ANGIOGENESIS IN GASTRIC CANCERS

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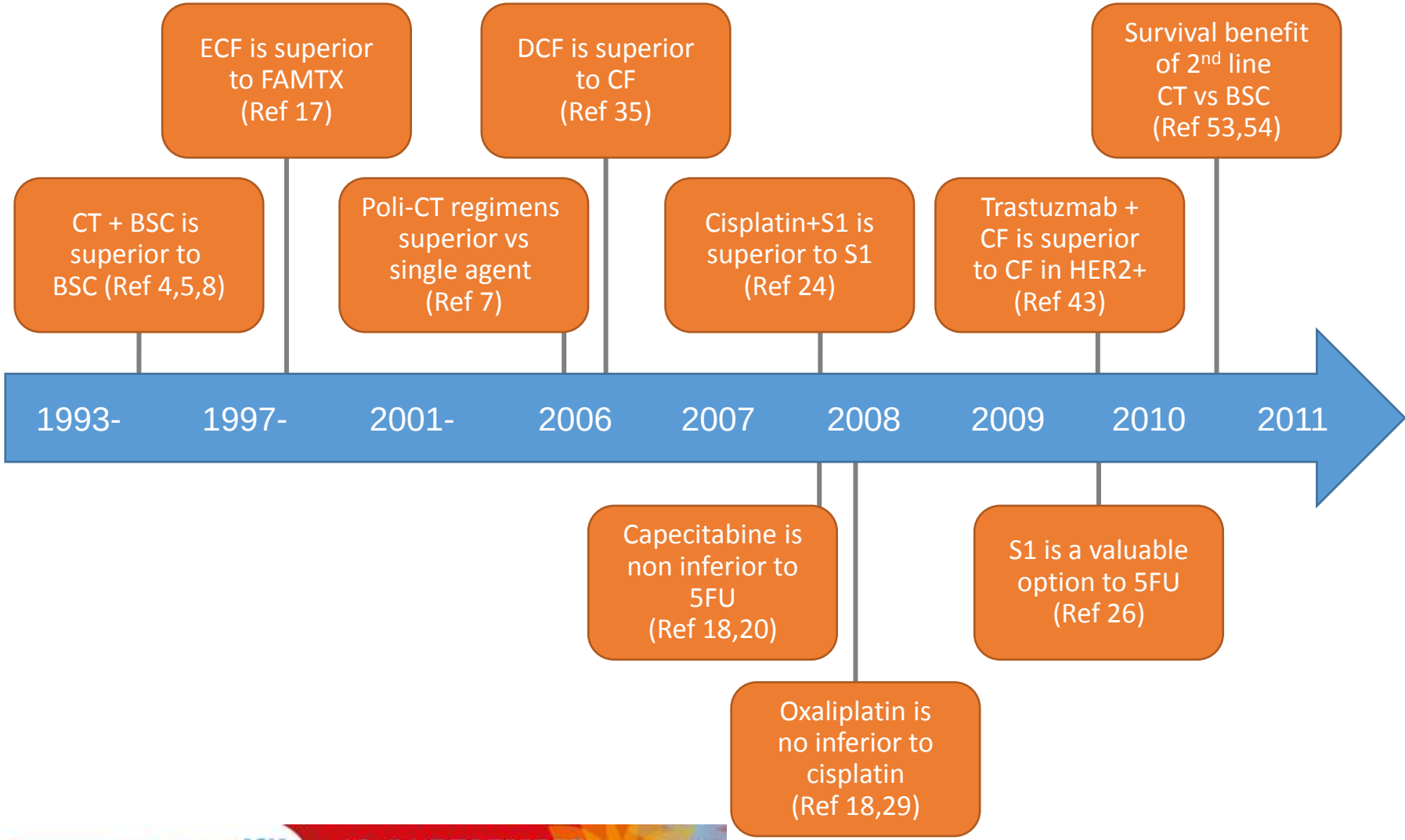
Disclosure slide

- Research grants from Roche, Genentech, Merck Serono, MSD, Bayer, Amgem, Takeda and Merrimack
- Advisor role in Roche, Lilly and Merck Serono.
- Speaker for Roche, Lilly, Merck Serono, Amgem and Bayer

Key discoveries in advanced gastric cancer



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Redrawn from Cervantes A, *et al*. Cancer Treat Rev 2013;39:60–67

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Targeted therapies in first-line treatment for advanced gastric cancer: Summary of Phase III Trials

Trial	Chemotherapy	Biological	HR OS	P value	Increase in median survival
ToGA[1]	**Cisplatin+5-FU/ capecitabine**	**Trastuzumab**	**0.74**	**0.04**	**+2.8 months**
AVAGAST[2]	Cisplatin+ capecitabine	Bevacizumab	0.87	0.10	+2.0 months
EXPAND[3]	Cisplatin+ capecitabine	Cetuximab	1.00	0.95	-1.3 months
REAL-3[4]	Oxaliplatin+ epirubicin + capecitabine	Panitumumab	1.37	0.013	-2.5 months
RILOMET-1[5]	Cisplatin+ epirubiicin+ capecitabine	Rilotumumab	--	--	Stopped in futility analysis
METGASTRIC[6]	FOLFOX6	Onartuzumab	1.06	0.83	-0.6 months

1. Bang YJ, et al. Lancet 2010;376:687–697. 2. Van Cutsem E, J Clin Oncol 2012;30 (17):2119–2127. 3. Lordick F, Lancet Oncol 2013;14:490–499. 4. Waddell T, Lancet Oncol 2013;14:481–489. 5. Cunigham ASCO 2015.. 6. Shah M. J Clin Oncol 2015;33(15)

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Targeted therapies against HER2 in advanced gastric cancer: Summary of Phase III Trials on lapatinib

TRIAL	Chemotherapy backbone	Line of therapy number	HR OS	P value	Response rate	Increase in median survival
ToGA[1]	**Cisplatin+5-FU/ capecitabine**	**First 584**	**0.74**	**0.04**	**51% vs 37% p=0.0017**	**+2.8 months**
LOGiC[2]	Oxaliplatin/ capecitabine	First 545	0.91	0.35	53% vs 39% P=0.0031	+1.7 months
TyTAN[3]	Paclitaxel	Second 261	0.84	0.20	27% vs 9% p=0.001	+2.1 months

1. Bang YJ, et al. Lancet 2010;376:687–697.
2. Hecht JR, et al. J Clin Oncol 2015; on line.
3. Satoh N, et al. J Clin Oncol 2014; 32:2039–2049.

