Metastatic gastric cancer: What are the indications and what is the impact of angiogenesis inhibitors?

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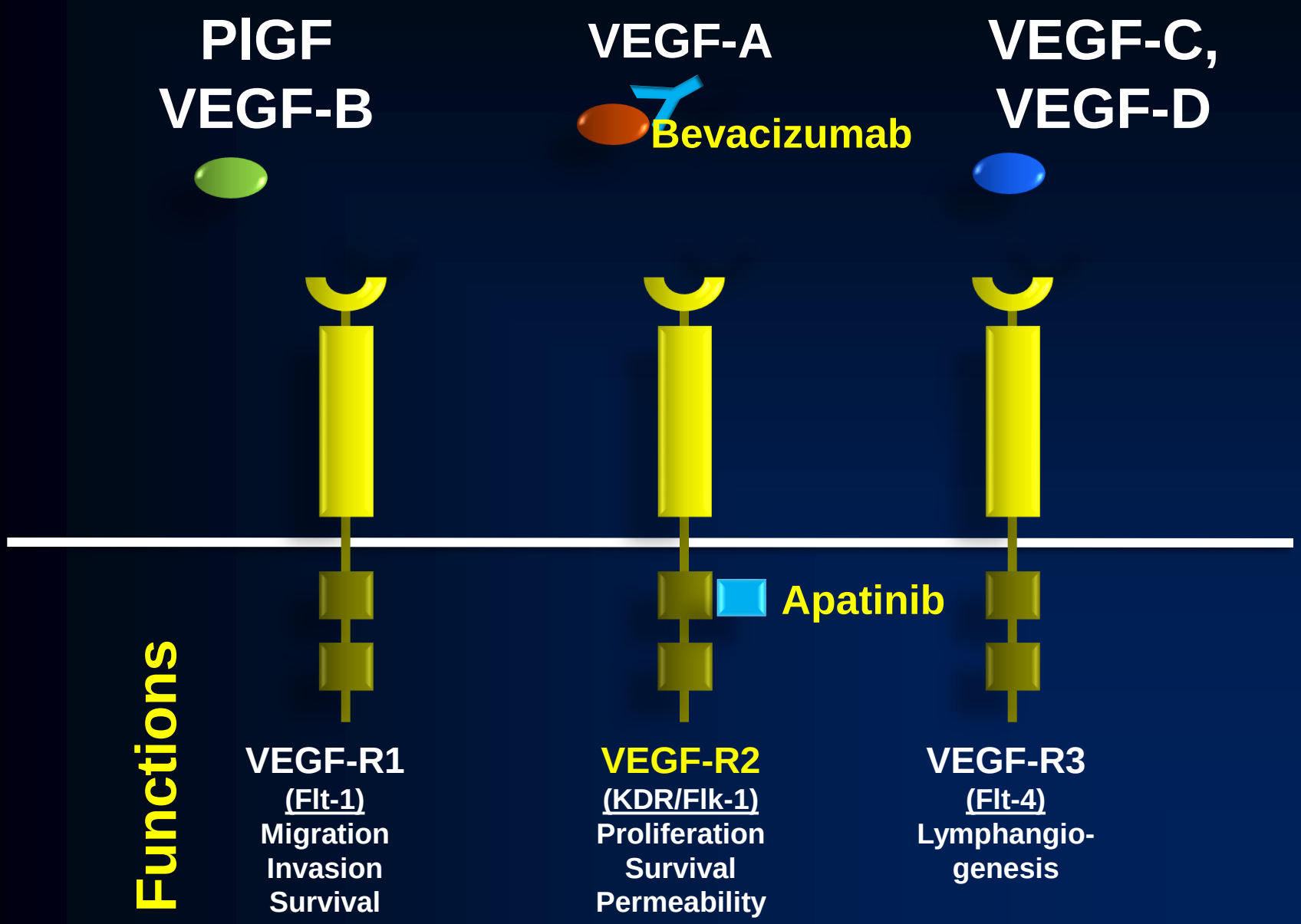
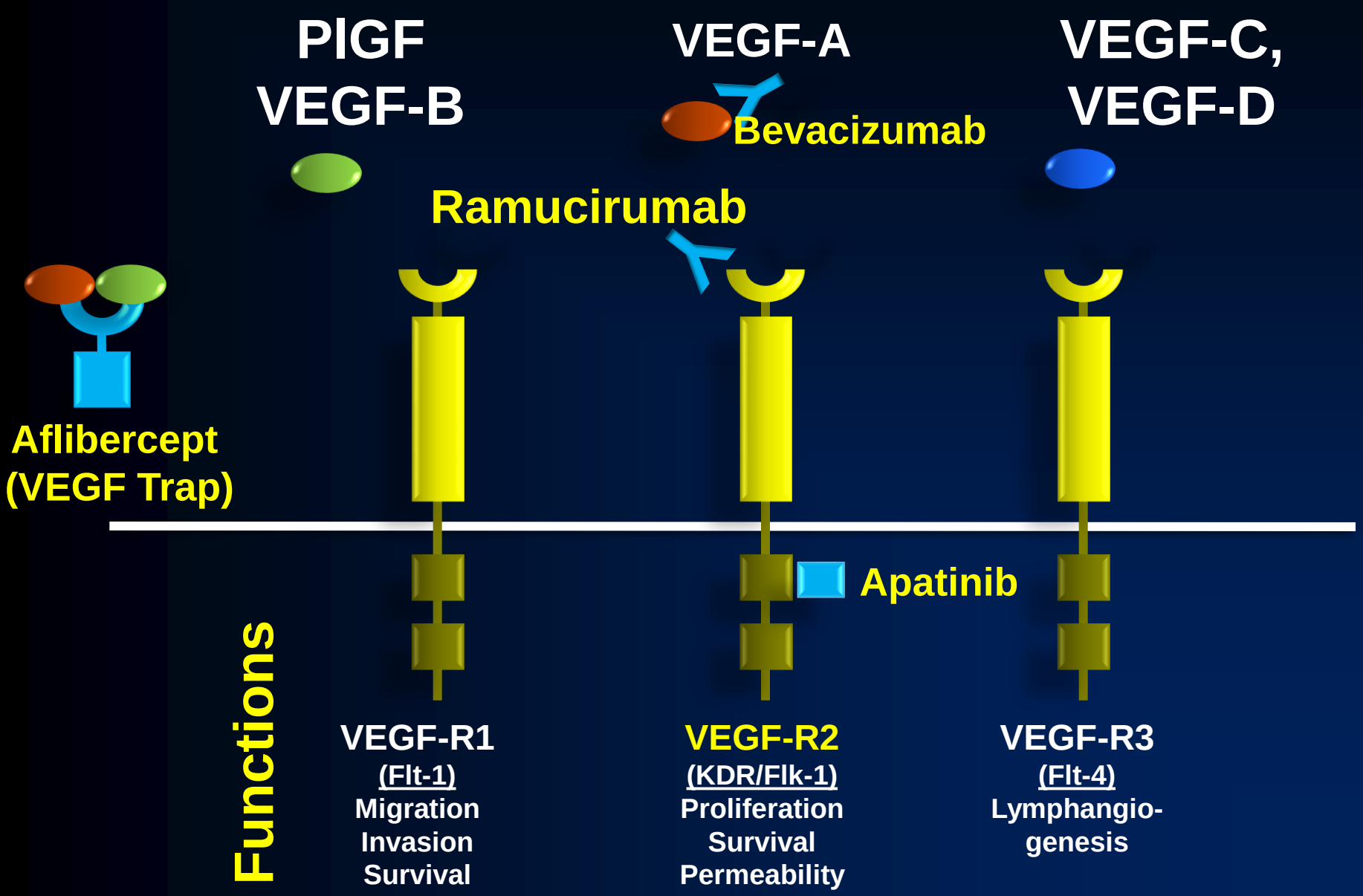
DISCLOSURES

