The VEGF Pathway in Patients With Pancreatic Neuroendocrine Tumors: Efficacy of Everolimus by Baseline Marker Level, and Prognostic and Predictive Effect Analyses From RADIANT-3

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Disclosure slide

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Background and Rationale

- Neuroendocrine tumors (NET) are highly vascular tumors that express vascular endothelial growth factor (VEGF) pathway markers[1]
- Everolimus is an mammalian target of rapamycin (mTOR) inhibitor with anti-angiogenic activity[2]
- The RADIANT-3 phase 3 study showed that everolimus significantly improved progression-free survival (PFS) in patients with NET compared with placebo[3]
  - 11.0 months vs 4.6 months, respectively; hazard ratio for disease progression or death from any cause with everolimus, 0.35; 95% confidence interval (CI) 0.27-0.45; *P* <.001[3]
- We investigated the prognostic and predictive potential of VEGF pathway markers among patients with pancreatic NET (pNET)

1. Terris B, et al. *Histopathology* 1998;32:133-138.
2. Scoazec JY. *Neuroendocrinology* 2012 April 25 [Epub ahead of print].
3. Yao JC, et al. *N Eng J Med* 2011;364:514-523.

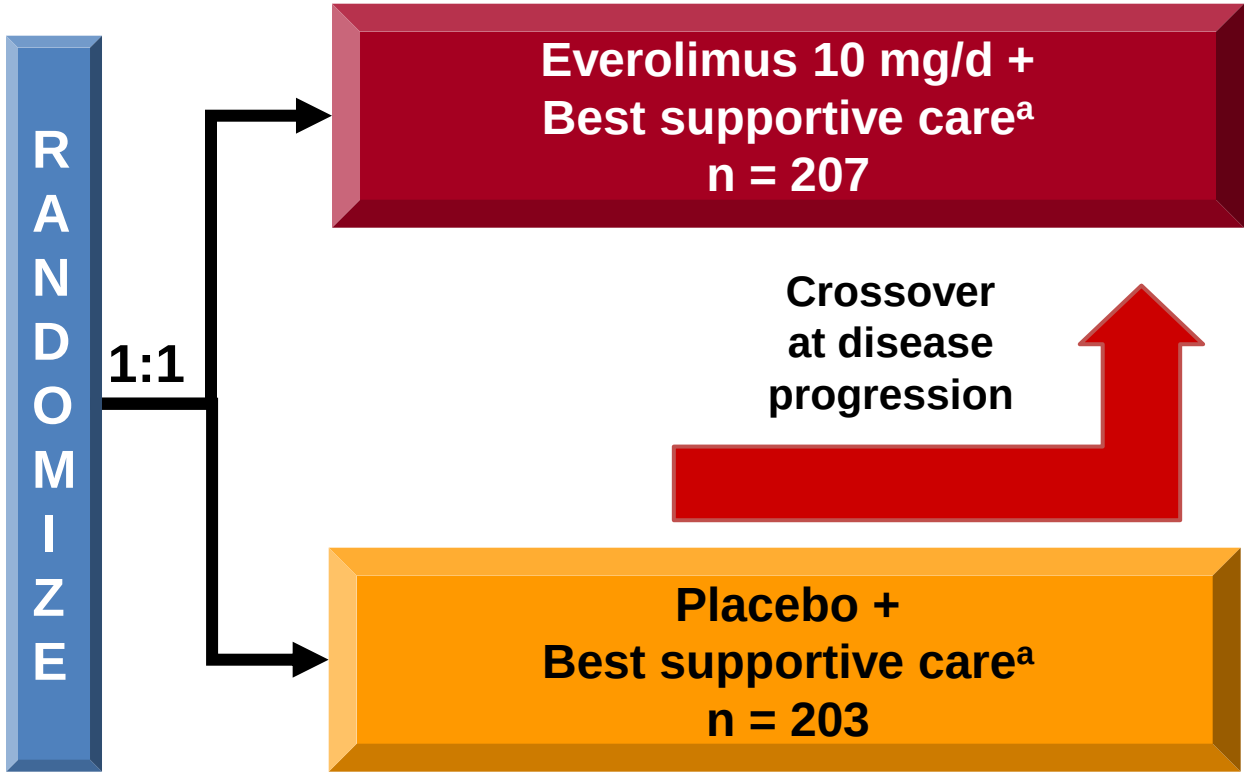
RADIANT-3 Study Design

International, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Trial

Low- or intermediate-grade advanced pNET

(N = 410)

- **Radiologic progression within 12 months**
- **Previous antitumor therapy allowed**
- **WHO performance status ≤2**



[a]Concurrent somatostatin analogs allowed but not mandated.

Yao JC et al. *N Engl J Med*. 2011;364:514-523.