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Cisplatin and capecitabine +/- Bevacizumab in advanced gastric cancer: AVAGAST Trial

Arm	RESPONSE RATE (%)	PFS (months)	HR PFS	p value
Cispatin/ capecitbabine	37,4%	5,3	--	--
Cisplatin/ capecitabine Bevacizumab	**46% p:0.031**	**6,7**	**0.80**	**0.004**

Otshu A, et al, J Clin Oncol 2011;29:3968–3976.

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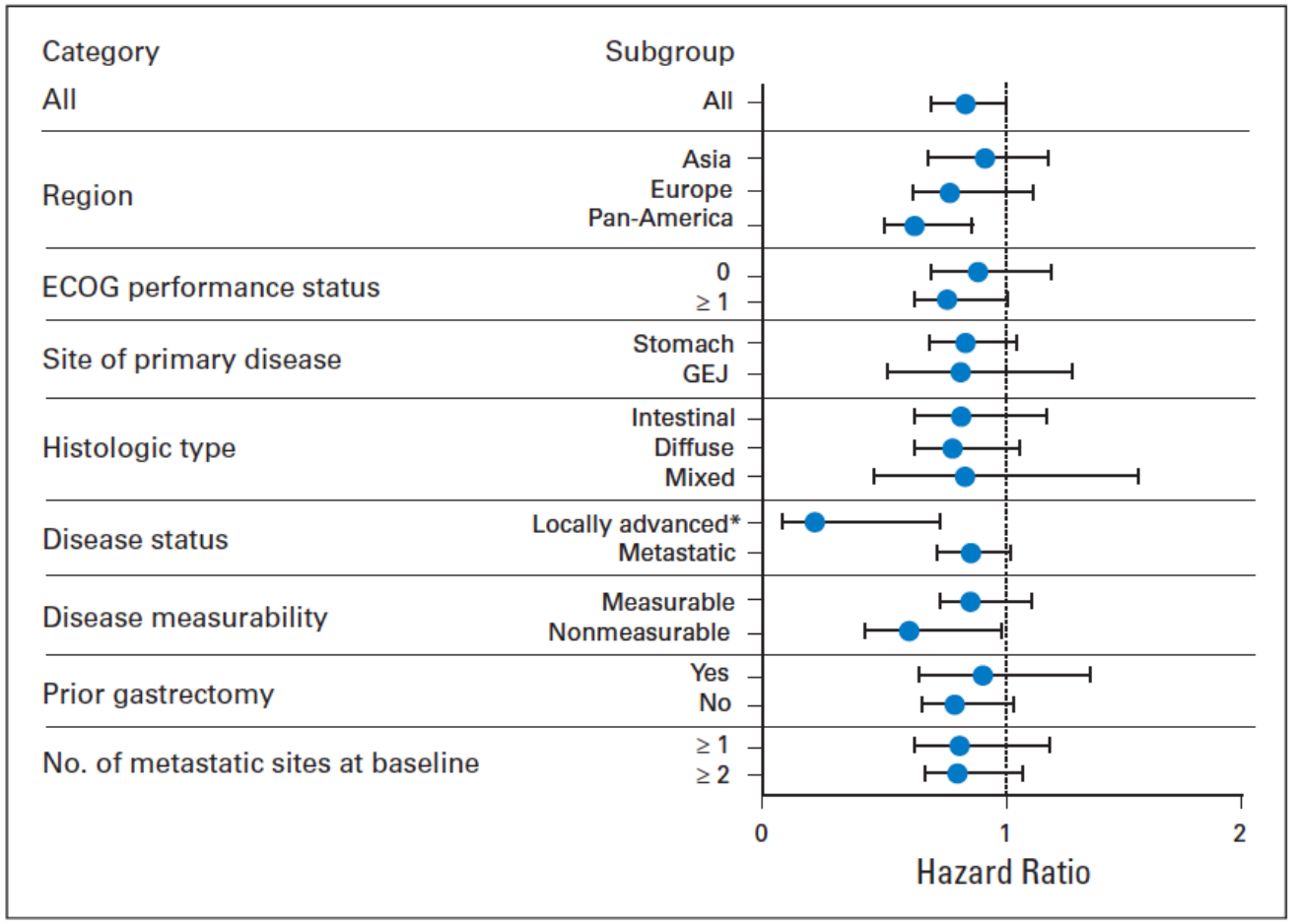
Cisplatin and capecitabine +/- Bevacizumab in advanced gastric cancer: AVAGAST Trial