Consulting fees from Bristol-Myers Squibb, Eli Lilly and Pfizer and funds for research support from Bristol-Myers Squibb, Merck, Amgen, Bayer, Boehringer Ingelheim, and Lilly

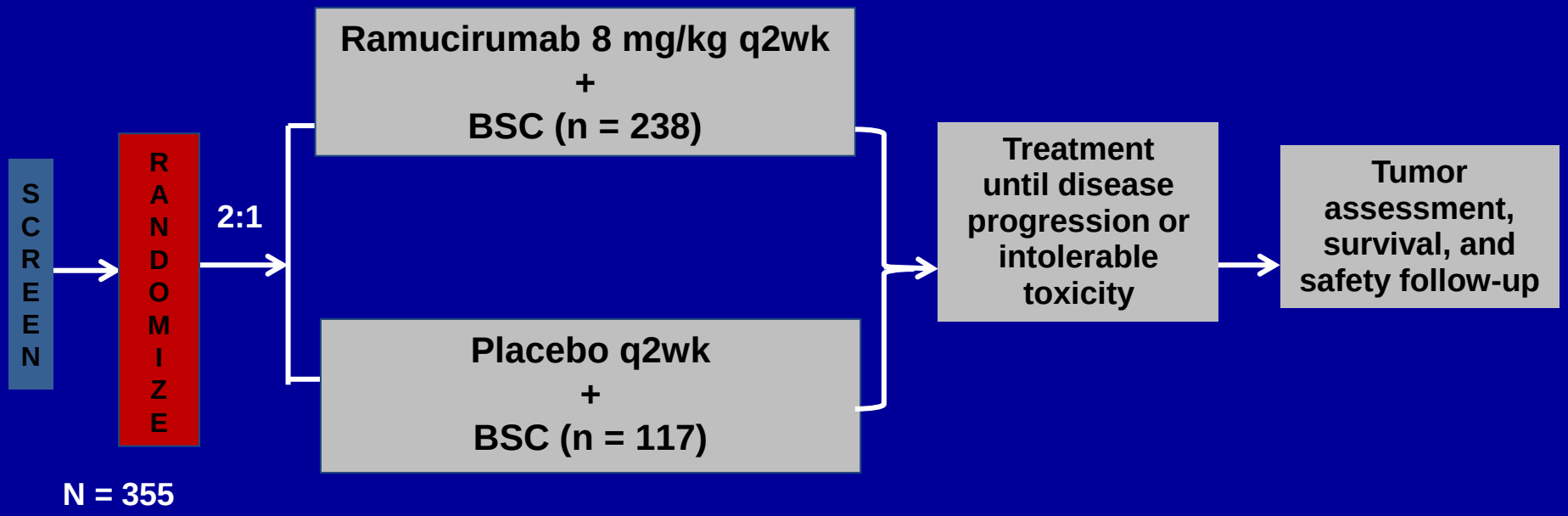
VEGF inhibitors



VEGF inhibitors



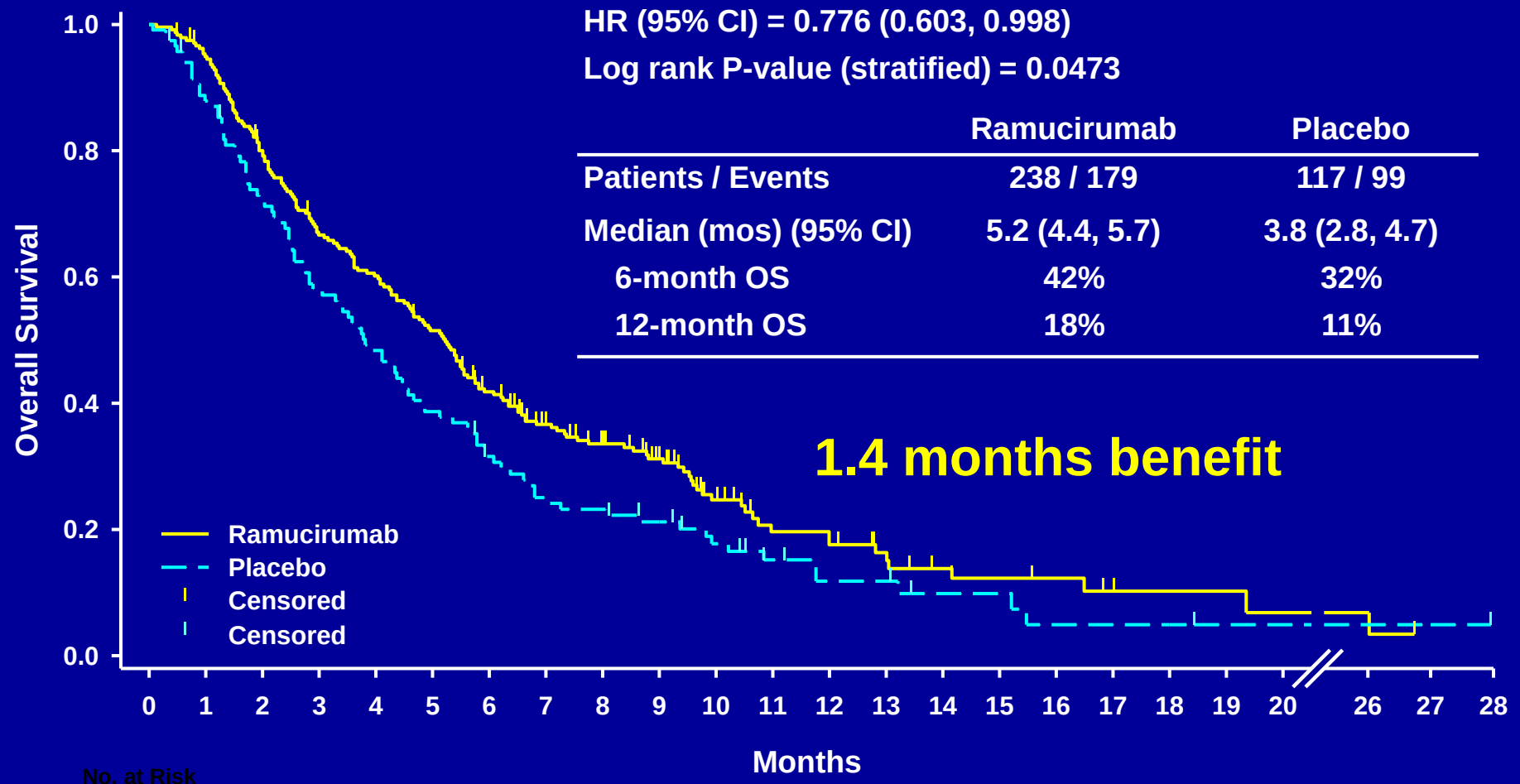
Phase III REGARD Study
RAMUCIRUMAB FDA approved In Second line Setting



- Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial
- Gastric or GEJ adenocarcinoma
- Stratification factors: region, weight loss (≥10% vs. <10% over 3 months), location of primary tumor (gastric vs. GEJ)
- Global: 6 continents, 30 countries, 120 study centers

BSC = best supportive care; GEJ = gastroesophageal junction; q = every; wk = weeks
Fuchs et al, 2013

REGARD: Overall Survival



HR (95% CI) = 0.776 (0.603, 0.998)

Log rank P-value (stratified) = 0.0473

	Ramucirumab	Placebo
Patients / Events	238 / 179	117 / 99
Median (mos) (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)
6-month OS	42%	32%
12-month OS	18%	11%

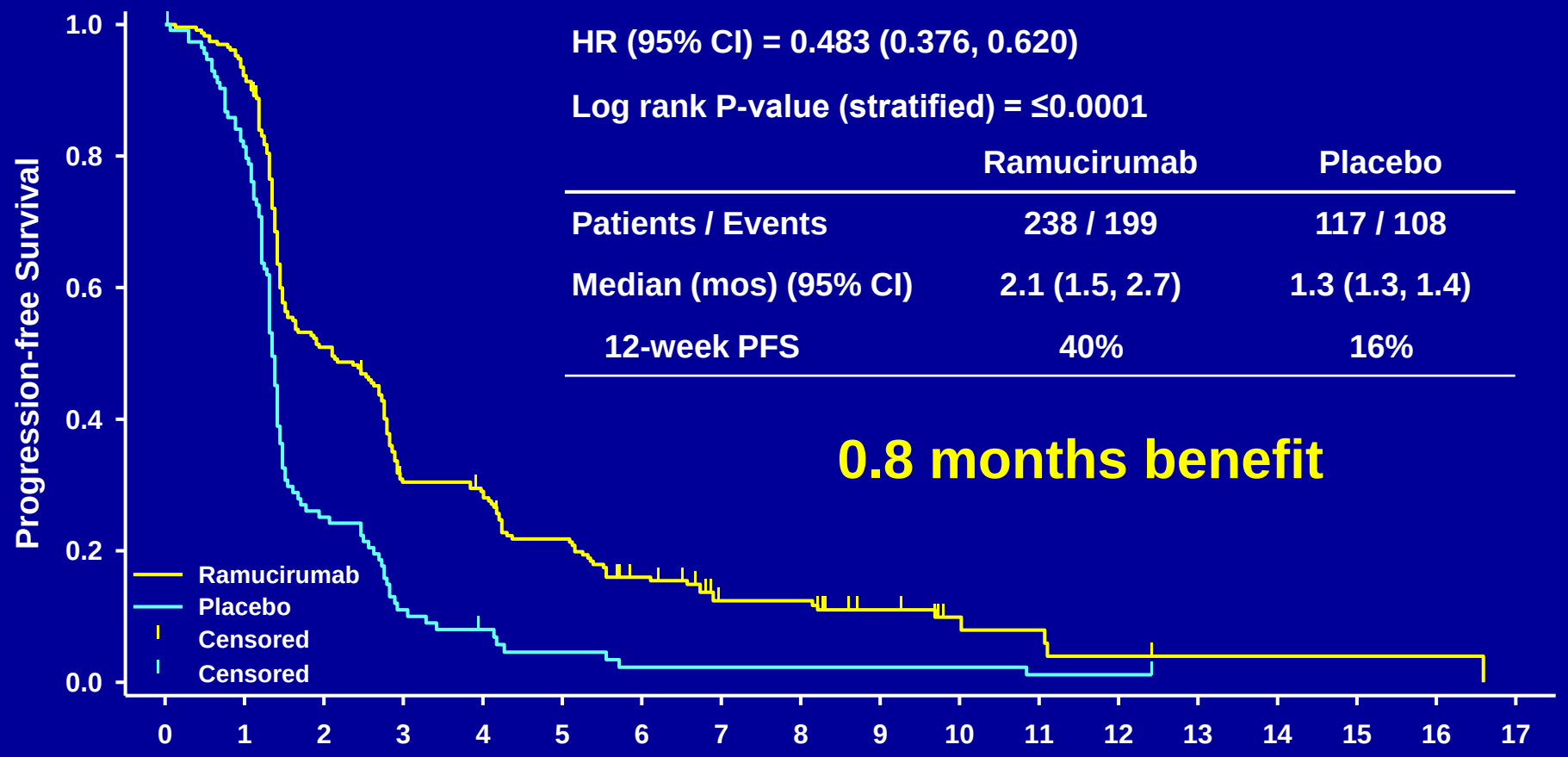
1.4 months benefit

No. at Risk

Ram	238	154	92	49	17	7	3	0	0
Plcb	117	66	34	20	7	4	2	1	0

Fuchs et al, 2013.

REGARD: Progression-Free Survival



HR (95% CI) = 0.483 (0.376, 0.620)

Log rank P-value (stratified) = ≤0.0001

	Ramucirumab	Placebo
Patients / Events	238 / 199	117 / 108
Median (mos) (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)
12-week PFS	40%	16%

