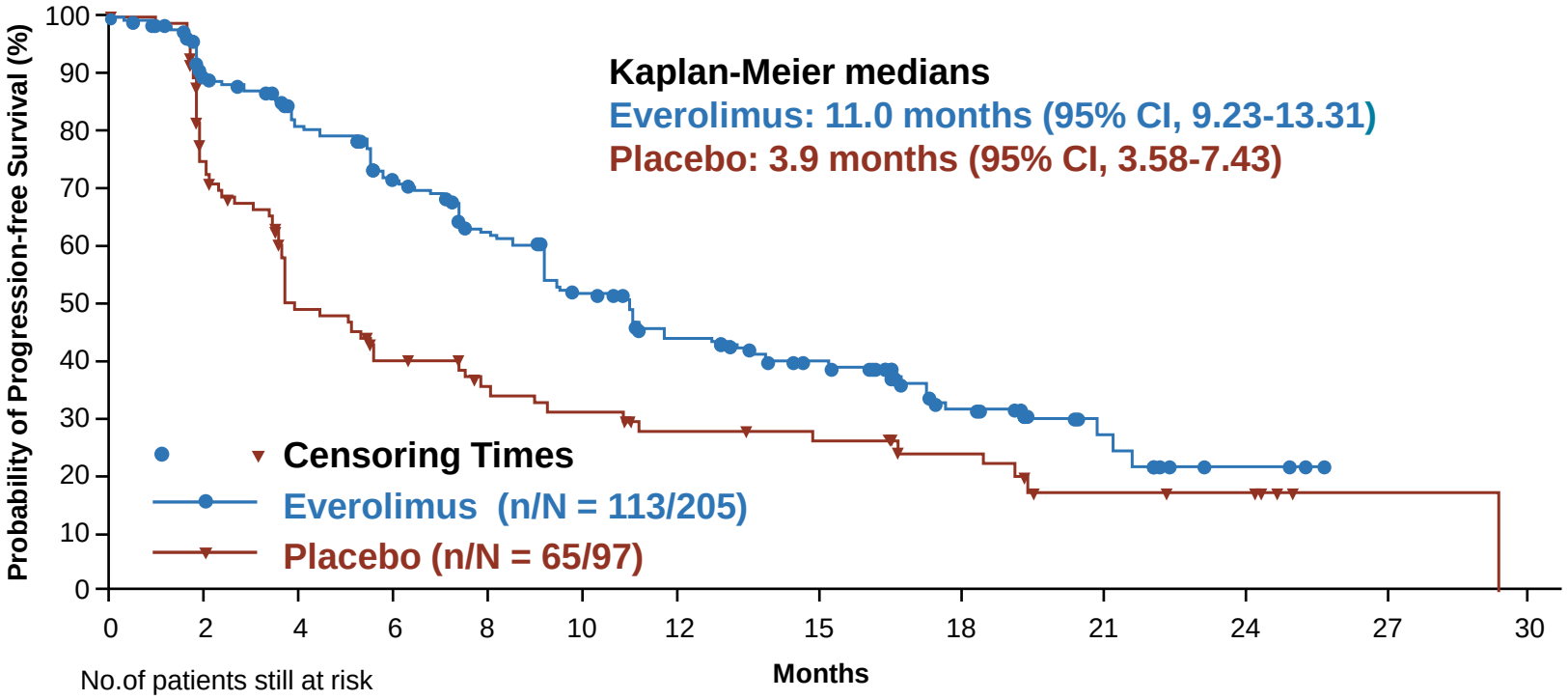
*Based on prognostic level, grouped as: **Stratum A (better prognosis)** - appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worse prognosis)** - lung, stomach, rectum, and colon except caecum.
Crossover to open label everolimus after progression in the placebo arm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

Baseline and Disease Characteristics

Characteristic	Everolimus N = 205	Placebo N = 97
Primary tumor site		
Lung	31%	28%
Ileum	23%	25%
Rectum	12%	16%
Jejunum	8%	6%
Stomach	3%	4%
Duodenum	4%	2%
Colon	2%	3%
NET of unknown primary	11%	13%
Tumor grade		
Grade 1 / grade 2	63% / 37%	67% / 33%
Prior treatments		
Somatostatin analogues	53%	56%