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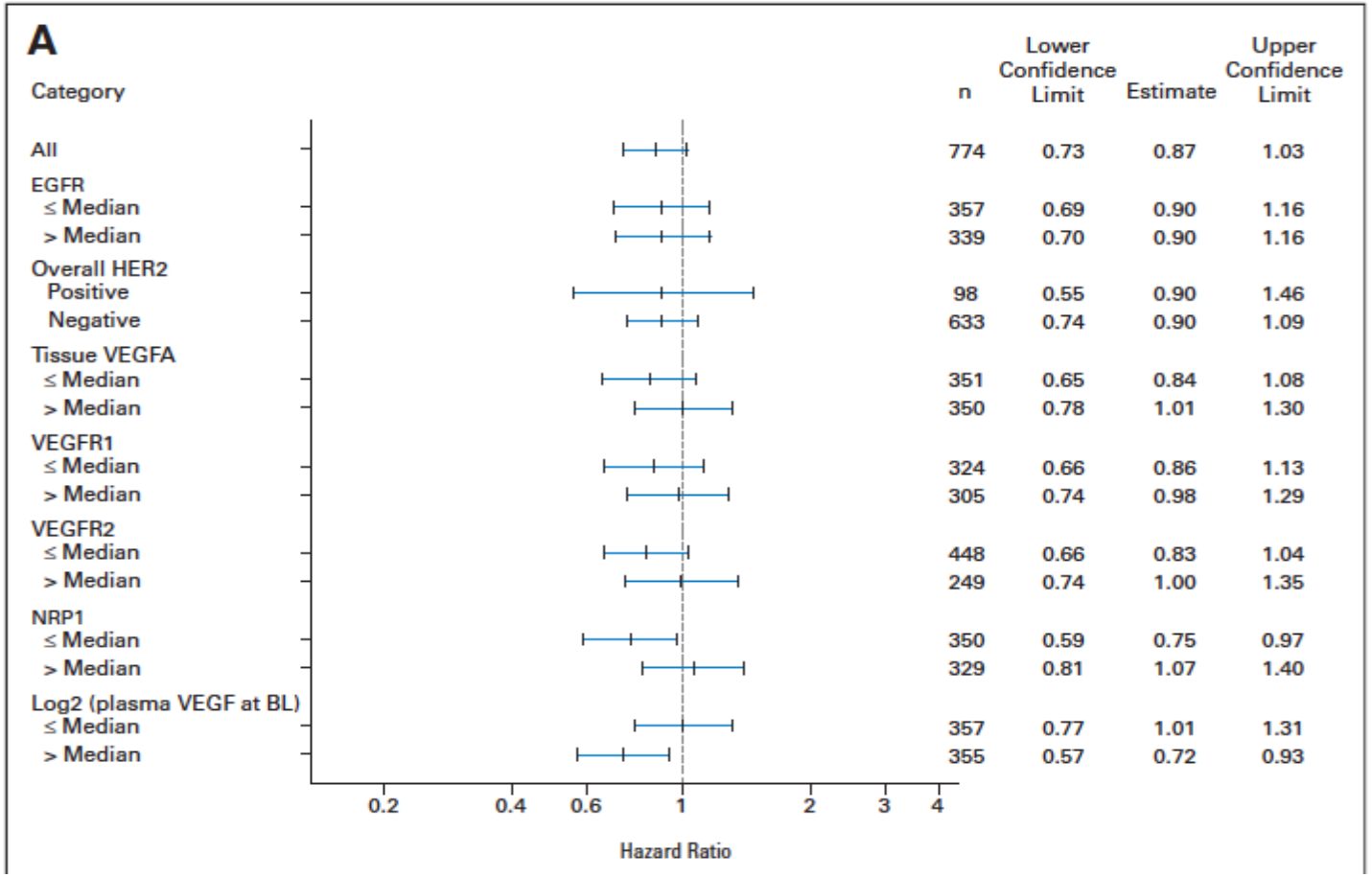
Potential predictive biomarkers in the AVAGAST Trial: Lower Neuropilin-1 and higher VEGF-A plasma levels



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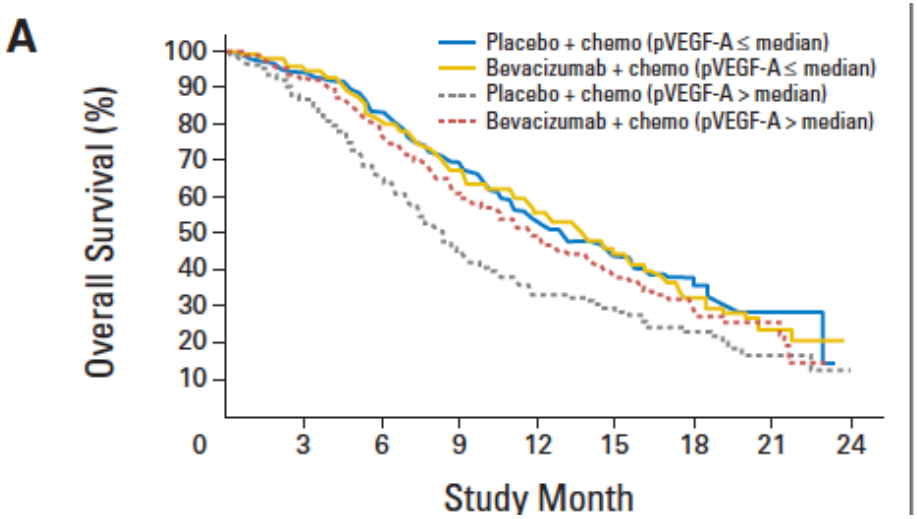

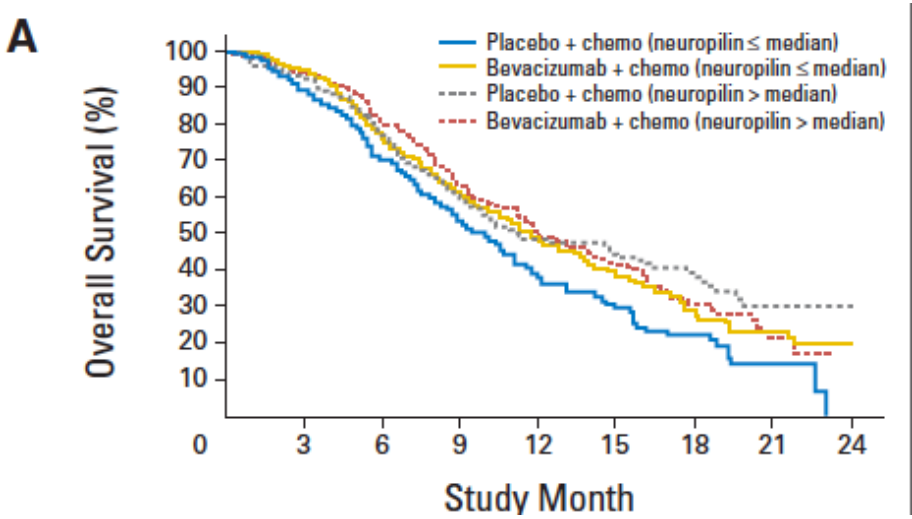

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Gastric cancer: Second line chemotherapy. Trials comparing BSC versus active treatment

Trial author	Year	Patients random (n)	Treatment	Response rate (%)	HR OS	P value	Gain in median survival
Thuss-Patience, et al.[1]	2011	40 1:1	Irinotecan	NR SD 58%	0.48	0.0023	2.4 months
Kang, et al.[2]	2012	193 2:1	Irinotecan Docetaxel	NR	0.65	0.004	1.3 months
Ford, et al.[3]	2014	168 1:1	Docetaxel	NR	0.67	0.01	1.6 months

1. Thuss-Patience PC, et al. Eur J Cancer 2011;47:2306–2314.
2. Kang JH, et al. J Clin Oncol 2012;30:1513–1518.
3. Ford HE, et al. Lancet Oncol 2014;15:78–86.