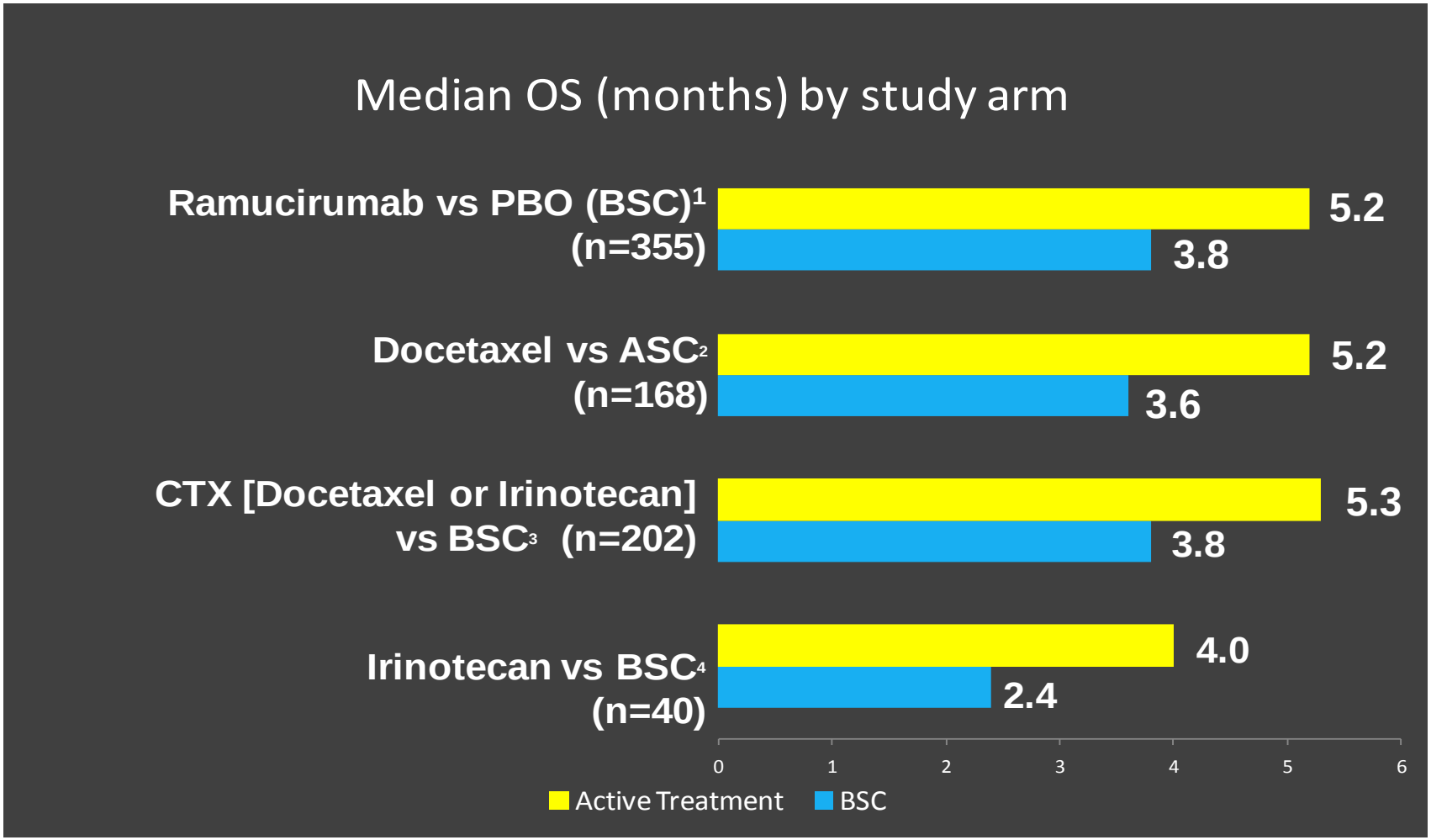
0.8 months benefit

No. at Risk

Ram	238	213	113	65	61	45	30	18	18	11	5	4	2	1	1	1	1	0
Plcb	117	92	27	11	7	4	2	2	2	2	2	1	1	0	0	0	0	0

Fuchs et al, 2013.

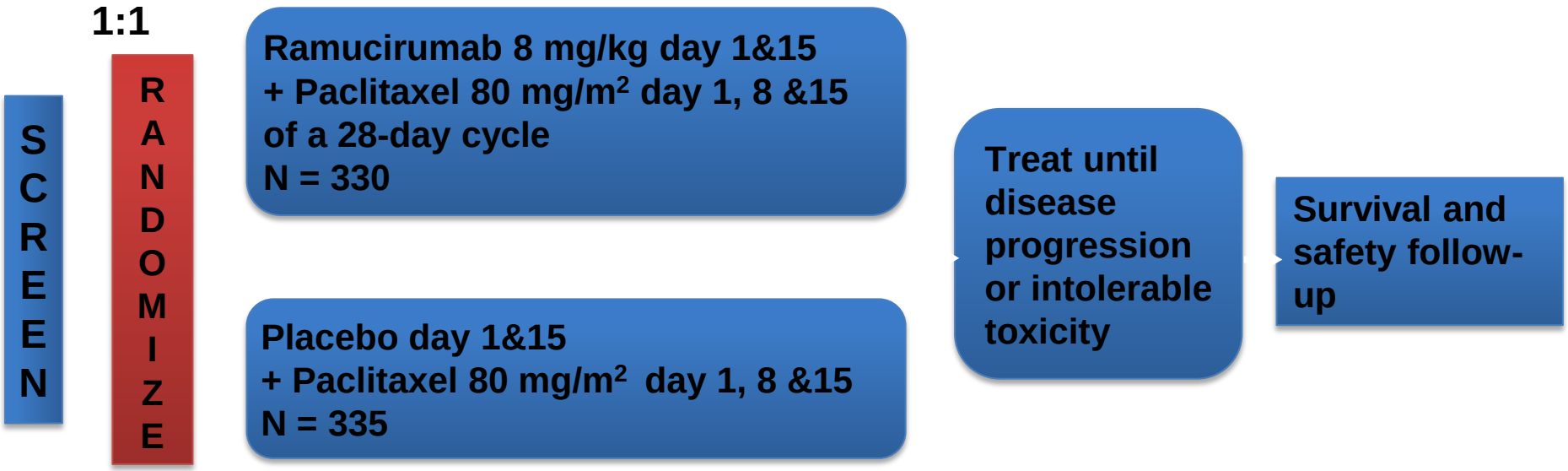
Median OS in Randomized 2nd-line Gastric Cancer Studies Presented/Published in 2009-2013



PBO = placebo; ASC = active symptom control; CTX = chemotherapy; BSC = best supportive care; OS = overall survival..

[1]Fuchs et al, 2013; [2]Ford et al, 2013; [3]Kang et al, 2012 ; [4]Thuss-Patience et al, 2011.