Methods

- Pre-treatment plasma levels of VEGF-A, PlGF, sVEGFR1, and sVEGFR2 were determined by ELISA
  - Markers were evaluated using the MSD platform Growth Factor Panels I and II (Tandem Labs, now part of LabCorp)
- Optimal cutoffs for baseline marker levels were explored using the "survival tree analysis" with PFS as the endpoint
- Stratified Kaplan-Meier and Cox proportional hazards model was used to assess the prognostic and predictive effect of baseline biomarker; Cox proportional hazards modeling including the interaction of treatment and baseline marker status (< or ≥ cutoff) was used to evaluate the predictive effect of baseline biomarkers
- Multivariate Cox proportional hazards model using stepwise regression was used to select the most significant prognostic biomarkers

Baseline Biomarker Values

Marker	Overall N = 393 Median (range)	Cutoff[1]	Everolimus n = 198 Median (range)	Placebo n = 195 Median (range)
VEGF-A	197 (18-2466)	246.1	167 (18-2466)	203 (46-1904)
PlGF	23 (10-3986)	32.1	22 (10-3986)	23 (10-651)
sVEGFR1	211 (83-3320)	226.2	210 (92-3320)	212 (83-1898)
sVEGFR2	30136[a] (11169-61360)	24503.1	29266[b] (12971-61360)	30697[c] (11169-59130)

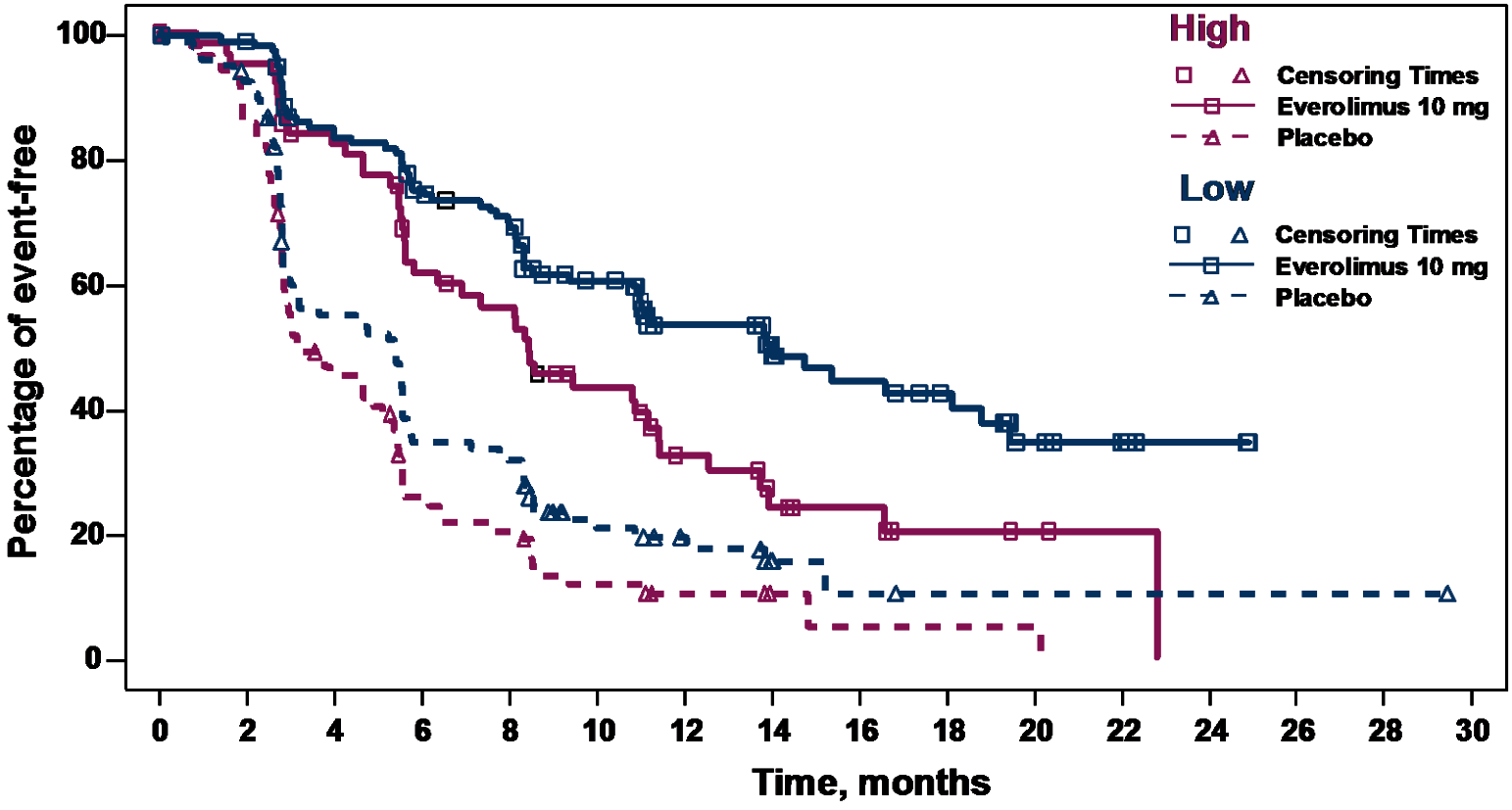
Values in pg/mL. [1]Cutoff determined by survival tree method in pg/mL.
[a]n = 390. [b]n = 197. [c]n = 193.