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Gastric cancer second line chemotherapy: Docetaxel vs BSC (COUGAR-02 Trial) is improving survival

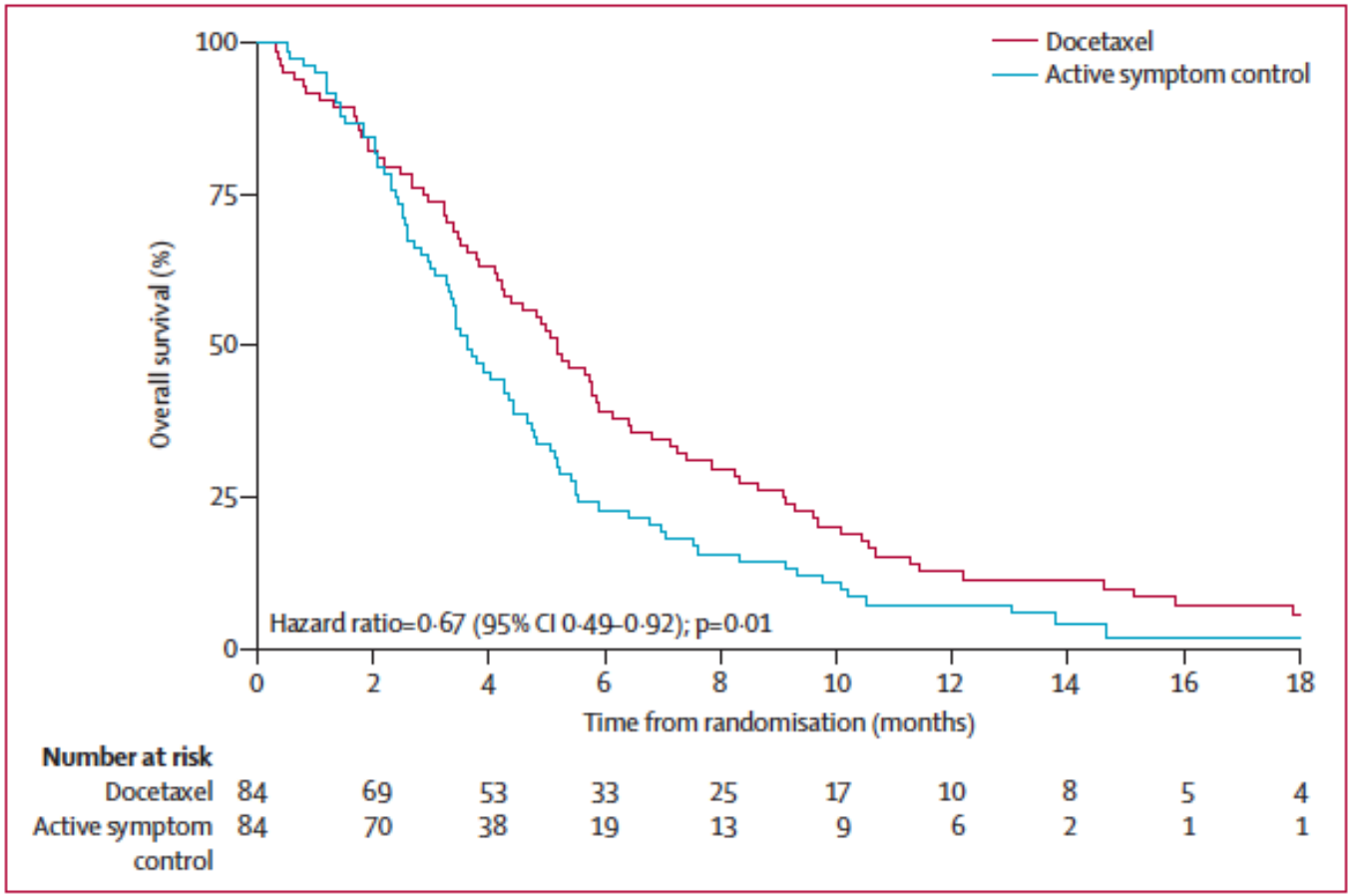

Figure 2: **Kaplan-Meier plot of overall survival**

Ford HE, et al. Lancet Oncol 2014;15:78-86.

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Gastric cancer: Second line chemotherapy trials comparing BSC *versus* active treatment

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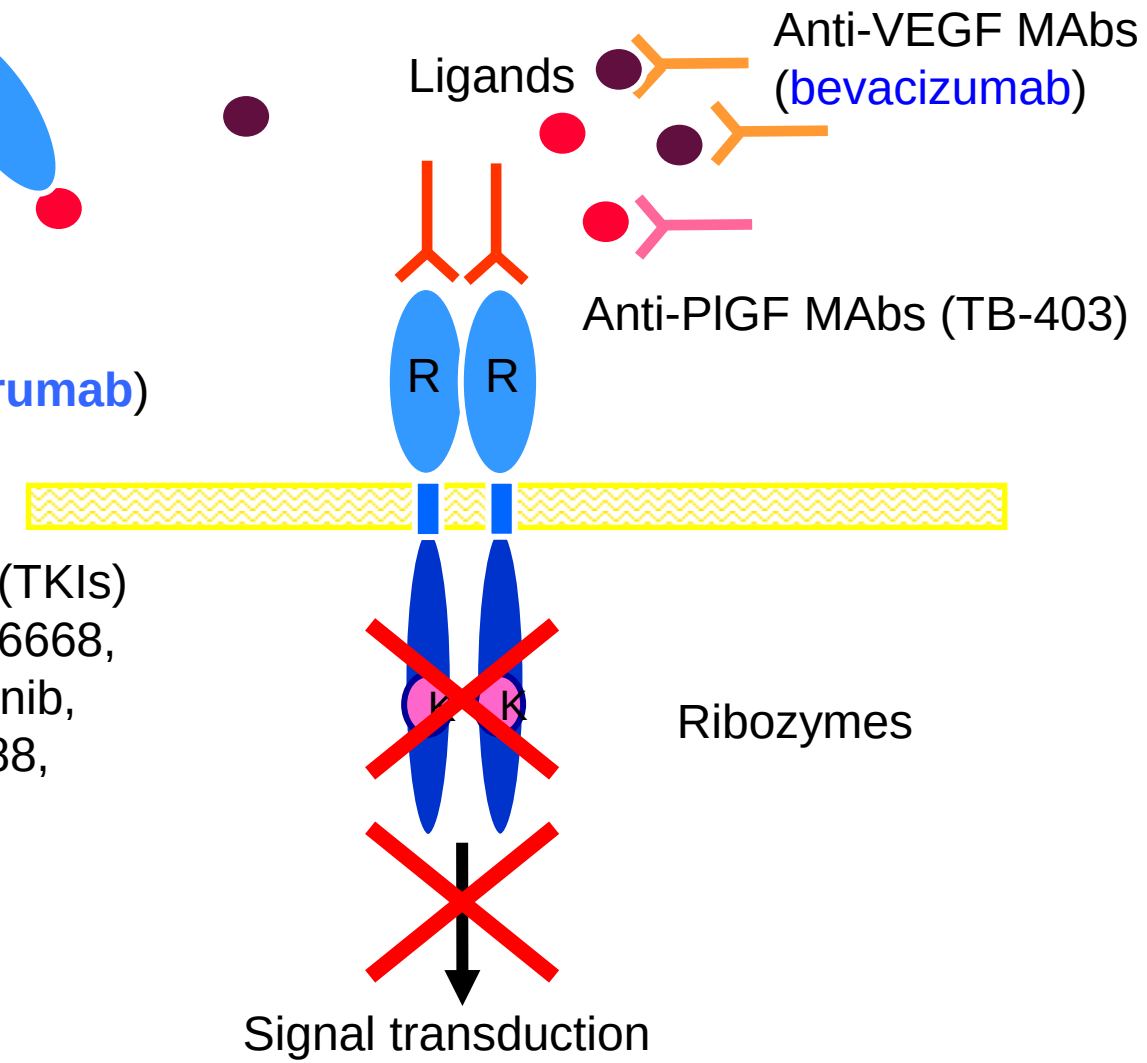
Ford, *et al*.[3]	2014	168 1:1	Docetaxel	0.67	0.01	1.6 months
Otshu, *et al.*[4]	2013	656 2:1	Everolimus	0.90	0.124	0.9 months
Fuchs, *et al*.[5]	**2014**	**355 2:1**	**Ramucirumab**	**0.77**	**0.047**	**1.4 months**