Primary Endpoint: PFS by Central Review

52% reduction in the relative risk of progression or death with everolimus vs placebo
HR = 0.48 (95% CI, 0.35-0.67); *P* < 0.00001

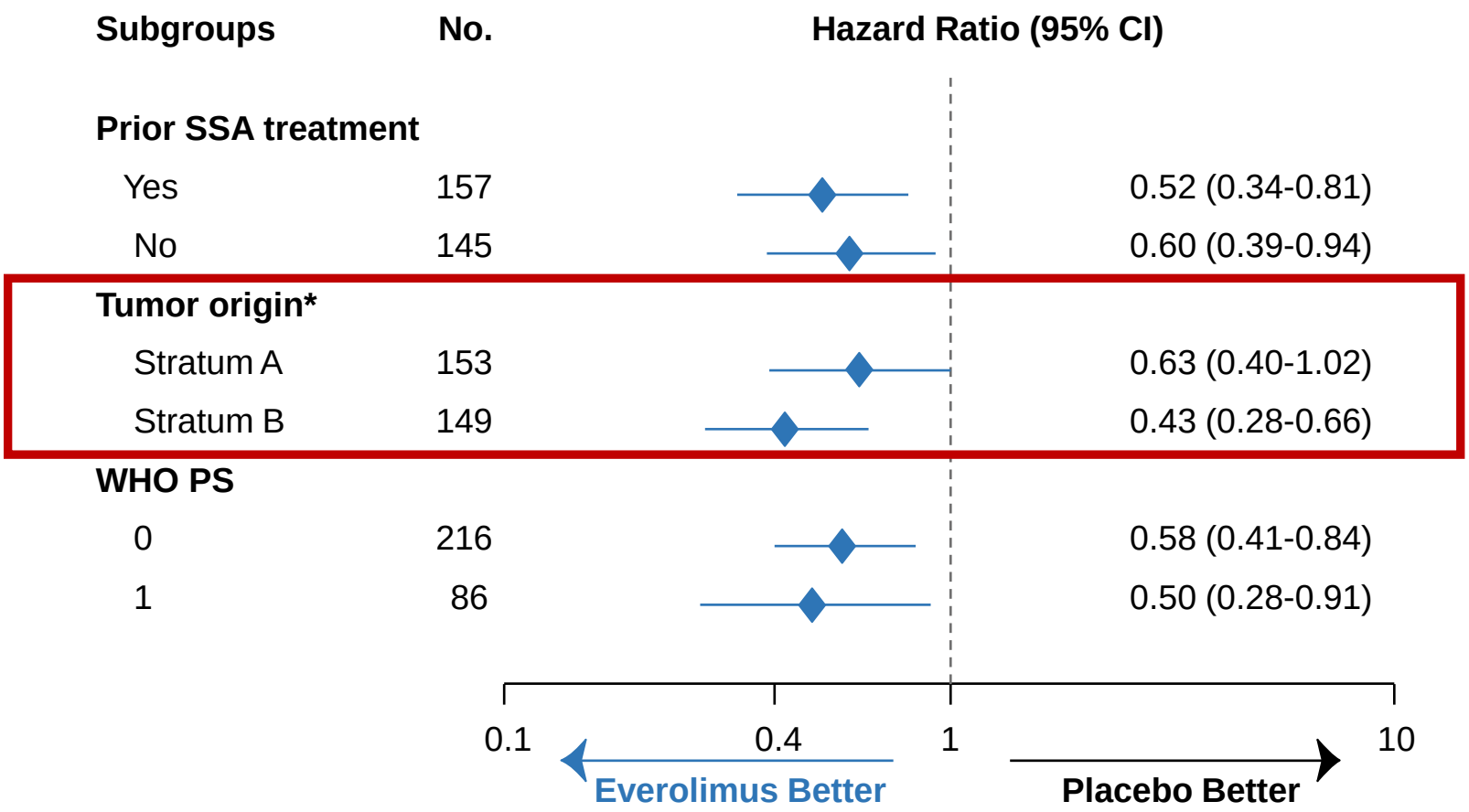


No.of patients still at risk

Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

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

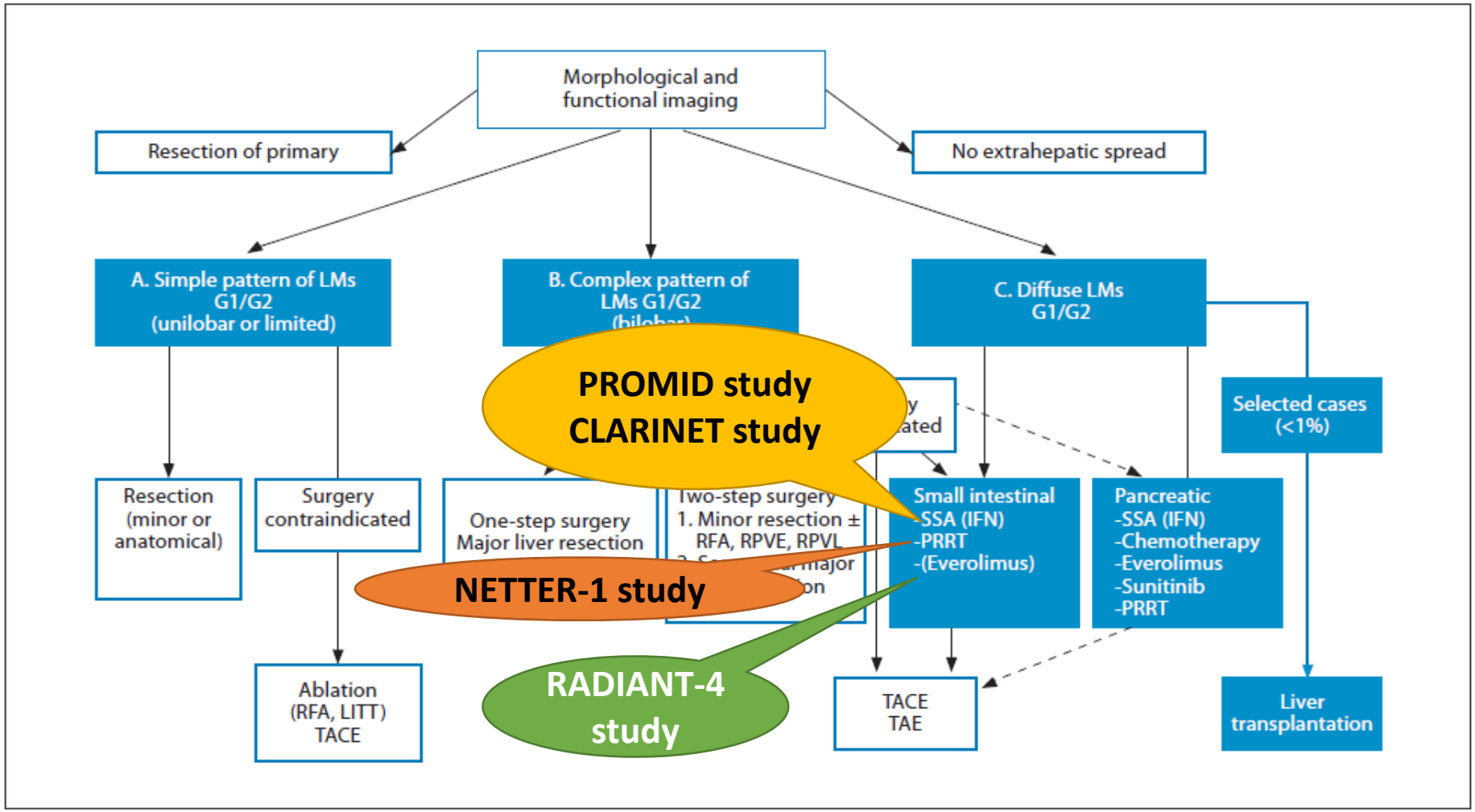
Consistent PFS HR by Stratification Factors, Central Review



*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).

