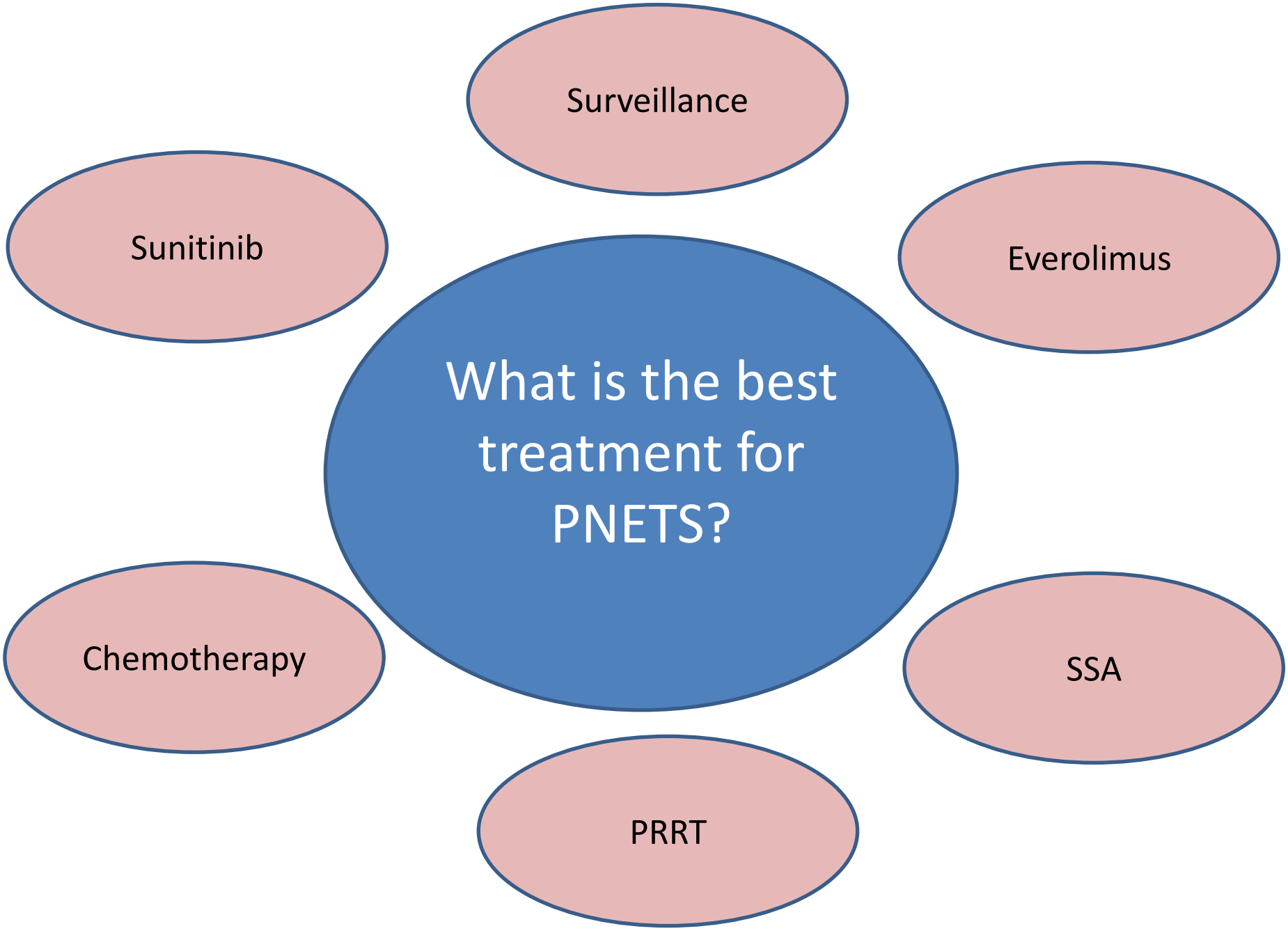

Surveillance
Sunitinib
Everolimus
What is the best treatment for PNETS?
Chemotherapy
SSA
PRRT