Prognostic Value of Biomarkers

Marker	Cutoff[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

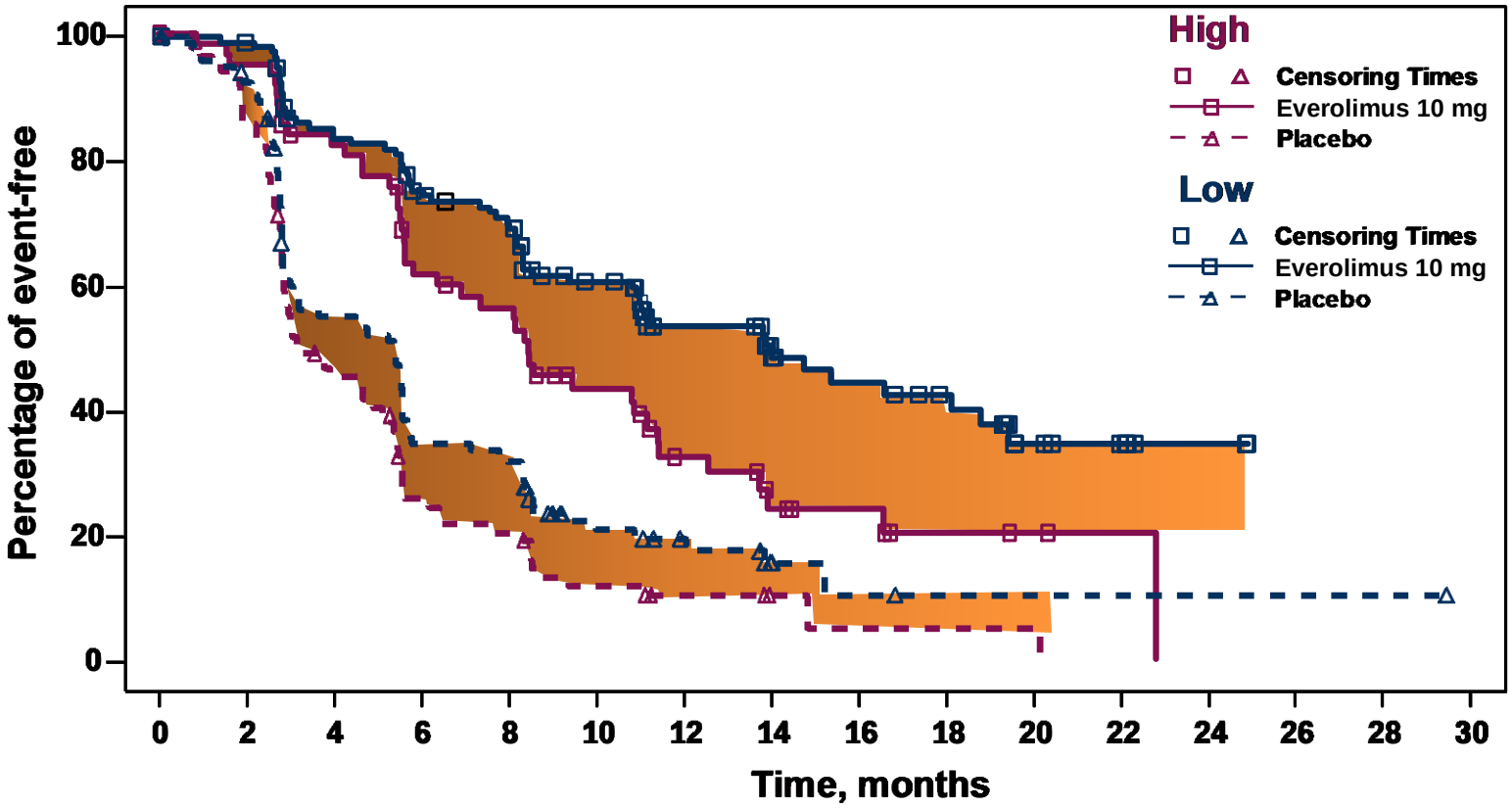
[1]Cutoff determined by survival tree method in pg/mL.
[2]PFS from patients pooled from both arms.