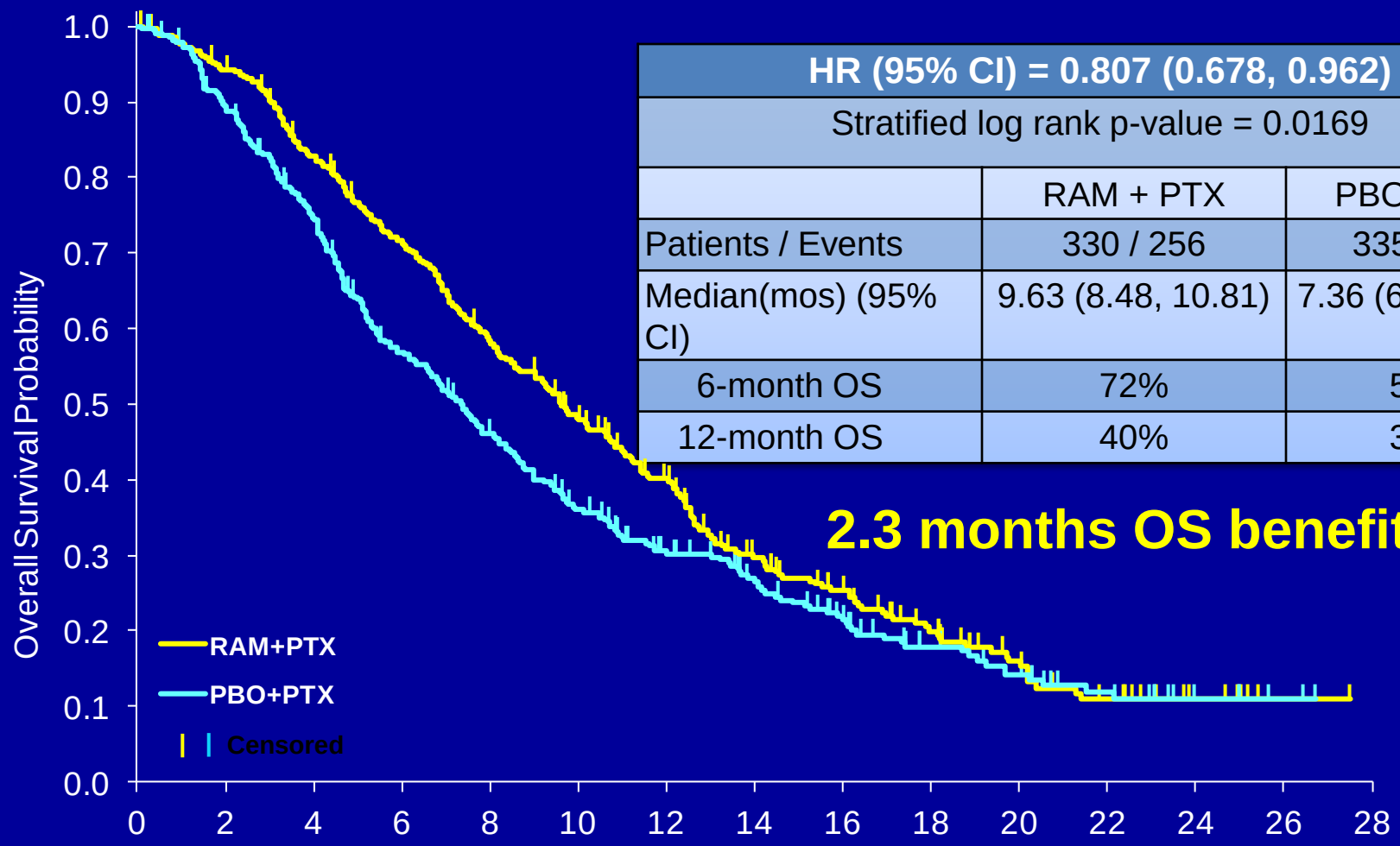
RAINBOW: Study Design



- **Important inclusion criteria:**
  - Metastatic or loc. adv. unresectable gastric or GEJ* adenocarcinoma
  - Progression after 1st line platinum/fluoropyrimidine-based chemotherapy
- **Stratification factors:**
  - Geographic region
  - Measurable vs non-measurable disease
  - Time to progression on 1st line therapy (< 6 mos vs. ≥ 6 mos)

*GEJ= gastroesophageal junction; gastric and GEJ will be summarized under the term GC
Wilke et al, 2014.

RAINBOW: Overall Survival



HR (95% CI) = 0.807 (0.678, 0.962)		
Stratified log rank p-value = 0.0169		
	RAM + PTX	PBO + PTX
Patients / Events	330 / 256	335 / 260
Median(mos) (95% CI)	9.63 (8.48, 10.81)	7.36 (6.31, 8.38)
6-month OS	72%	57%
12-month OS	40%	30%

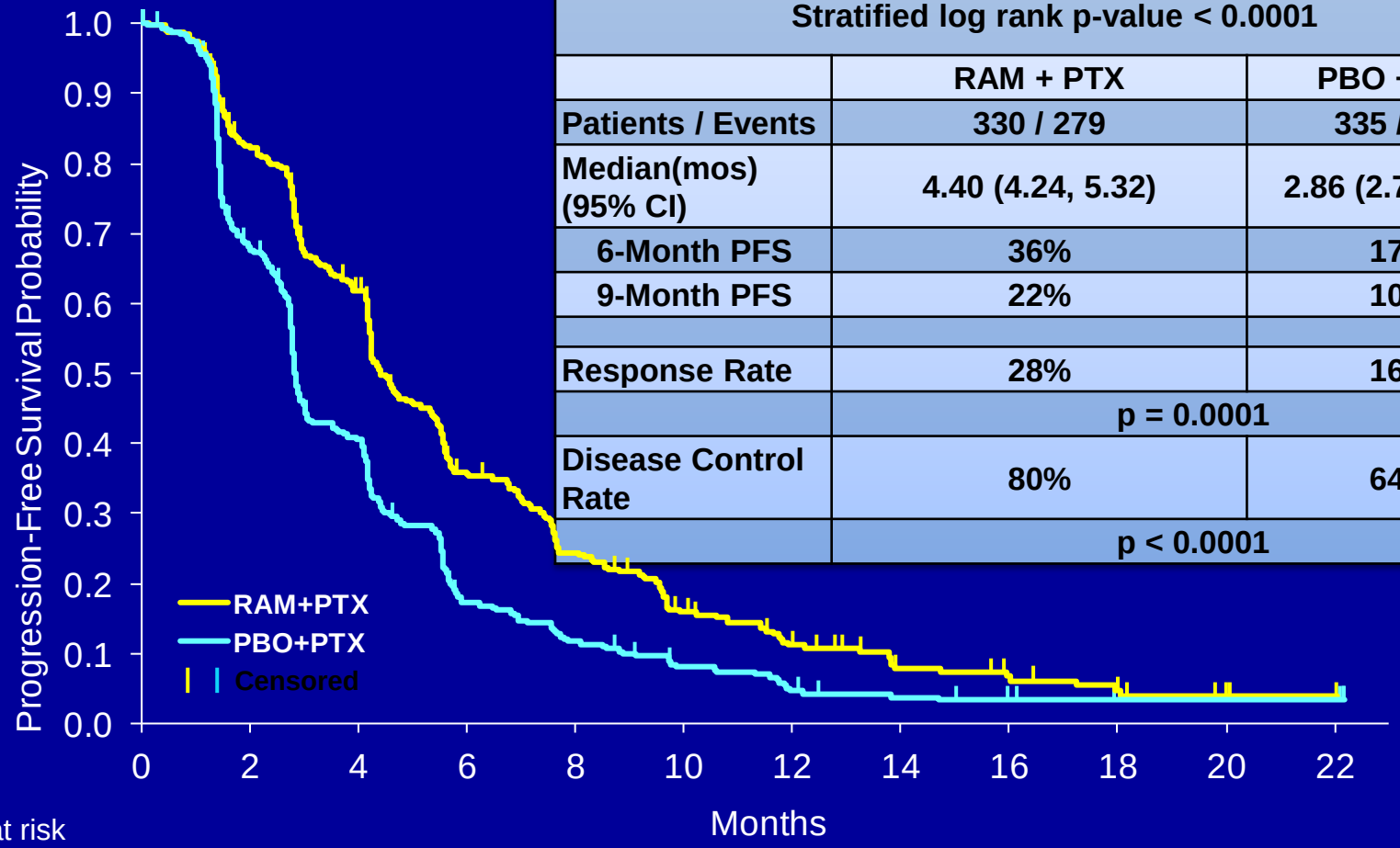
2.3 months OS benefit

No. at risk

RAM + PTX	**330**	**308**	**267**	**228**	**185**	**148**	**116**	**78**	**60**	**41**	**24**	**13**	**6**	**1**	**0**
PBO + PTX	**335**	**294**	**241**	**180**	**143**	**109**	**81**	**64**	**47**	**30**	**22**	**13**	**5**	**2**	**0**

RAM = ramucirumab; PTX = paclitaxel; PBO = placebo.
Wilke et al, 2014.