Chemotherapy for pancreatic NETs

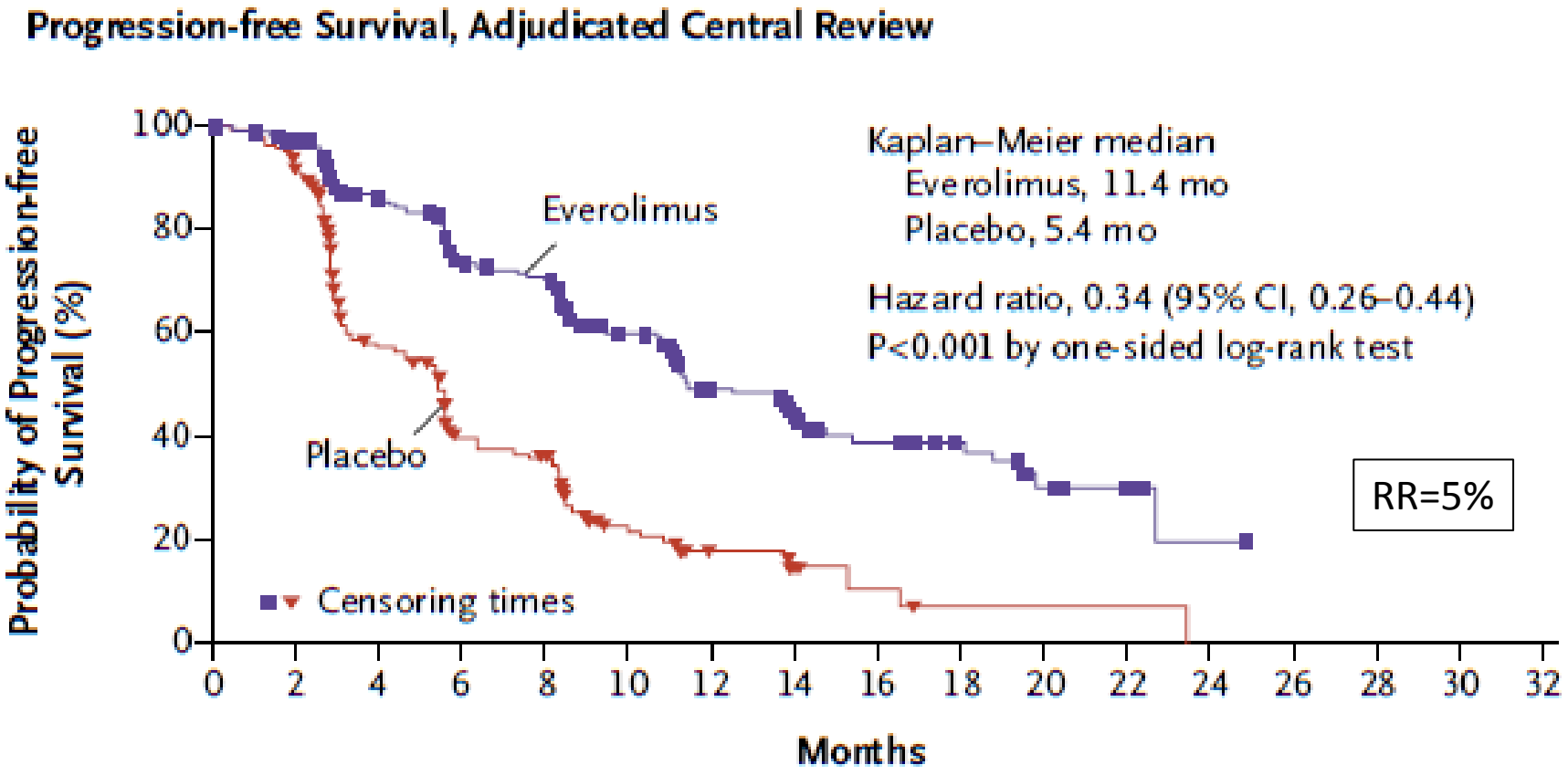
Randomised Controlled trials

Author	Date	Regimen	Number Patients	Response %	Survival months	P value
Moertel	1980	STZ	42	36	16.4	NSD
		5FU/STZ	42	63	26	
Moertel	1992	CZT	33	30	18	P<0.03
		5FU/STZ	34	45	17	P<0.004
		DOX/STZ	38	69	26	