VEGF-A: Treatment Effect

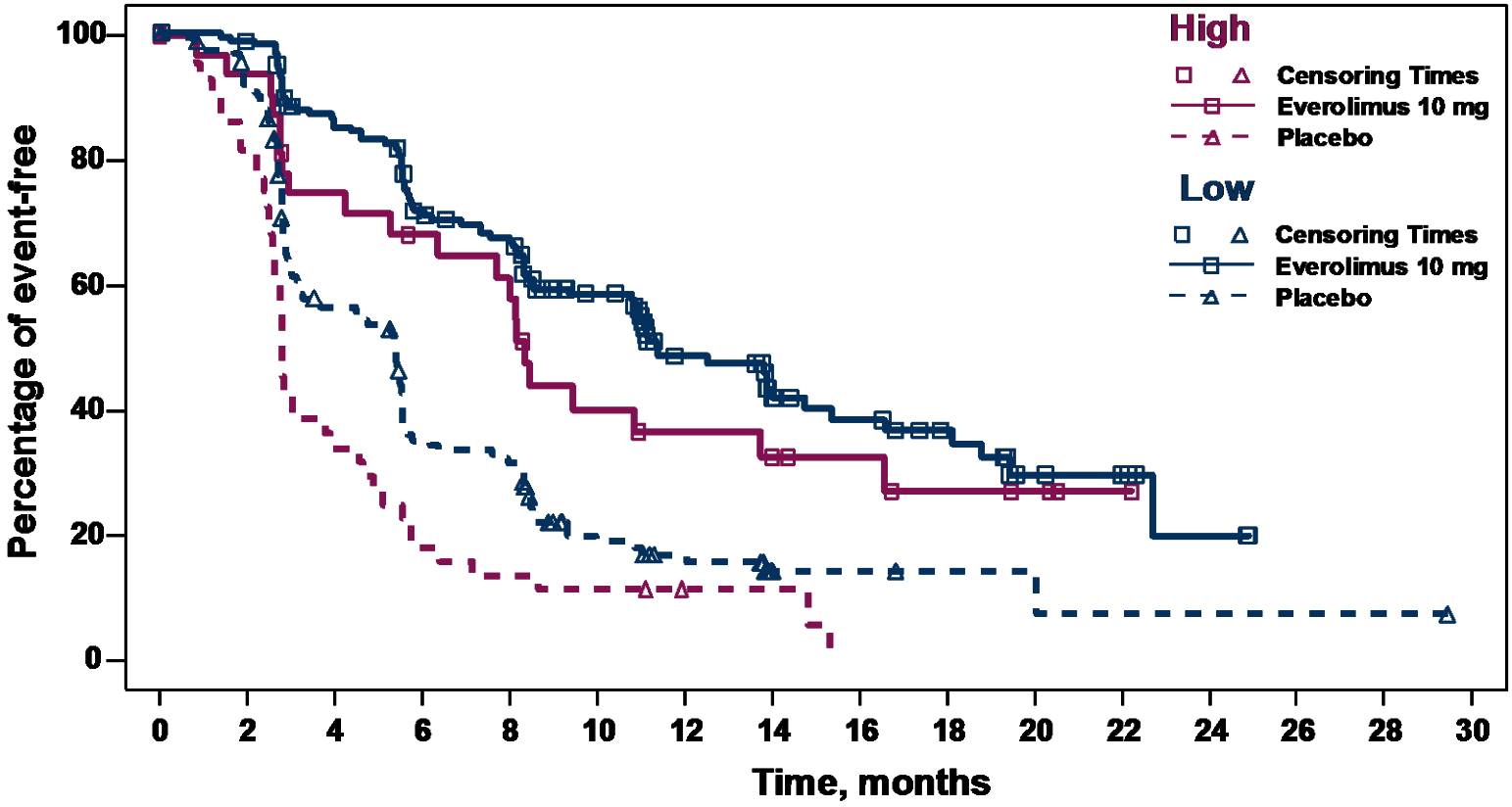


	High		Low	
	Everolimus n/N = 43/65	Placebo n/N = 73/84	Everolimus n/N = 61/133	Placebo n/N = 85/111
Median PFS (months)	8.4	3.3	14.0	5.4
Hazard ratio (95% CI)	0.40 (0.27-0.59)		0.34 (0.24-0.48)	
Log-rank *P* value	<.0001		<.0001	