Conclusion

- Everolimus is the first drug to show a significant activity in lung NETs in a randomized trial -> Practice changing
- Everolimus is effective in grade 1 or 2 NET, in spite of primary tumor site with tolerable toxicity.
- We have new therapeutic options in non-functional NETs
  - Octreotide: midgut NET
  - Lanreotide: indolent, GEP-NET
  - Everolimus, Sunitinib: Pancreatic NET
  - Everolimus: Advanced GI/Lung NET (RADIANT-4)



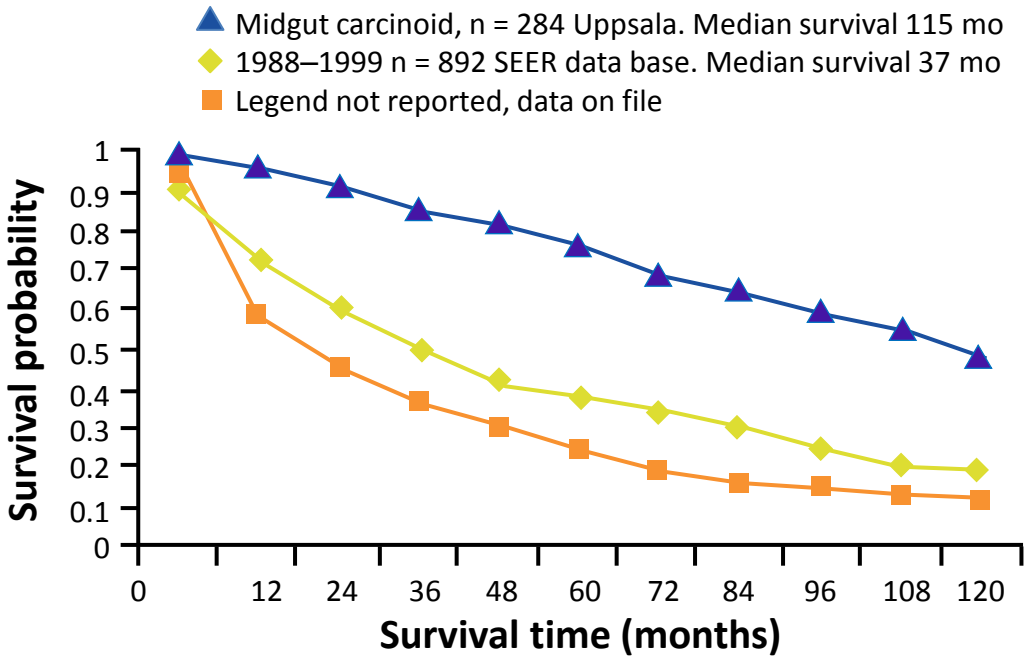
Marianne Pavel et al. Neuroendocrinology 2012

Multidisciplinary Team Care Improves Patient Survival

- MDT care is strongly advised in NET[3]
- Consultation with multiple specialists may result in fragmented care

- Advantages of using an MDT[1]
  - Accurate diagnosis/staging
  - Evaluation of PS and QoL
  - Consensus regarding care plan
  - Cohesive delivery of support, therapy, and prognosis to patient
  - Continuous reassessment, discussion, review of care plan

Data From Centers of Excellence vs Nonspecialist Centers[2]



MDT, multidisciplinary care; PS, performance status; QOL, quality of life.

1. Tamagno G et al. *Endocrine* 2013;44(2):504-509. 2. Reproduced from de Herder WW, et all. Tumori. 2010;96(5):833-846. 3. NCCN Clinical Practice Guidelines in Oncology. Neuroendocrine Tumors. Version 1. 2015

Biomarker study from RADIANT-3 (Everolimus vs BSC in pNET, n=410)

Prolongation of PFS with Everolimus by Baseline CgA or NSE Levels: Prognostic

Population	Median PFS, months		Hazard Ratio (95% CI)	*P*
	Everolimus	Placebo		
Overall	11.0 n = 207	4.6 n = 203	0.35 (0.27-0.45)	<.0001
Elevated CgA (>2 × ULN)				
Yes	8.5 n = 84	4.3 n = 103	0.31 (0.21-0.46)	<.001
No	11.2 n = 121	4.9 n = 97	0.38 (0.27-0.53)	<.001
Elevated NSE (>1 × ULN)				
Yes	8.1 n = 48	2.8 n = 56	0.35 (0.21-0.59)	<.001
No	13.9 n = 155	5.4 n = 138	0.34 (0.25-0.47)	<.001

NR = not reported

Strosberg J, et al. ASCO 2011; Chicago, IL. Abstract 4009 and Poster.