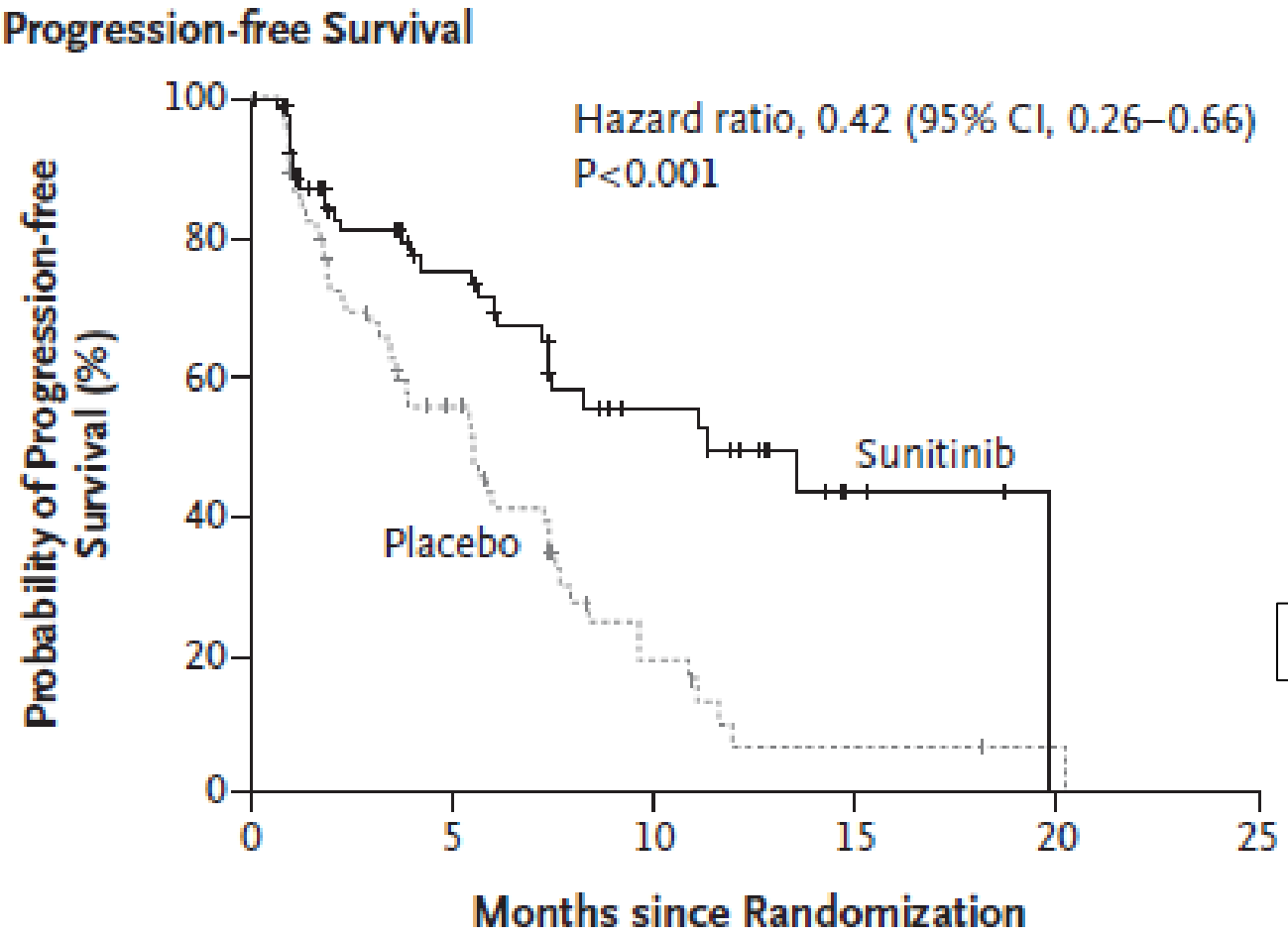
Case Series

Author	Date	Regimen	Number Patients	Response %	Survival months
Delaunoit	2004	DOX/STZ	45	36	24
Kouvaraki	2004	5FU/DOX/STZ	84	39	37
Turner	2010	5FU/CIS/STZ	49	38	32

Everolimus for WDPNET (Yao NEJM 2011)



Sunitinib for WDPNET (Raymond NEJM 2011)



RR =9%

What do we need to know?

1. Who needs treatment?
2. What is the anti-tumour effect ?
3. Which patients benefit?
4. What are the side effects?

What is the survival benefit?

- Everolimus
  - 73% crossover
  - Median OS not reached HR 1.05; 95% CI, 0.71 to 1.55; P = 0.59
  - Final analysis when 250 deaths occur

Abstract 11550 - Faivre et al

What is the real survival benefit from Sunitinib for WDPNET?

OS - Secondary endpoint

- Initial report (Raymond NEJM 2011)
  - Deaths; S: 9 vs P: 21
  - HR 0.41 95% CI, 0.19 to 0.89; P<0.02
- 2 year report (59/85 crossed over = 70%)
  - Deaths; S: 40 vs P: 47
  - Median OS S: 33.0 m vs 26.7m
  - HR: 0.71 95% CI: 0.47−1.09 P=0.115

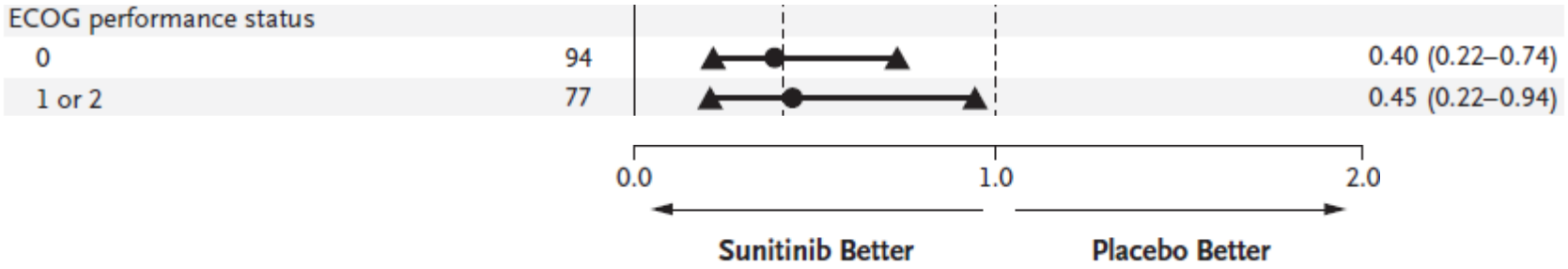
Analysis of OS with Adjustment for Crossover