RAINBOW: Progression-Free Survival & Response Rates



HR (95% CI) = 0.635 (0.536, 0.752)		
Stratified log rank p-value < 0.0001		
	RAM + PTX	PBO + PTX
Patients / Events	330 / 279	335 / 296
Median(mos) (95% CI)	4.40 (4.24, 5.32)	2.86 (2.79, 3.02)
6-Month PFS	36%	17%
9-Month PFS	22%	10%
Response Rate	28%	16%
	p = 0.0001	
Disease Control Rate	80%	64%
	p < 0.0001	

No. at risk

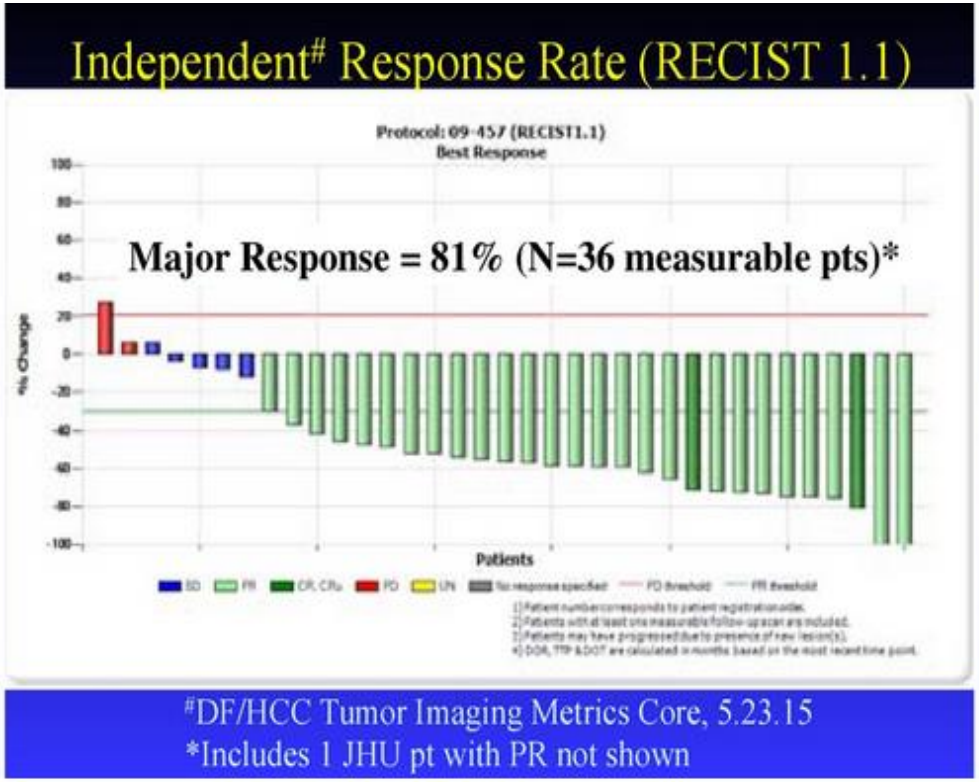
RAM + PTX	**330**	**259**	**188**	**104**	**70**	**43**	**28**	**15**	**11**	**7**	**3**	**1**
PBO + PTX	**335**	**214**	**124**	**50**	**34**	**21**	**12**	**8**	**5**	**3**	**3**	**3**

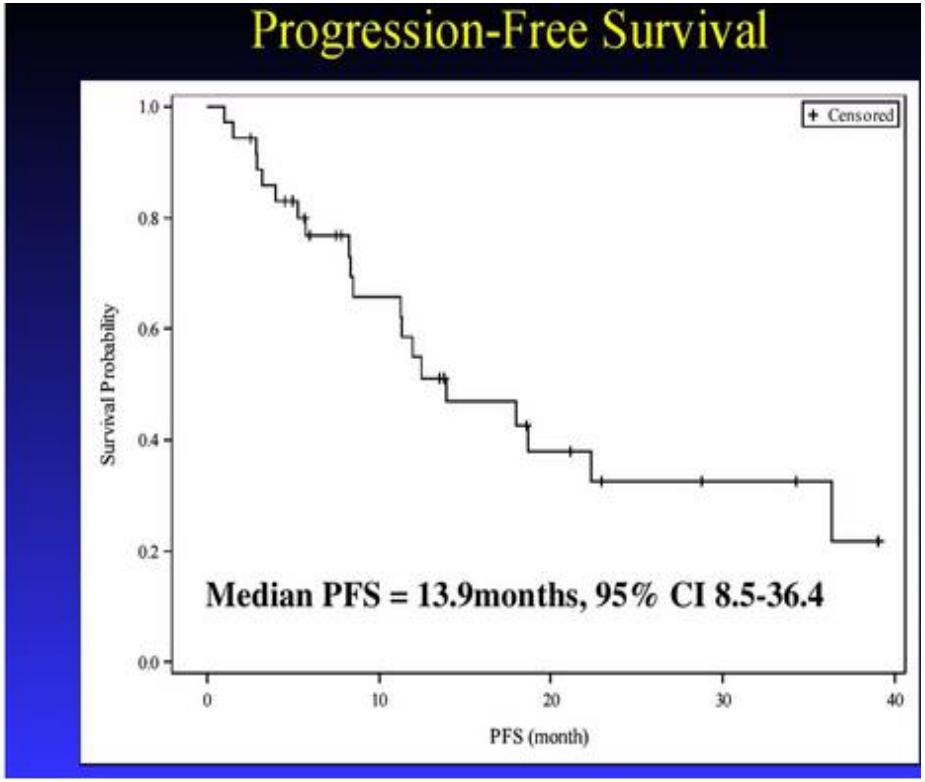
RAM = ramucirumab; PTX = paclitaxel; PBO = placebo.
Wilke et al, 2014.