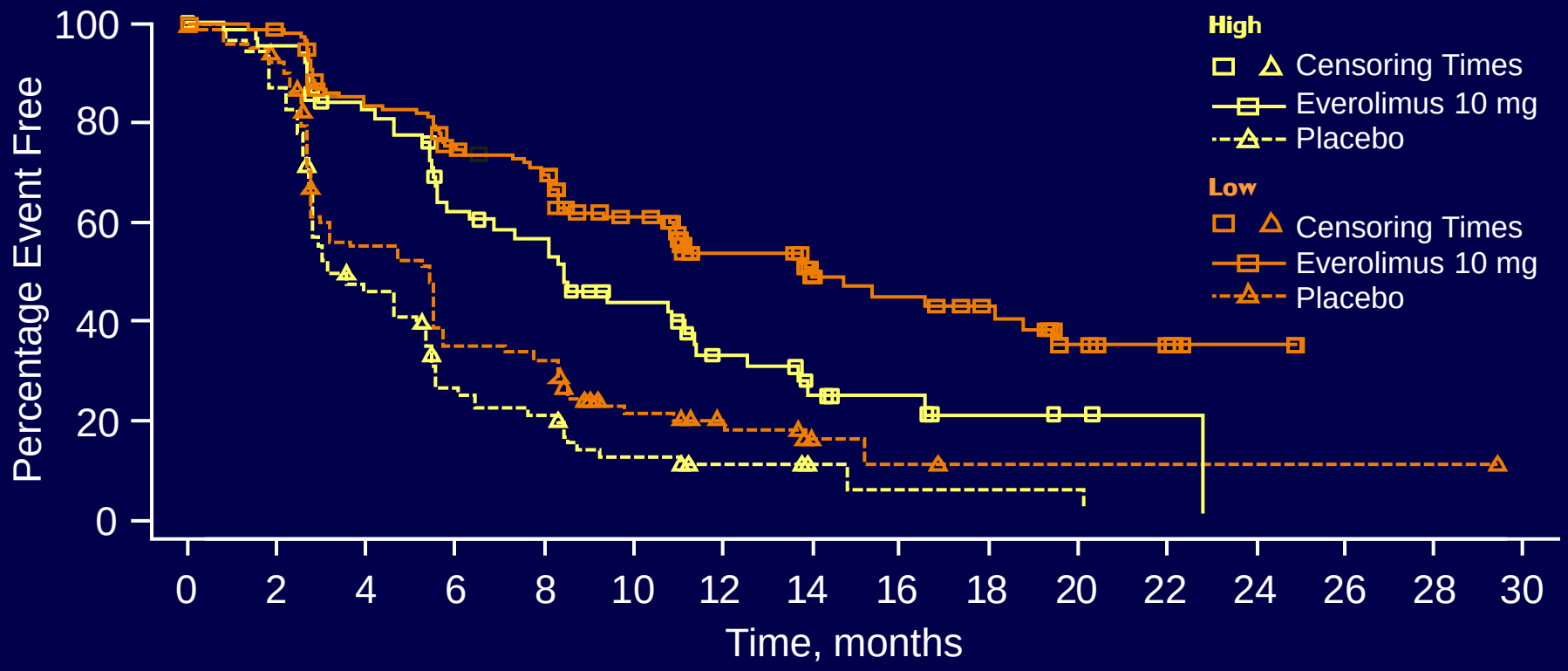
Prognostic Value of Angiogenesis-related Biomarkers

Marker	Cuttoff[1]	Median PFS[2] Low vs. High (months)	Prognostic Hazard Ratio (95% CI)	*P* Value
VEGF-A	246.1	8.3 vs 5.5	1.50 (1.17-1.92)	<.001
PlGF	32.1	8.0 vs 4.2	1.52 (1.14-2.02)	.004
sVEGFR1	226.2	8.3 vs 5.5	1.62 (1.27-2.07)	<.001
sVEGFR2	24503.1	10.8 vs 5.7	1.30 (0.96-1.76)	.090

[1]Cutoff determined by survival tree method in pg/mL.
[2]PFS from patients pooled from both arms.