OS analysis/treatment group	Deaths	Median (months)	HR[a]	95% CI	P
ITT − no adjustment for crossover					
Sunitinib (n=86)	40	33.0			
Placebo (n=85)	47	26.7	0.713	0.468–1.088	0.115
Adjustment for crossover (placebo; n=85)					
Censoring at crossover	20	16.3	0.428	0.239–0.767	0.004
Time-dependent Cox model	47	26.7	0.492	0.285–0.851	0.010
RPSFT model	41[b]	16.4	0.431	0.170–1.200[c]	0.115[d]
Extended RPSFT model adjusted for crossover time[e]	40[b]	19.1	0.568	0.184–1.086[c]	0.115[d]

[a]Sunitinib vs. placebo
[b]After recensoring
[c]From 20,000 bootstrap samples
[d]The RPSFT method does not alter the P value obtained using the ITT method
[e]Assuming active treatment effect was reduced by 30% if crossover occurred 3 months after start of placebo treatment

Possible Bias

- Performance status ?
  - PS 0 ; S 62% vs P 48%



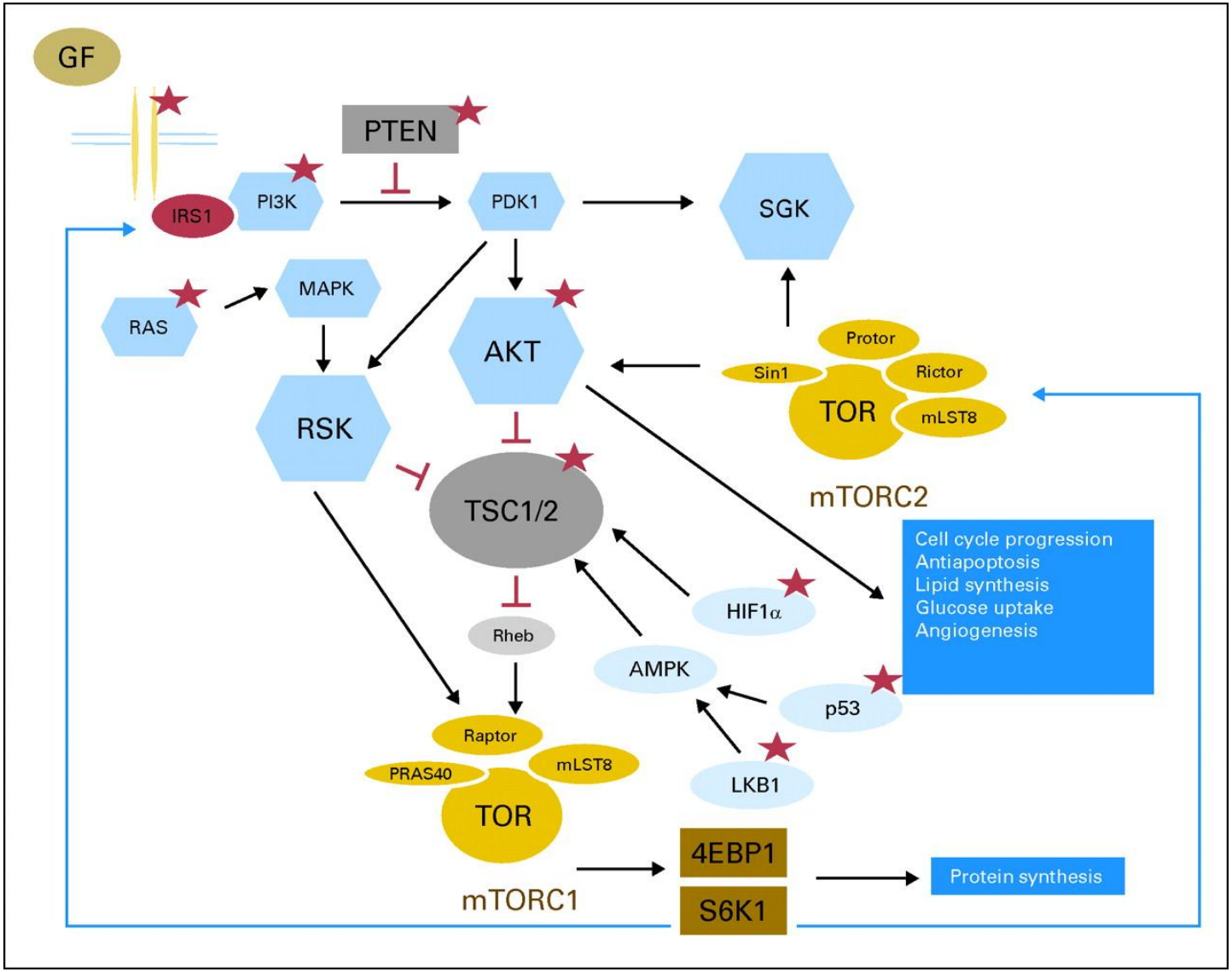
Conclusion

- OS benefit from sunitinib
  - Worst case 6.3 months
  - Best case 16.7 months
  - In this case PFS seems to be surrogate for OS
- Need comparative analysis for everolimus