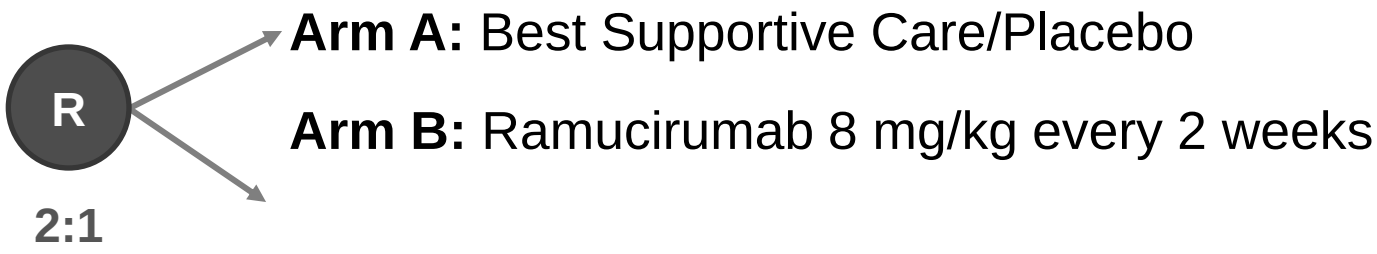
1. Thuss-Patience PC, *et al.* Eur J Cancer 2011;47:2306–2314. 2. Kang JH, *et al*. J Clin Oncol 2012;30:1513–1518.
3. Ford HE, *et al.* Lancet Oncol 2014;15:78–86. 4. Otshu A. *et al*. J Clin Oncol 2013;31:3935–3943.
5. Fuchs CS, *et al*. Lancet 2014;383:31–39.

Clinical anti-VEGF pathway therapies



Modified from Tabernero J, *et al.* Ann Oncol 2005;16:1740–1748, by permission of the European Society of Medical Oncology

Gastric cancer second line treatment: Ramucirumab *vs.* BSC (REGARD Trial)



Main aim: Overall survival

- Stratification by:
  - Weight Loss: < or > 10%
  - Site: Oesophagus *vs.* junction *vs.* gastric
  - Geographic region
- 615 patients needed to show a HR of 0.71 in favour of ramucirumab with two-sided alfa 0.05 and 90% power

Fuchs CS, *et al*. Lancet 2014;383:31–39.

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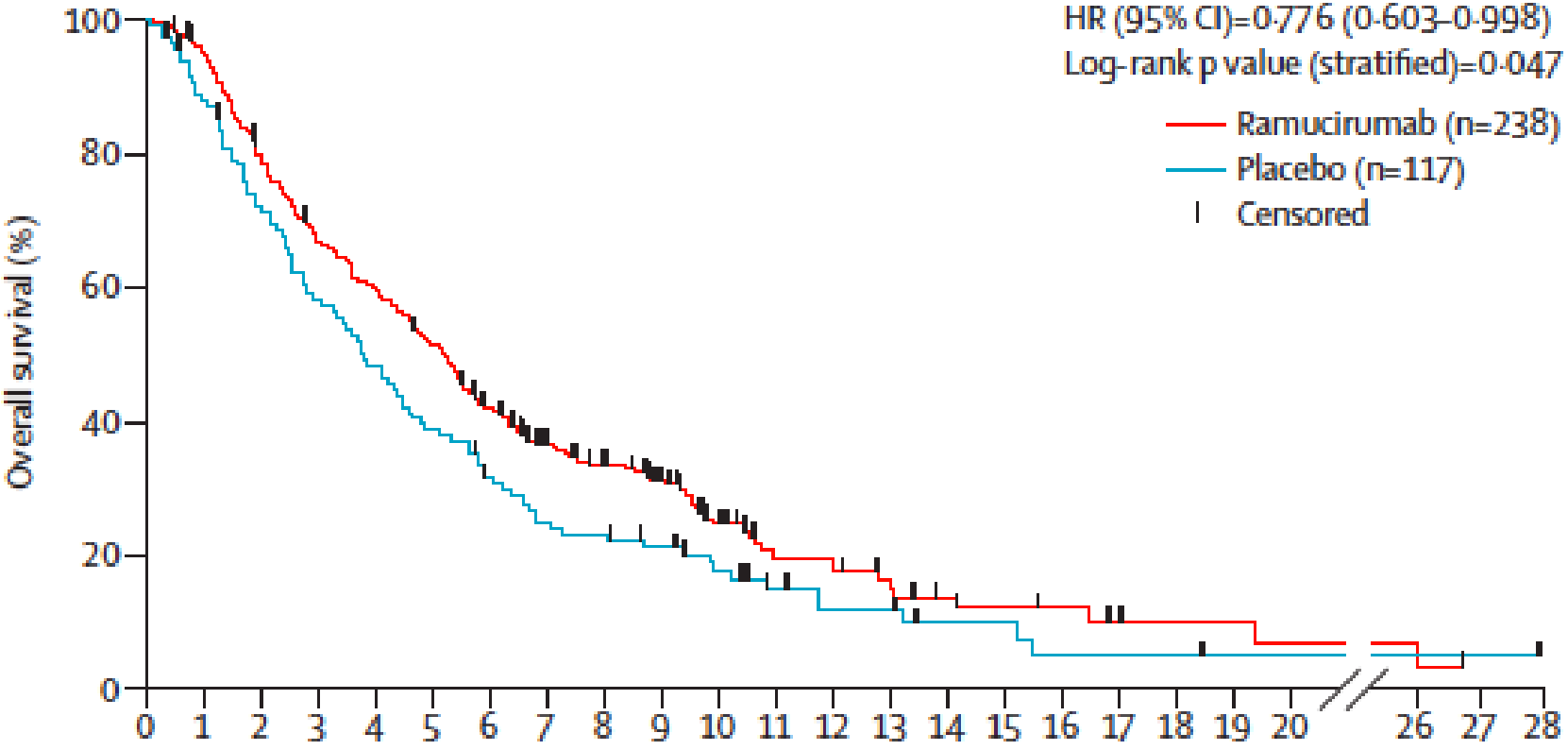
Gastric cancer second line treatment: Ramucirumab *vs.* BSC (REGARD Trial) is improving survival