Yao, et al. *Annals of Oncology*. 2012; Vol.23 Supplement 9-September: p.7-30

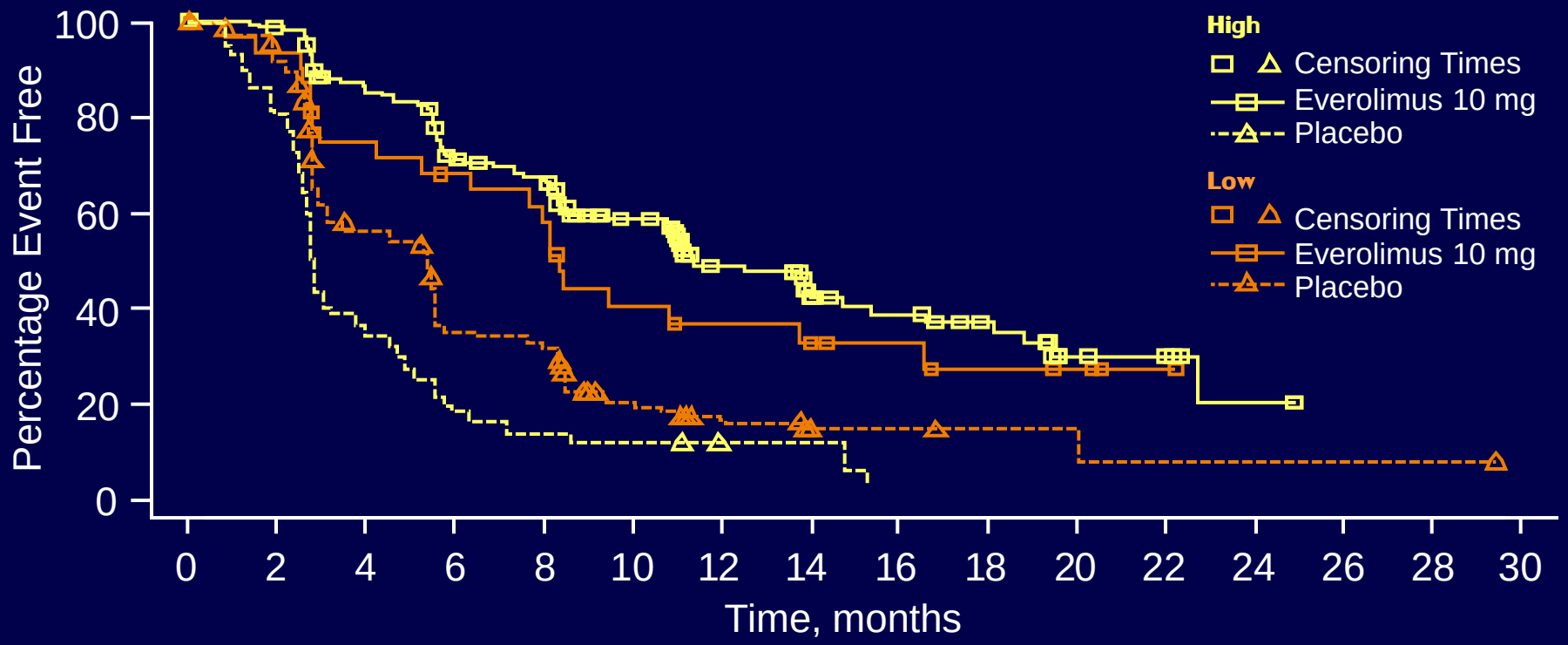
VEGF-A: Treatment Effect



	High		Low	
	Everolimus n/N = 43/65	Placebo n/N = 73/84	Everolimus n/N = 61/133	Placebo n/N = 85/111
Median PFS (months)	8.4	3.3	14.0	5.4
Hazard ratio (95% CI)	0.40 (0.27-0.59)		0.34 (0.24-0.48)	
Log-rank P value	<.0001		<.0001	