Abstract 11540 – Yao et al

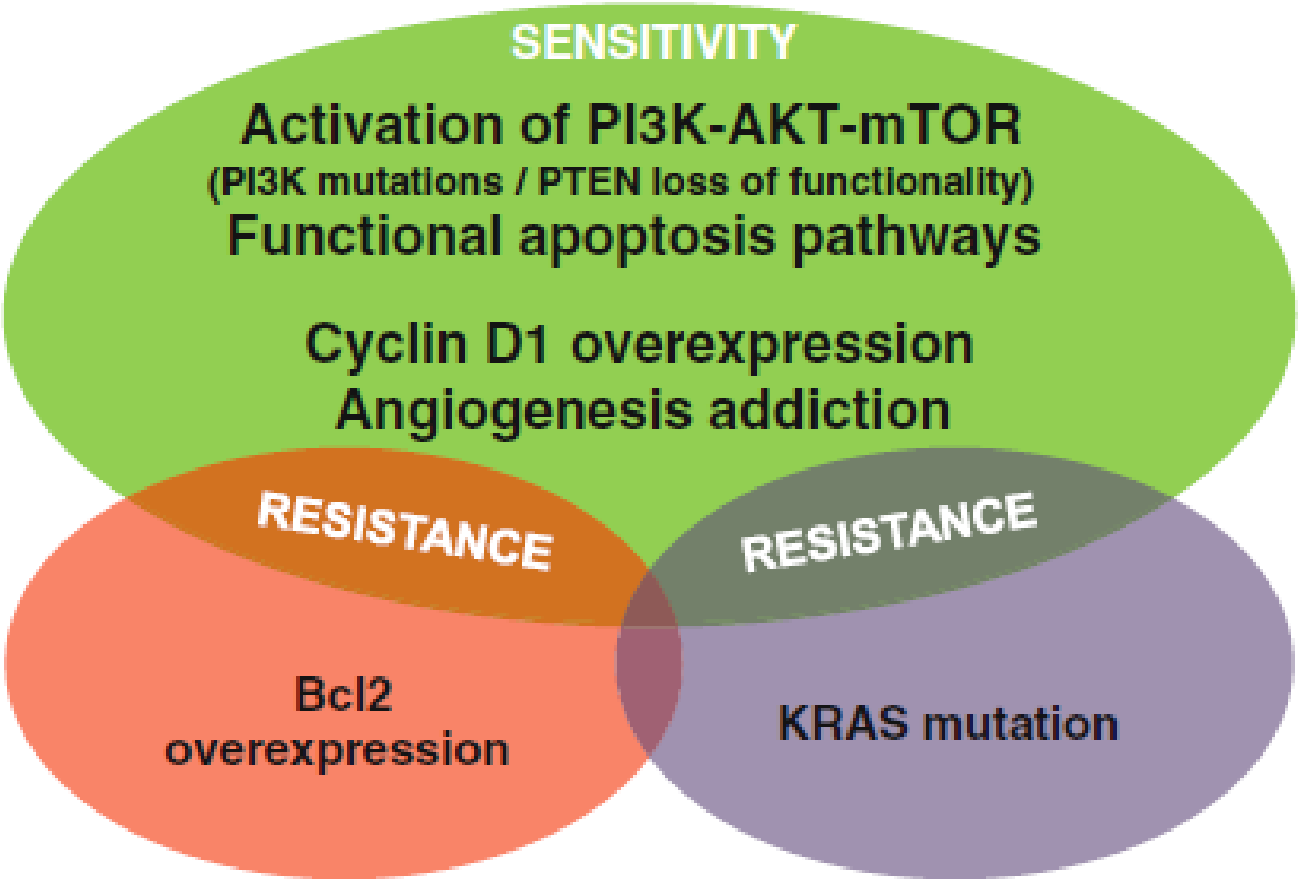
Two questions regarding circulating angiogenic cytokines in PNETs