Adverse Events of Special Interest

	RAM + PTX (N=327)		PBO + PTX (N=329)	
Category of event†	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
Bleeding/Hemorrhage	41.9	4.3	17.9	2.4
Epistaxis	30.6	0	7.0	0
Hypertension	25.1	14.7	5.8	2.7
Proteinuria	16.8	1.2	6.1	0
GI hemorrhage	10.1	3.7	6.1	1.5
Renal failure	6.7	1.8	4.3	0.9
Infusion-related reaction	5.8	0.6	3.6	0
Venous thromboembolic	4.0	2.4	5.5	3.3
Cardiac failure	2.4	0.6	1.2	0.6
Arteriothromboembolic	1.8	0.9	1.5	0.9
GI perforation	1.2	1.2	0.3	0

Best response and PFS with trastuzumab, bevacizumab, and capecitabine/oxaliplatin

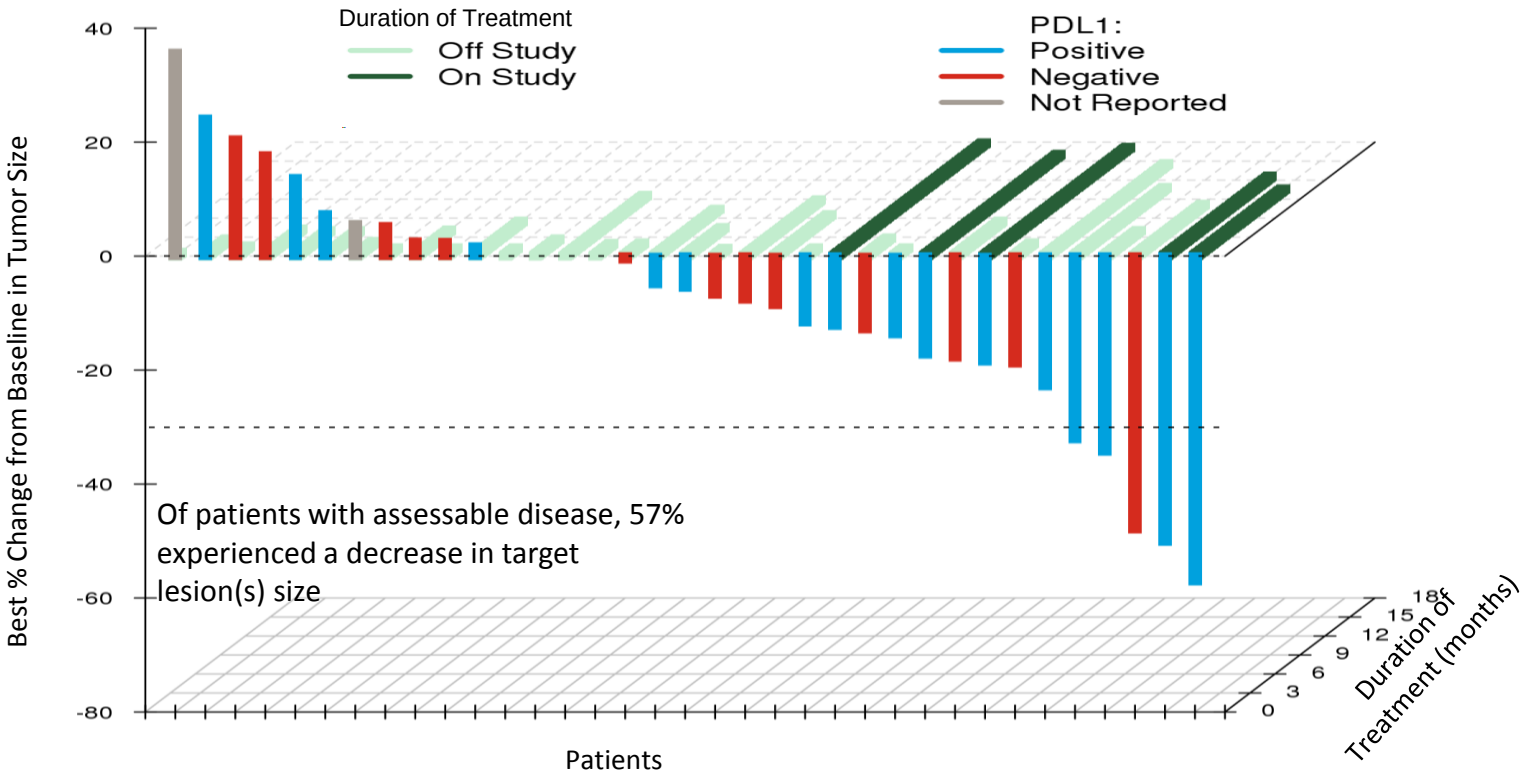




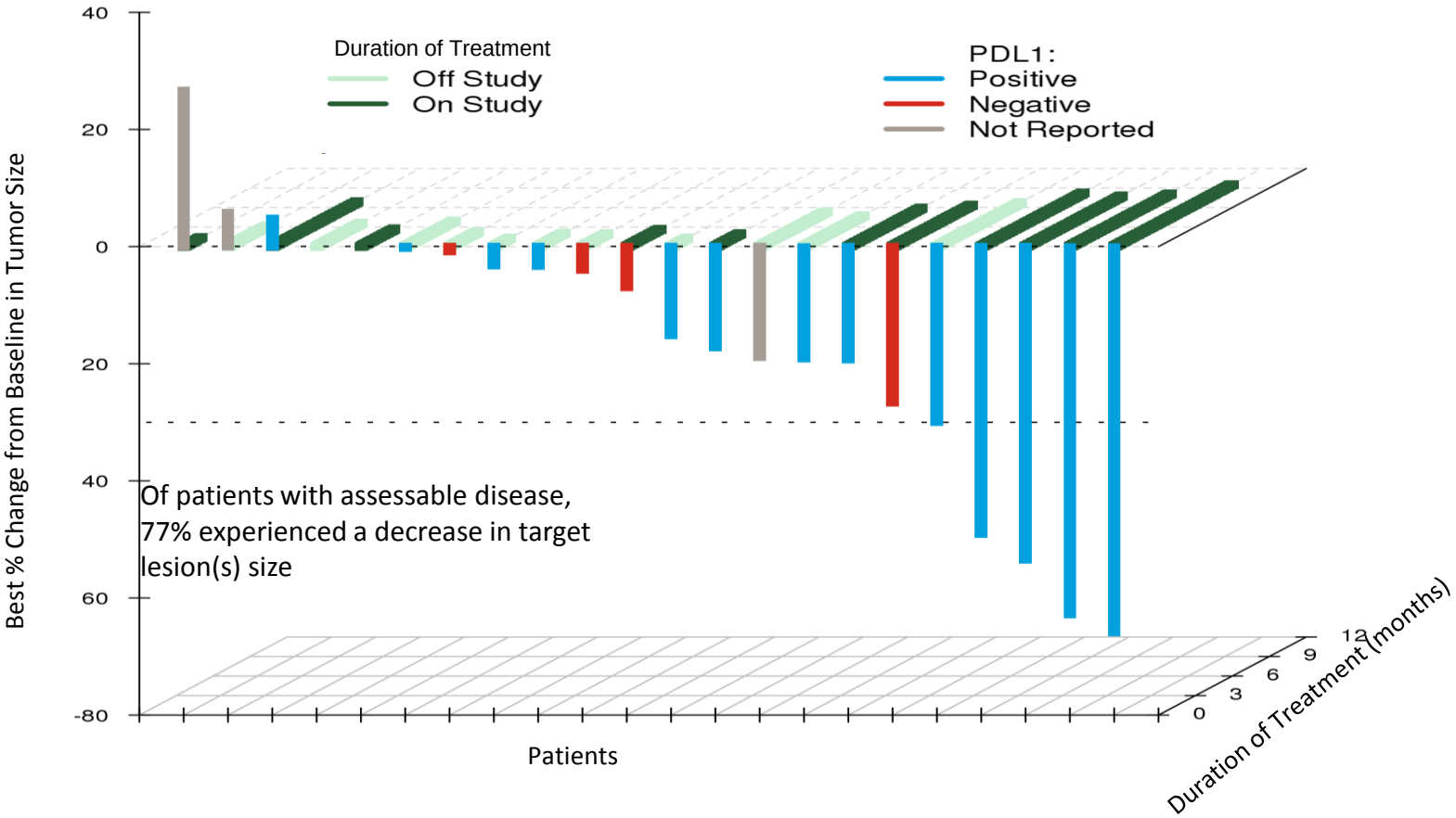
75% of patients progression free at 6 months, median OS 26.92 months (95%CI, 11.31 - 36.36)