VEGF-A: Prognostic Effect

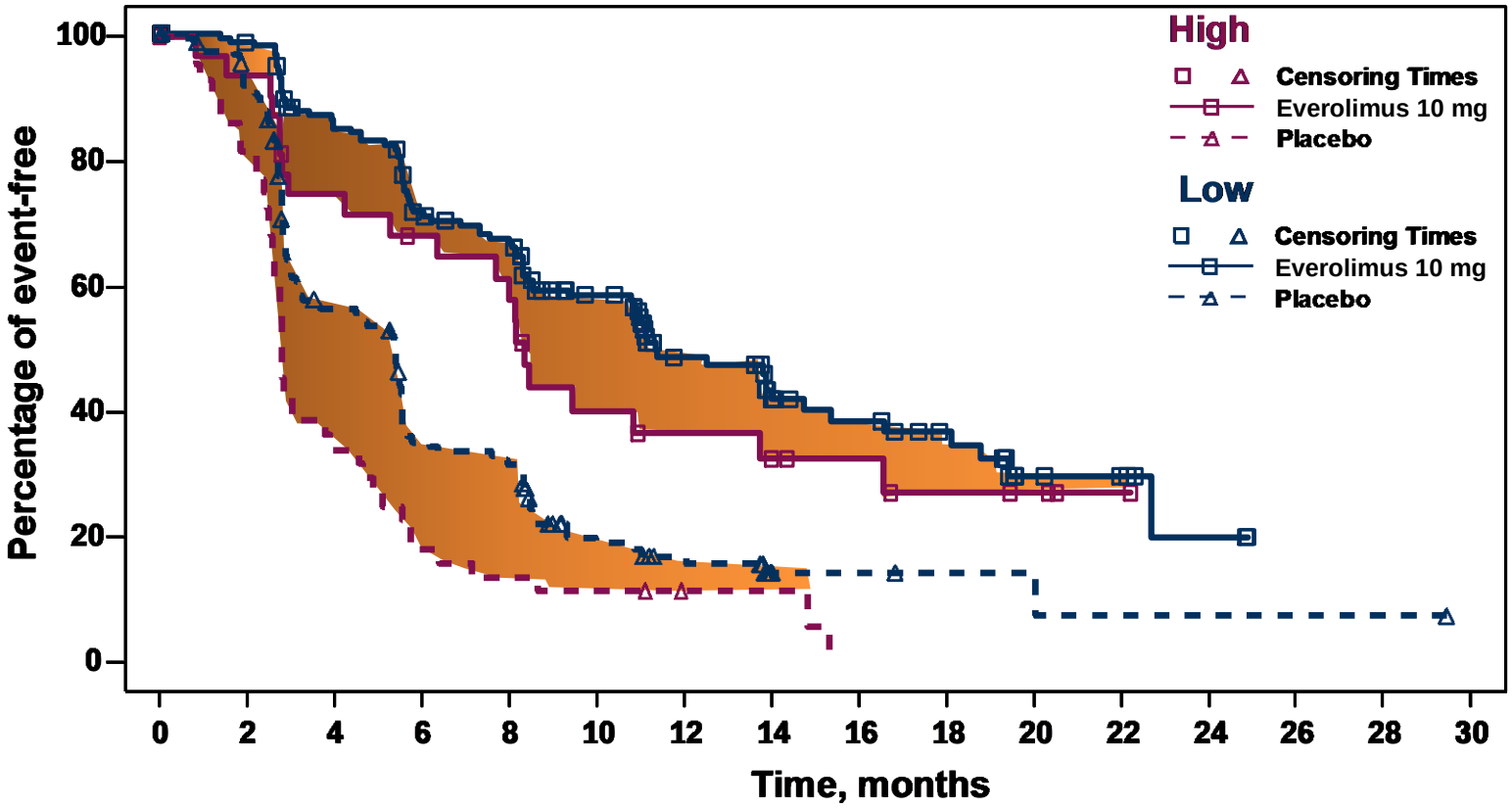


PlGF: Treatment Effect

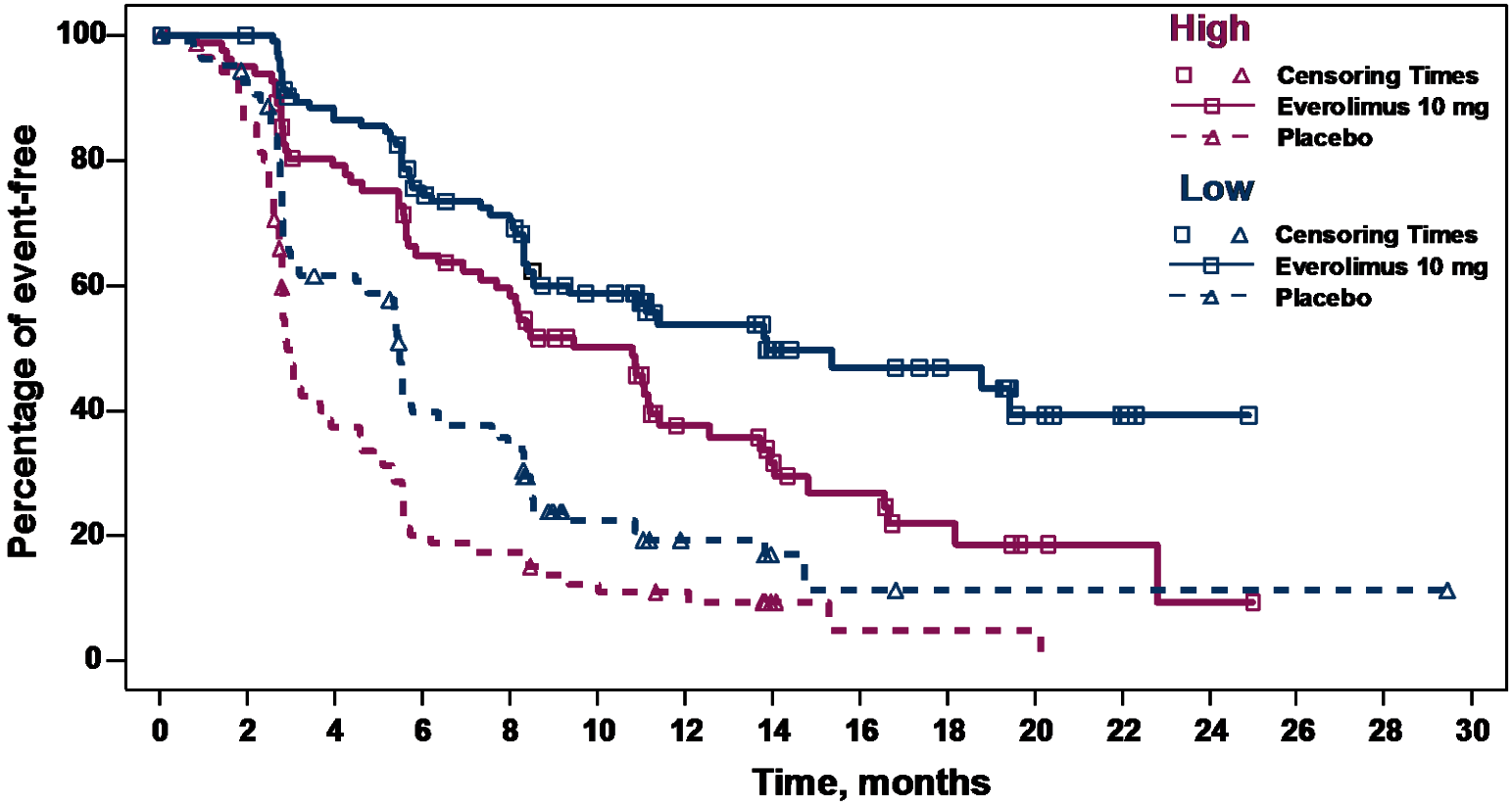


	High		Low	
	Everolimus n/N = 21/33	Placebo n/N = 41/44	Everolimus n/N = 83/165	Placebo n/N = 117/151
Median PFS (months)	8.3	2.8	11.4	5.4
Hazard ratio (95% CI)	0.34 (0.20-0.59)		0.37 (0.28-0.49)	
Log-rank *P* value	<.0001		<.0001	