Number at risk

Ramucirumab	238	154	92	49	17	7	3	0	0
Placebo	117	66	34	20	7	4	2	1	0

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Gastric cancer second line treatment: Ramucirumab *vs.* BSC (REGARD Trial) is improving disease control

	Ramucirumab (n=238)	Placebo (n=117)	P value
Best overall response			
Complete response	1 (<1%)	0	-
Partial response	7 (3%)	3 (3%)	-
Stable disease	108 (45%)	24 (21%)	-
Progressive disease	78 (33%)	63 (54%)	-
Not evaluable	44 (18%)	27 (23%)	-
Objective response	8 (3%)	3 (3%)	0.76
Disease control rate*	116 (49%)	27 (23%)	<0.0001

Data are n (%), unless otherwise indicated. *Denotes best response for complete response, partial response or stable disease.

Fuchs CS, *et al*. Lancet 2014;383:31–39.

Gastric cancer second line treatment: Ramucirumab *vs.* BSC (REGARD Trial) delays deterioration

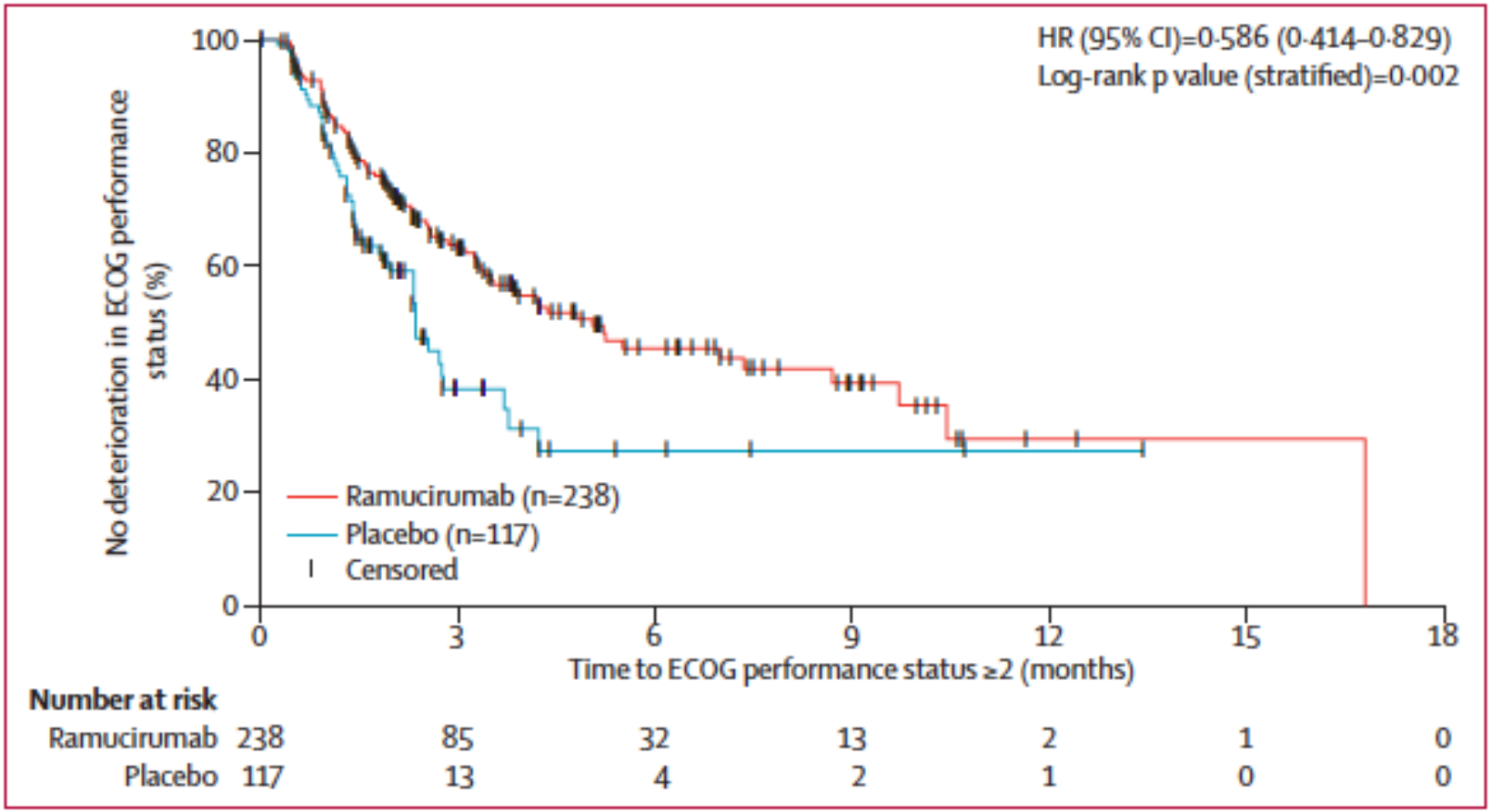

Figure 6: **Time to deterioration in ECOG performance status to a score of 2 or worse**
HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group.