1. Can they predict benefit from everolimus?
2. Are they prognostic?



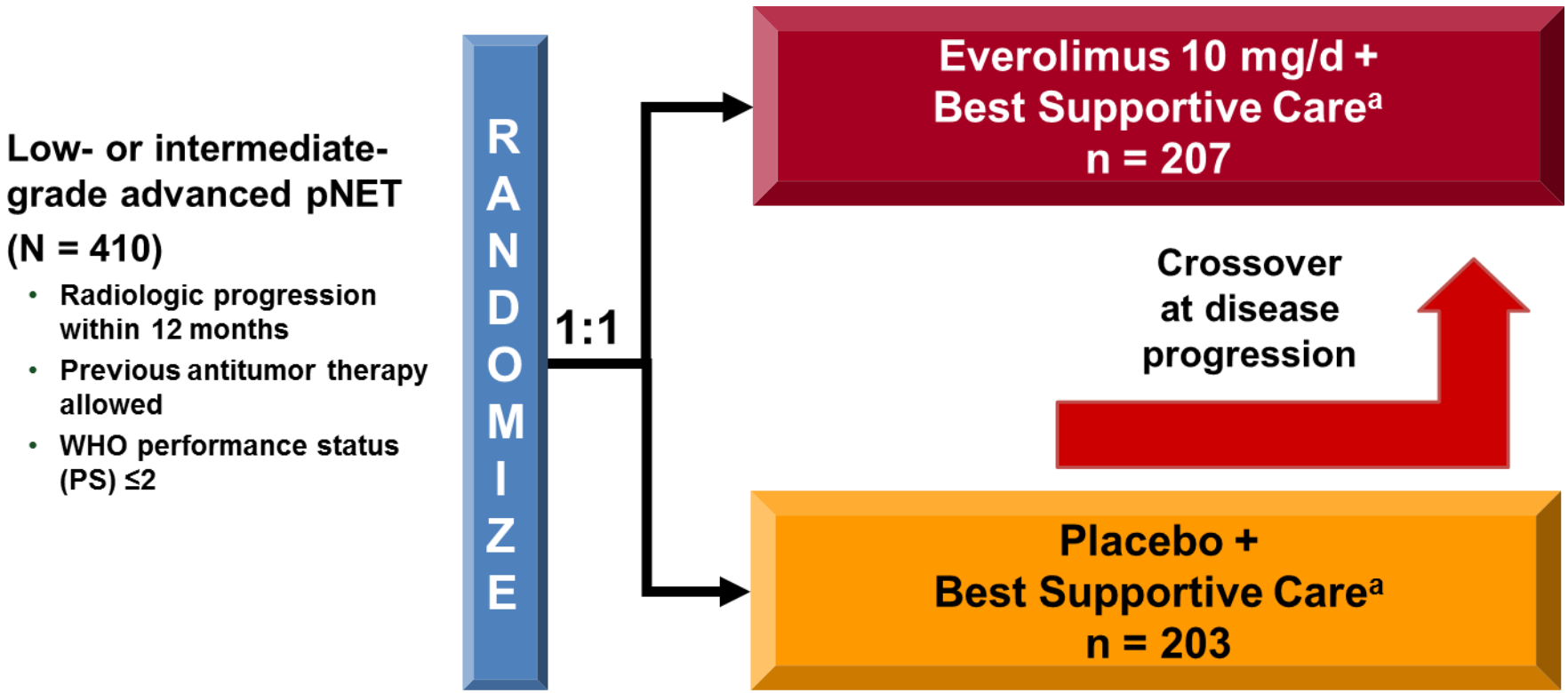
Hidalgo M JCO 2012;30:85-87

Response to mTOR inhibitors



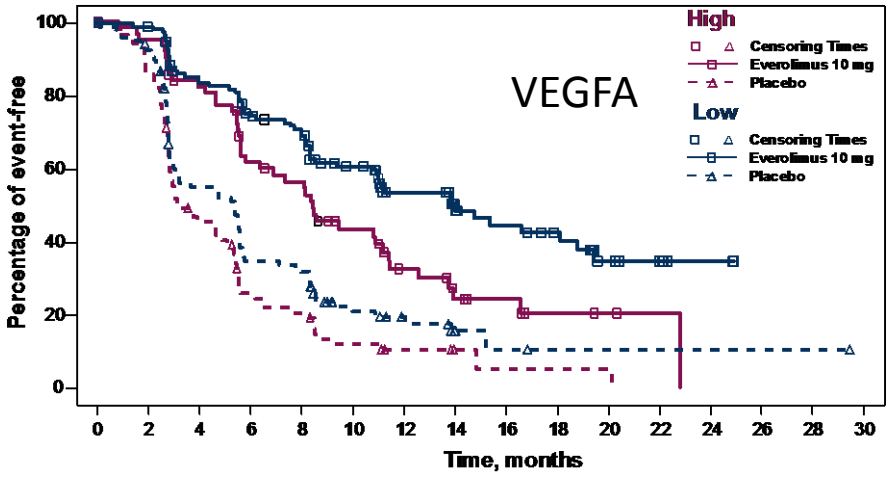
Delbaldo et al Targ Oncol 2011

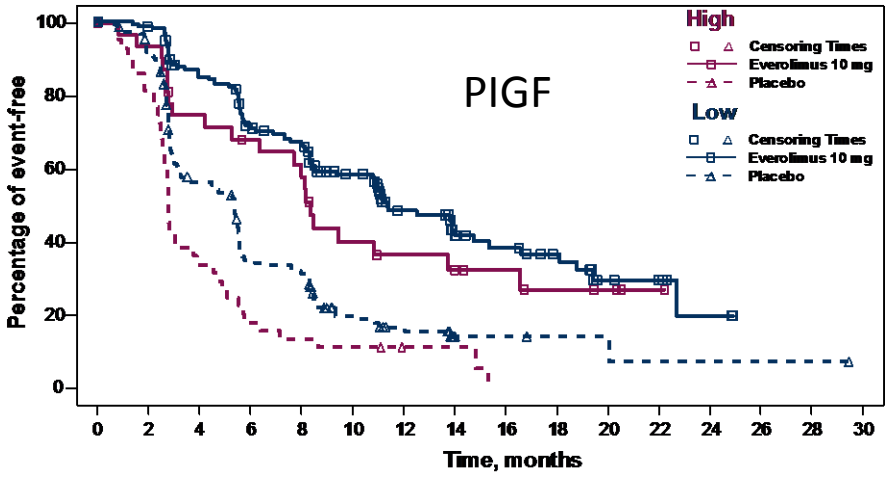
RADIANT-3

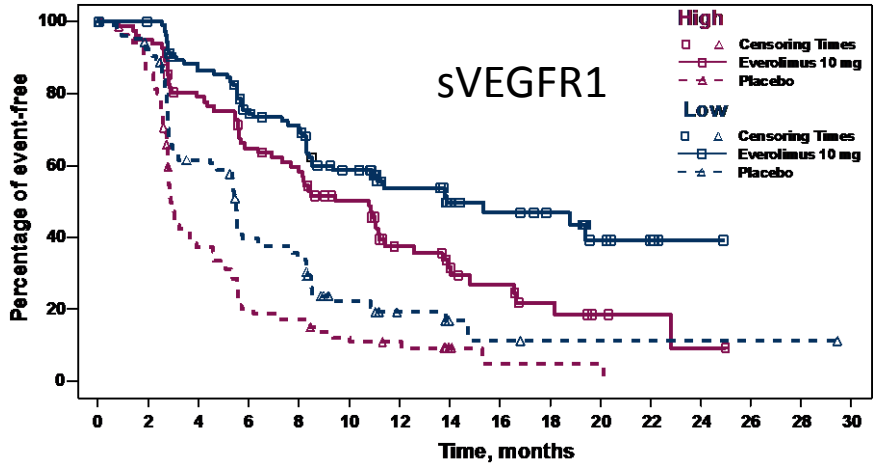

Low- or intermediate-grade advanced pNET
(N = 410)
• Radiologic progression within 12 months
• Previous antitumor therapy allowed
• WHO performance status (PS) ≤2
RANDOMIZE
1:1
Everolimus 10 mg/d + Best Supportive Care[a] n = 207
Crossover at disease progression
Placebo + Best Supportive Care[a] n = 203

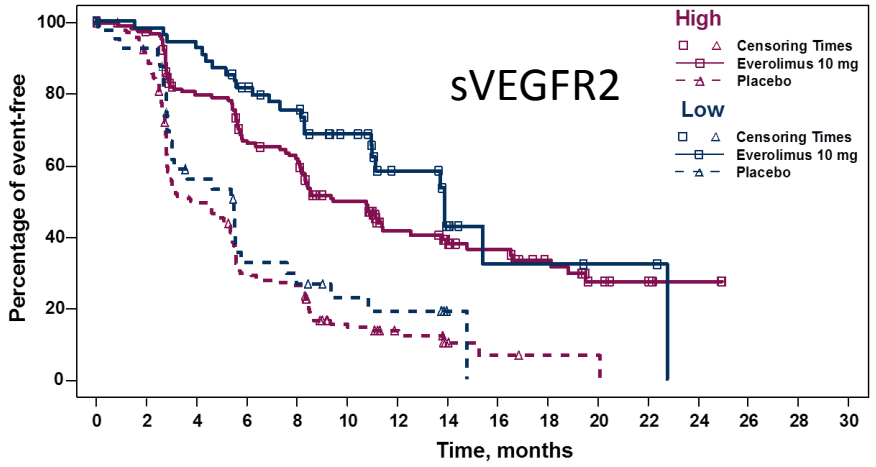
Ideal for Biomarker study

- Large
- Prospective
- Multicentre
- Placebo controlled


VEGFA
High
Censoring Times
Everolimus 10 mg
Placebo
Low
Censoring Times
Everolimus 10 mg
Placebo
Percentage of event-free
Time, months


PIGF
High
Censoring Times
Everolimus 10 mg
Placebo
Low
Censoring Times
Everolimus 10 mg
Placebo
Percentage of event-free
Time, months


sVEGFR1
High
Censoring Times
Everolimus 10 mg
Placebo
Low
Censoring Times
Everolimus 10 mg
Placebo
Percentage of event-free
Time, months


sVEGFR2
High
Censoring Times
Everolimus 10 mg
Placebo
Low
Censoring Times
Everolimus 10 mg
Placebo
Percentage of event-free
Time, months

Pre-treatment plasma levels of VEGF-A, PIGF, sVEGFR1,2 do not predict benefit from everolimus in patients with PNET

Why not?