PlGF: Prognostic Effect

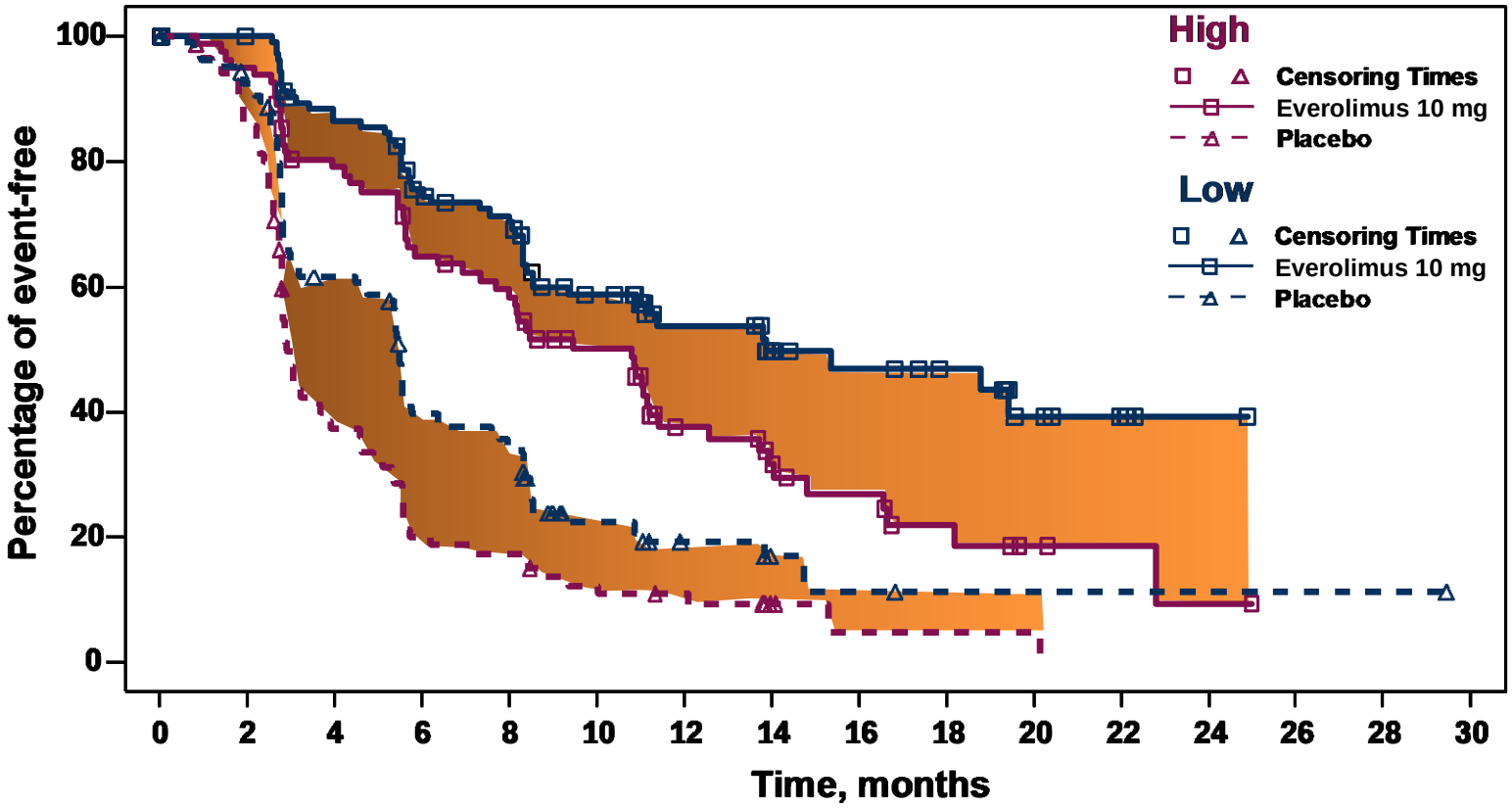


sVEGFR1: Treatment Effect

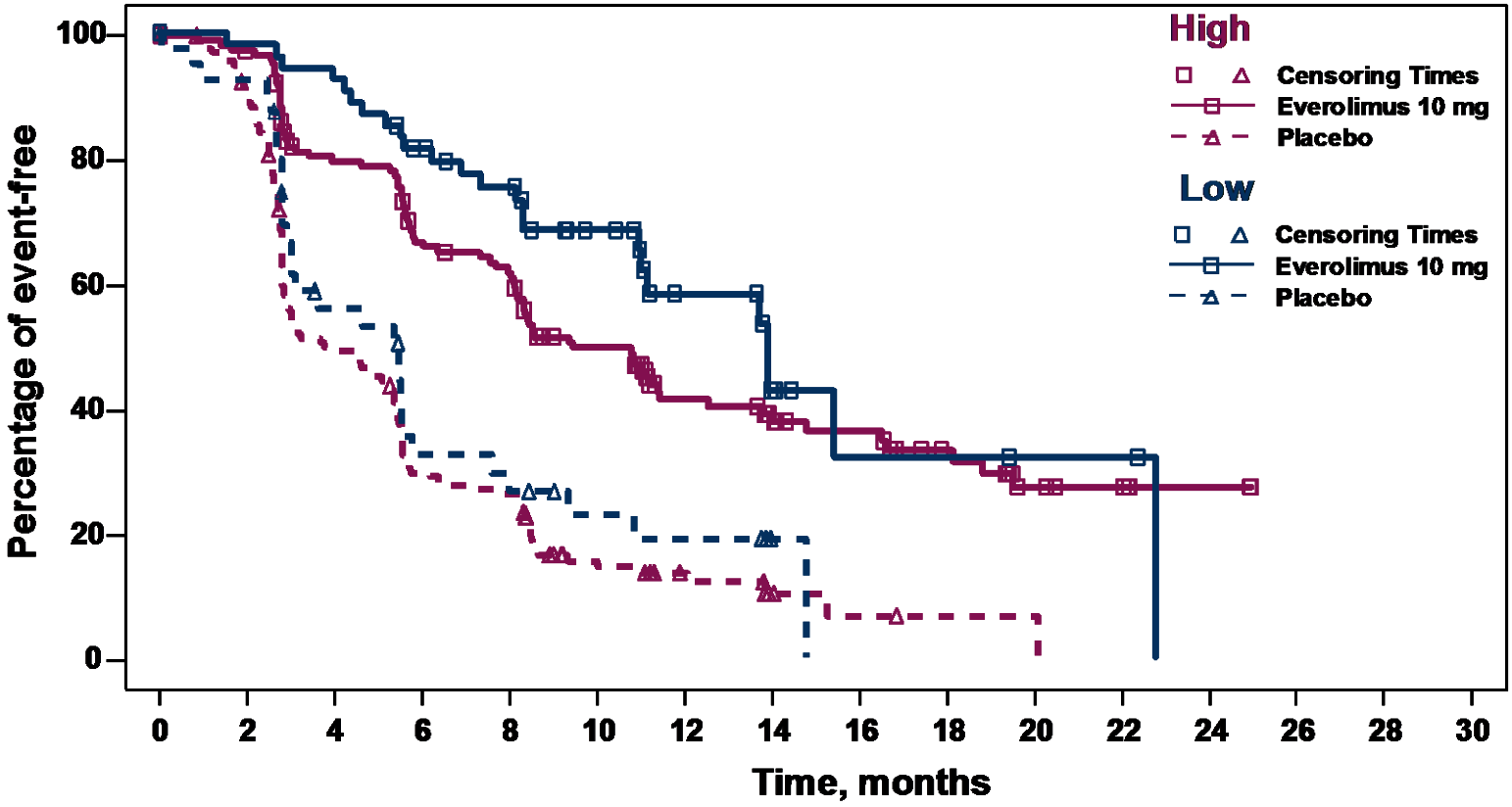


	High		Low	
	Everolimus n/N = 56/86	Placebo n/N = 76/86	Everolimus n/N =48/112	Placebo n/N = 82/109
Median PFS (months)	10.8	2.2	13.9	5.5
Hazard ratio (95% CI)	0.36 (0.25-0.51)		0.35 (0.24-0.50)	
Log-rank *P* value	<.0001		<.0001	