Reprinted from Fuchs CS, *et al.* Lancet Oncol 2014;383:31–39; © (2005) with permission from Elsevier

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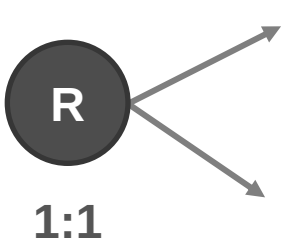
Gastric cancer: Second line chemotherapy trials comparing two active treatments

Trial author	Year	Patients (n)	Treatment	HR OS	P value	Gain in median survival
Hironaka, *et al*.[1]	2013	223	Irinotecan *vs.* paclitaxel	1.13	0.38	0.9 months for irinotecam
Wilke *et al.*[2]	**2014**	**665**	**Paclitaxel+/-ramucirumab**	**0.80**	**0.017**	**2.2 months**

1. Hironaka S, *et al*. J Clin Oncol 2013;31:4438–4444.
2. Wilke H, *et al*. Lancet Oncol 2014;15:1224–1235.

Gastric cancer second line treatment: Paclitaxel+/- Ramucirumab (Rainbow Trial)



Arm A: Paclitaxel 80 mg/m^2 day 1, 8, 14 every 28 days plus Placebo

Arm B: Paclitaxel 80 mg/m^2 day 1, 8, 14 every 28 days
Ramucirumab 8 mg/kg every 2 weeks

Main aim: Overall survival

- Stratification by:
  - Measurable *vs.* non-measurable
  - Time to progression after first line: < or > 6 month
  - Geographic region
- 663 patients needed to show a HR of 0.75 in favour of paclitaxel+ramucirumab with two-sided alfa 0.05 and 90% power

Wilke HJ, *et al*. Lancet Oncol 2014;15:1224–1235.

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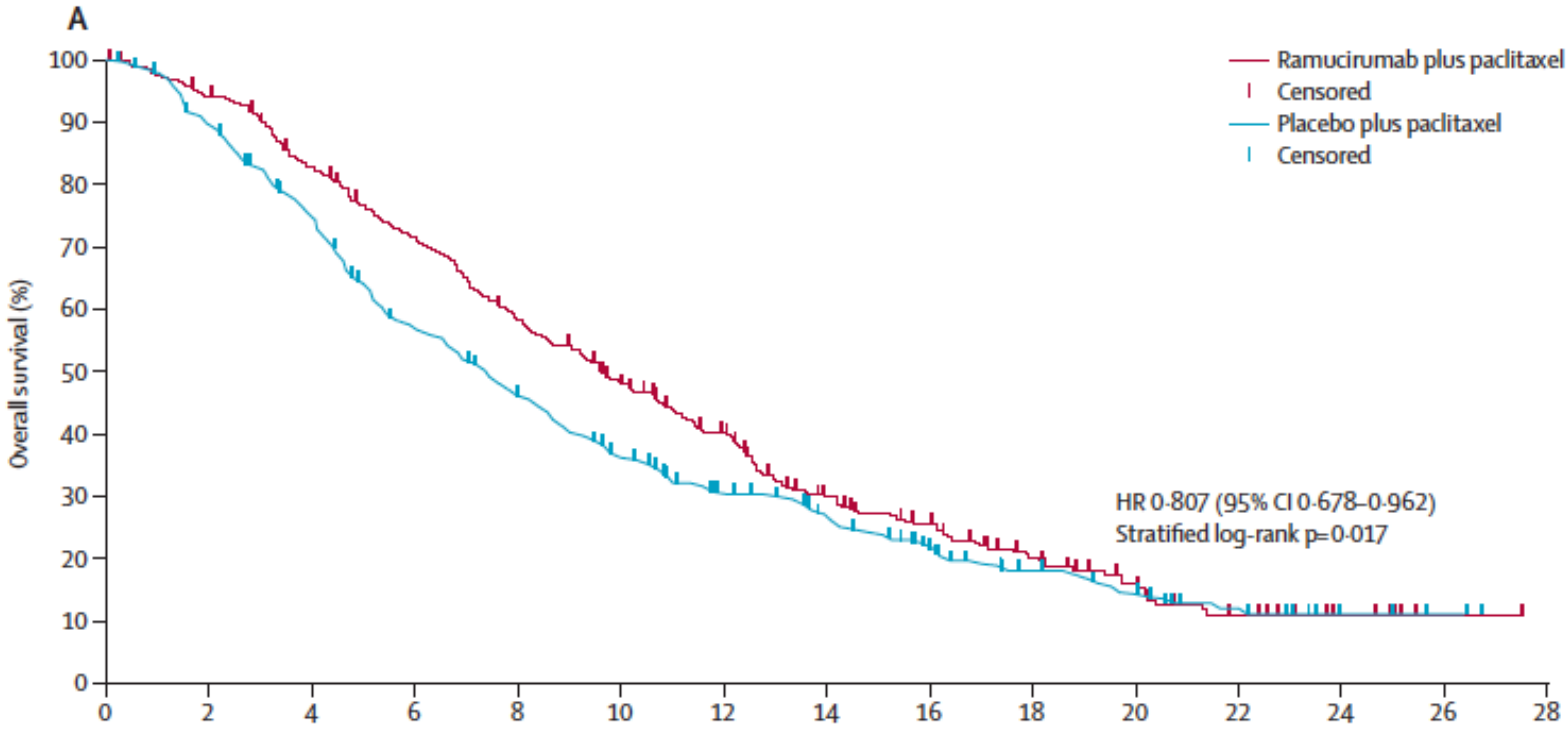
Gastric cancer second line treatment: Addition of ramucirumab to paclitaxel improves overall survival (Rainbow Trial)



Number at risk															
Ramucirumab plus paclitaxel	330	308	267	228	185	148	116	78	60	41	24	13	6	1	0
Placebo plus paclitaxel	335	294	241	180	143	109	81	64	47	30	22	13	5	2	0

Wilke HJ, *et al*. Lancet Oncol 2014;15:1224–1235; © (2005) with permission from Elsevier

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Gastric cancer second line treatment: Addition of Ramucirumab to paclitaxel improves response rate (Rainbow Trial)

	Ramucirumab plus paclitaxel (N=330)	Placebo plus paclitaxel (N=335)
Best overall response		
Complete response	2 (<1%)	1 (<1%)
Partial response	90 (27%)	53 (16%)
Stable disease	172 (52%)	159 (47%)
Progressive disease	43 (13%)	83 (25%)
Not evaluable or not assessed	23 (7%)	39 (12%)

Data are number (%) or number (%; 95% CI), unless otherwise indicated.