Yao, et al. *Annals of Oncology*.2012; Vol.23 Supplement 9-September: p.7-30

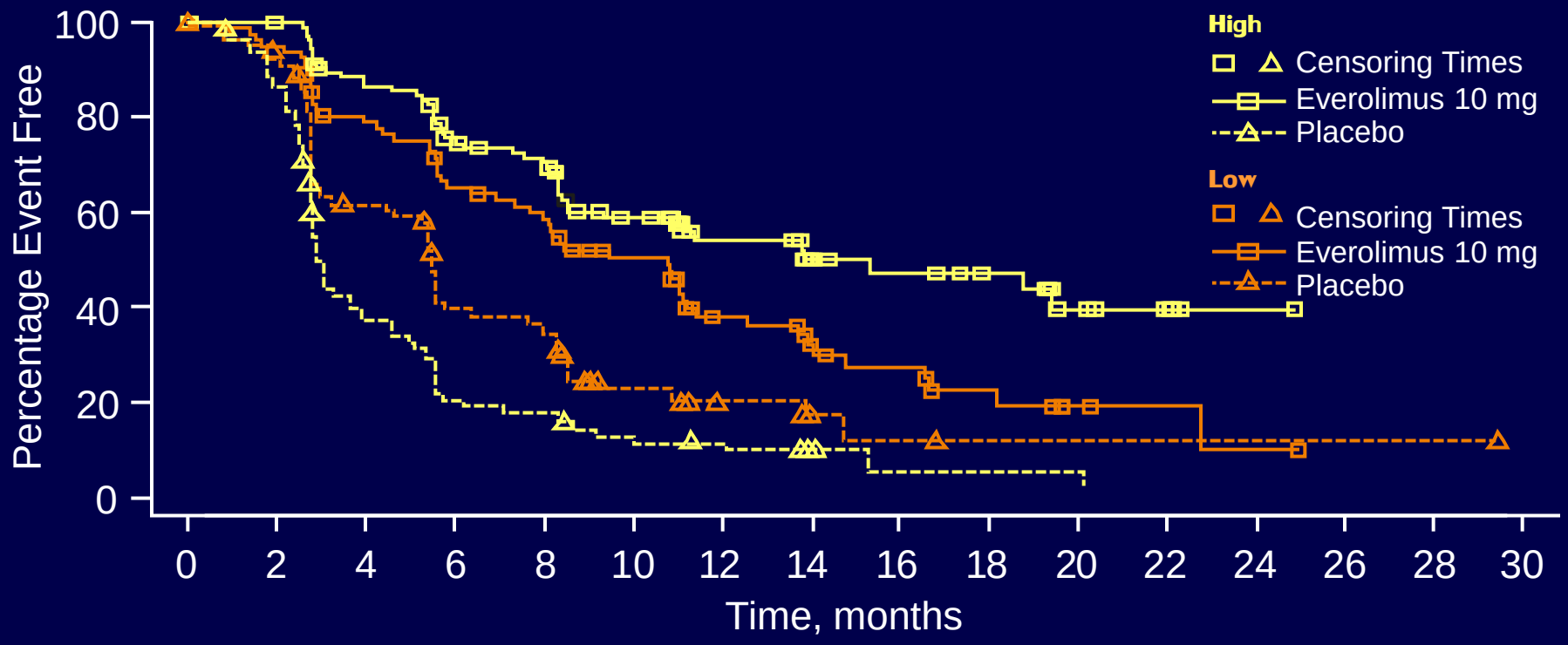
PlGF: Treatment Effect



	High		Low	
	Everolimus n/N = 21/33	Placebo n/N = 41/44	Everolimus n/N = 83/165	Placebo n/N = 117/151
Median PFS (months)	8.3	2.8	11.4	5.4
Hazard ratio (95% CI)	0.34 (0.20-0.59)		0.37 (0.28-0.49)	
Log-rank P value	<.0001		<.0001	

Yao, et al. *Annals of Oncology*.2012; Vol.23 September: p.7-30 -Supplement 9

sVEGFR1: Treatment Effect



	High		Low	
	Everolimus n/N = 56/86	Placebo n/N = 76/86	Everolimus n/N = 48/112	Placebo n/N = 82/109
Median PFS (months)	10.8	2.2	13.9	5.5
Hazard ratio (95% CI)	0.36 (0.25-0.51)		0.35 (0.24-0.50)	
Log-rank P value	<.0001		<.0001	

Yao, et al. *Annals of Oncology*.2012; Vol.23 September: p.7-30 -Supplement 9

Predictive Value of Biomarkers

Marker	Treatment Effect	Marker Effect	Interaction of Marker and Treatment
VEGF-A	<0.001	0.036	0.429
PlGF	<0.001	0.006	0.503
sVEGFR1	<0.001	0.003	0.887
sVEGFR2	<0.001	0.307	0.684

Yao, et al. *Annals of Oncology*.2012; Vol.23 September: p.7-30 -Supplement 9

Next step

- Biomarkers for selecting the proper patient
- Ongoing trials with angiogenesis inhibitors
- Combination vs sequential
  - ✓CALGB 80701(RPII) in pNET trial (ASCO 2015)

Thank you!