sVEGFR1: Prognostic Effect

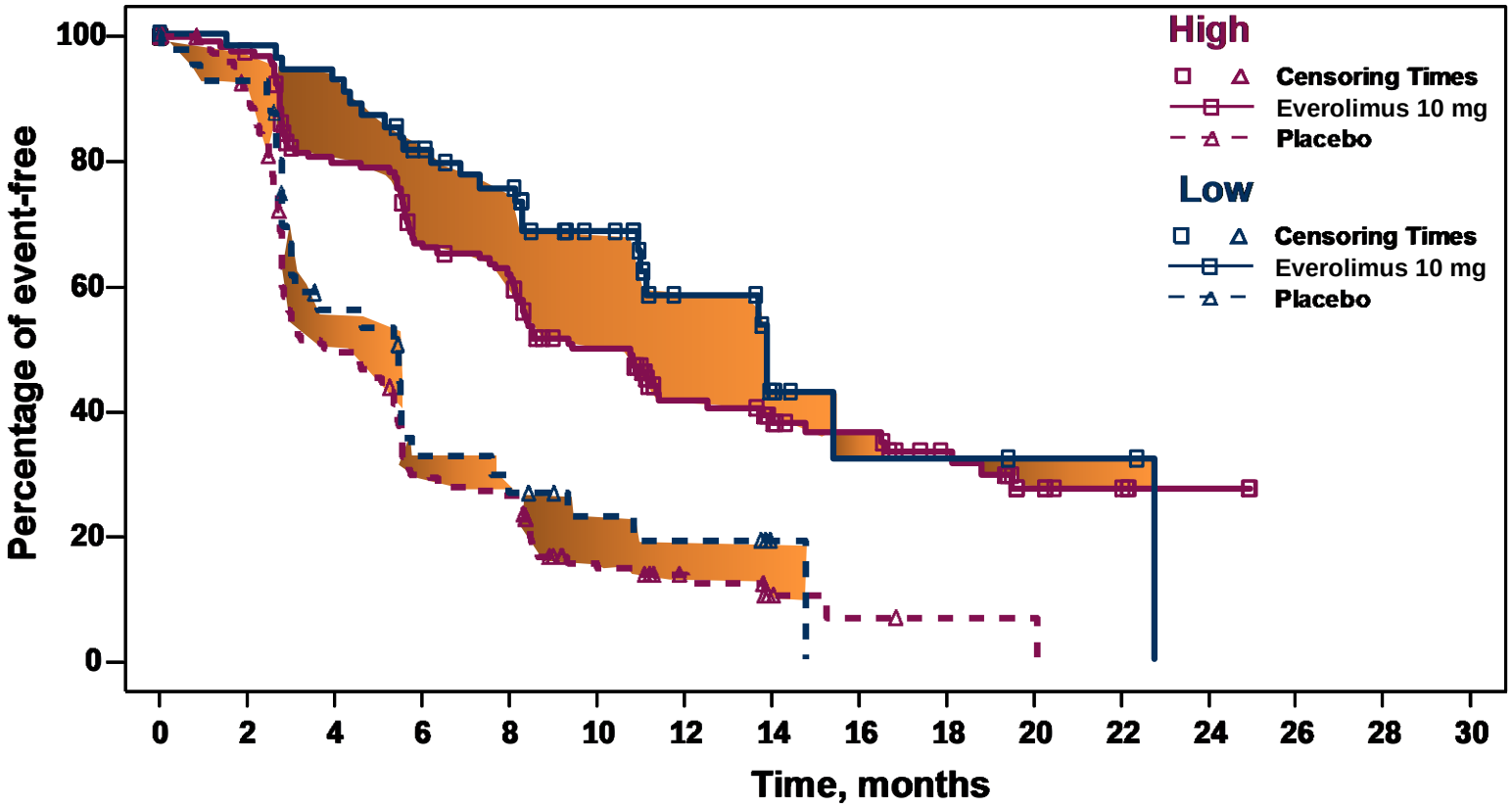


sVEGFR2: Treatment Effect



	High		Low	
	Everolimus n/N = 79/140	Placebo n/N = 127/151	Everolimus n/N =24/57	Placebo n/N = 30/42
Median PFS (months)	10.8	3.9	13.9	5.5
Hazard ratio (95% CI)	0.37 (0.28-0.50)		0.29 (0.16-0.50)	
Log-rank *P* value	<.0001		<.0001	

sVEGFR2: Prognostic Effect



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

Multivariate Analysis

Marker	HR (95% CI)	*P* Value
sVEGFR1	1.54 (1.20-1.98)	<.001
PlGF	1.35 (1.01-1.81)	.046

- Cox proportional hazards model stratified by treatment arm; stepwise regression to select significant prognostic markers
- The model included VEGF-A, sVEGFR1, sVEGFR2, and PlGF as high vs low based on the optimal cutoffs obtained from survival tree analysis
- sVEGFR1 and PlGF were significant prognostic markers from the multivariate analysis

Conclusions

- Lower baseline levels of sVEGFR1 and PlGF are potential positive prognostic factors for pNET

- Everolimus was effective in all patients with advanced pNET regardless of their baseline VEGF pathway biomarker levels