- All patients benefit
- Angiogenesis in not the main target
- Circulating cytokines are not a good indicator of angiogenesis in the tumour microenvironment.

Prognosis in NETs

Current markers

1. Proliferation markers; Ki67
2. Chromogranin A
3. Circulating tumour cells (CTCs)

Prognosis PNET – Ki67

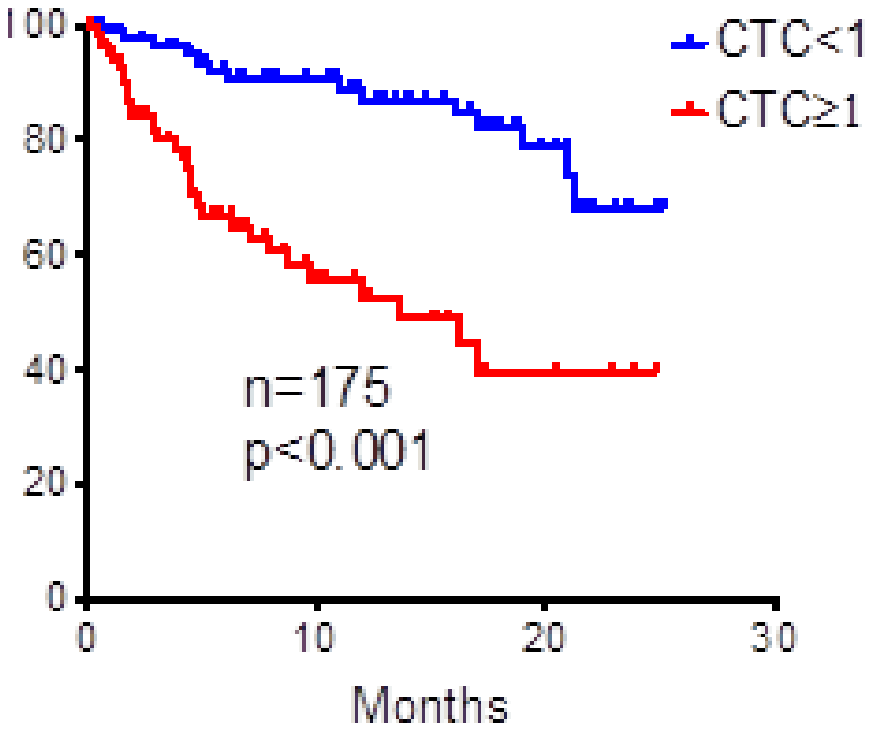
Author Date	Number Patients	Ki67 cut-off	HR	P value	Analysis
Ekeblad 2008	324	>2%	5.2	0.002	MV
Panzuto 2011	202	>5%	1.73	0.003	MV
Rindi 2012	1072	>4.7%	6.81	<0.001	UV

Radiant-3: Ki 67 not reported

Chromogranin A

- Non-specific
- PNET on Everolimus (Yao JCEM 2011)
  - MVA Cga >2x ULN (HR 0.7; CI, 0.37, 1.32 NSD)
- Radiant-2 (non-PNET) (Yao GI ASCO 2012)
  - MVA Cga >2x ULN (HR, 0.47; CI, 0.34-0.65; *P*<.001)

Prognosis PNETs - CTCs



Risk Factor	PFS HR (95% CI)	P - value
CTC		
<1 (n=89)	1.0	
≥1 (n=86)	3.3 (1.6-6.6)	0.001
CgA		
CgA≤120 (n=75)	1.0	
CgA>120 (n=100)	1.1 (0.5-2.2)	0.844
Grade (Ki67)		
1 (n=83)	1.0	
2 (n=63)	2.0 (0.9-4.2)	<0.001*
3 (n=29)	5.5 (2.4-12.3)	
Burden		
<25% (n=83)	1.0	
≥25% (n=92)	1.3 (0.6-2.6)	0.484
Age		
For every 10yrs	1.3 (1.1-2.1)	0.034

Khan M et al Clin Canc Res 2011 + ASCO 2012

RADIANT-4

Marker	Cutoff[1]	Median PFS[2] Low vs high (months)	Prognostic HR [95% CI]	P value
VEGF-A	246.1	8.3 vs 5.5	1.50 [1.17-1.92]	<.001
PlGF	32.06	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

Marker	HR [95% CI]	*P* value
sVEGFR1	**1.54 [1.20, 1.98]**	**<0.001**
PlGF	**1.35 [1.01, 1.81]**	**0.046**

Conclusion

- Largest circulating biomarker study in NETs
- Need to include known prognostic factors in the MV model
- What is the best method to stratify patients?