Enzinger et al ASCO 2015

Ramucirumab + Pembrolizumab ≥2nd-Line G/GEJ Adenocarcinoma

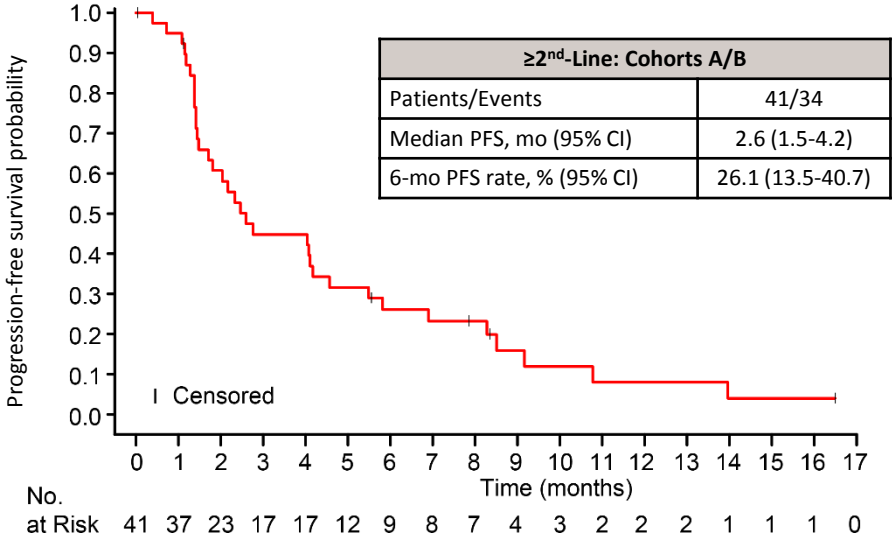


Ramucirumab + Pembrolizumab with 1st-Line G/GEJ Adenocarcinoma

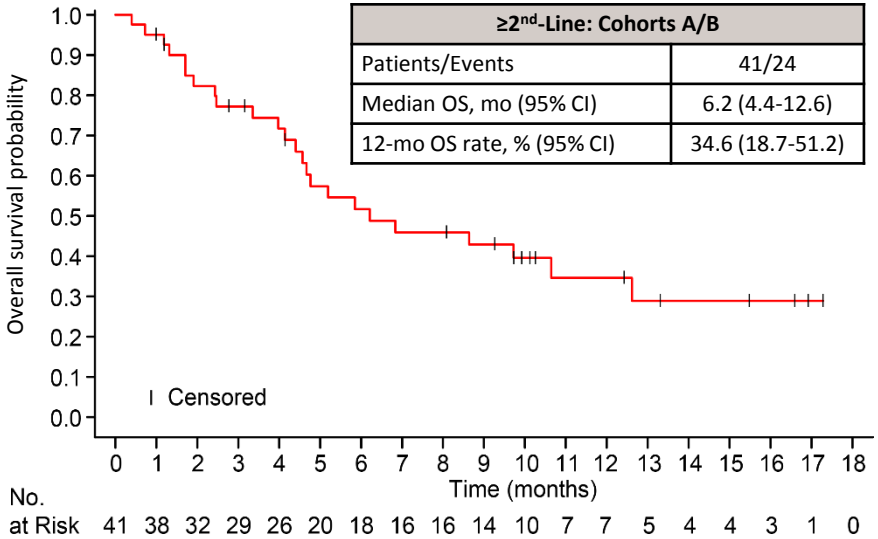


Of patients with assessable disease, 77% experienced a decrease in target lesion(s) size

Ramucirumab + Pembrolizumab Progression-free and overall survival in ≥2nd-Line G/GEJ Adenocarcinoma



≥2nd-Line: Cohorts A/B	
Patients/Events	41/34
Median PFS, mo (95% CI)	2.6 (1.5-4.2)
6-mo PFS rate, % (95% CI)	26.1 (13.5-40.7)



≥2nd-Line: Cohorts A/B	
Patients/Events	41/24
Median OS, mo (95% CI)	6.2 (4.4-12.6)
12-mo OS rate, % (95% CI)	34.6 (18.7-51.2)

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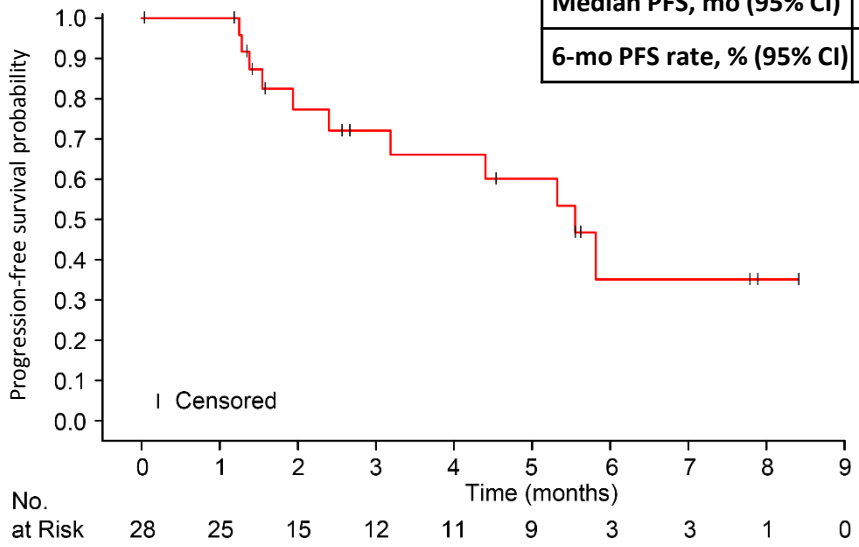
Ramucirumab + Pembrolizumab Progression-free Survival (Interim) in 1st-Line G/GEJ Adenocarcinoma

1st-Line Cohort A2	
Patients/Events	28/11
Median PFS, mo (95% CI)	5.6 (2.4-NR)
6-mo PFS rate, % (95% CI)	35 (11.5-60.2)



NR= not reached

- Median overall survival has not been reached for 1st-Line G/GEJ Adenocarcinoma Cohort A2

Conclusions

- **VEGFR2: Ramucirumab, active single agent and in combination with chemotherapy in 2nd line- improved disease control, PFS, OS**
- **Biomarkers to identify patients more likely to respond**
- **Cape/Cis+ ramucirumab 1st line trial**
- **Combination strategies**
  - **Ramucirumab + pembrolizumab**
  - **Ramucirumab + trastuzumab**