Wilke HJ, *et al*. Lancet Oncol 2014;15:1224–1235.

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Gastric cancer second line treatment: Addition of Ramucirumab to paclitaxel is tolerable (Rainbow Trial)

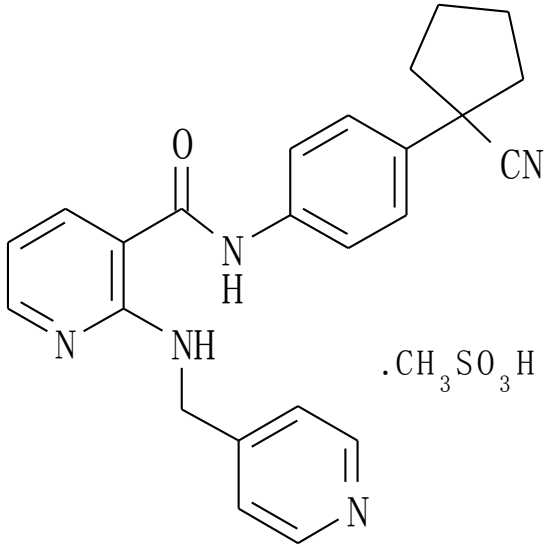
	Ramucirumab plus paclitaxel (n=327)				Placebo plus paclitaxel (n=329)			
	Grades 1-2	**Grade 3**	**Grade 4**	**Grade 5**	**Grades 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Bleeding or haemorrhage	123 (38%)	12 (4%)	1 (<1%)	1 (<1%)	51 (16%)	4 (1%)	2 (<1%)	2 (<1%)
Proteinuria	51 (16%)	4 (1%)	0	0	20 (6%)	0	0	0
Liver injury or failure	39 (12%)	12 (4%)	3 (<1%)	0	28 (9%)	11 (3%)	2 (<1%)	0
Hypertension	34 (10%)	48 (15%)	0	0	10 (3%)	9 (3%)	0	0
Gastrointestinal haemorrhage	21 (6%)	10 (3%)	1 (<1%)	1 (<1%)	15 (5%)	3 (<1%)	1 (<1%)	1 (<1%)

Wilke HJ, *et al.* Lancet Oncol 2014;15:1224–1235.

Background of apatinib

- Apatinib (YN968D1)[1]
  - A new small molecular tyrosine kinase inhibitor that highly and selectively inhibits the VEGFR2
  - The MTD is determined to be 850 mg/day administered orally

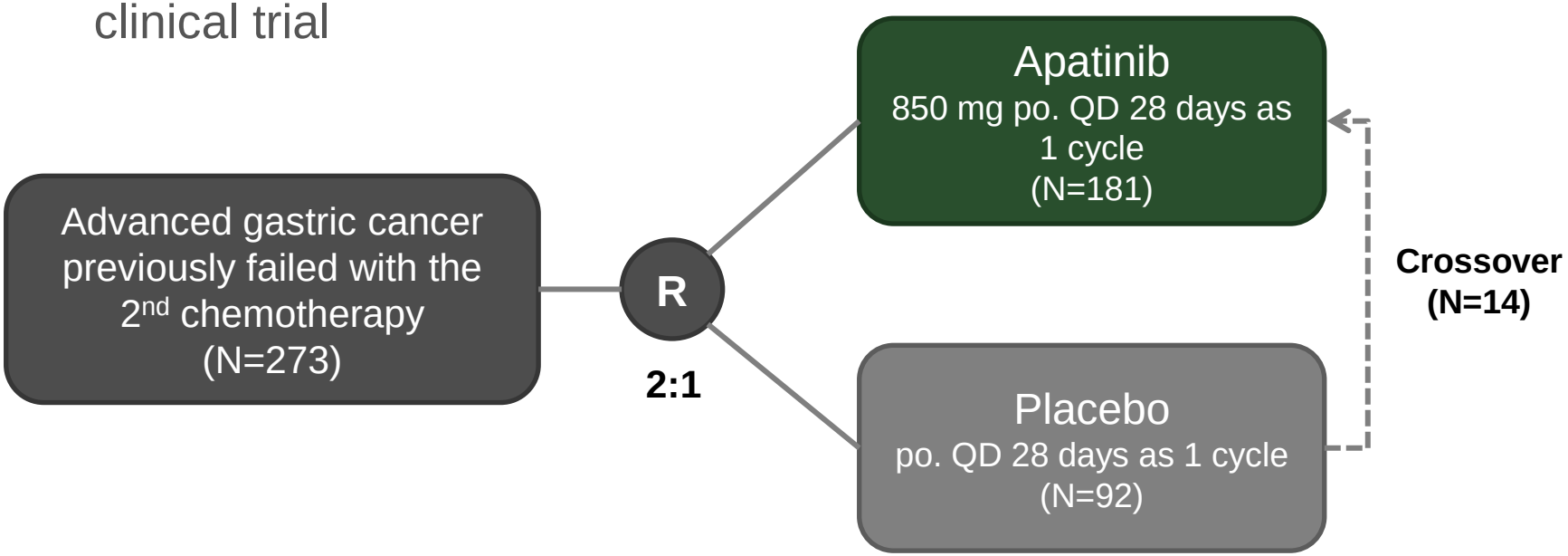
- Phase I / IIa study (N=65)[1]
  - CR: 1.54%, PR: 12.31%, SD: 66.15%
  - DCR: 80.00%
  - PD: 20.00%



Li J, *et al*. J Clin Oncol 2013;31:3219–3225.

Apatinib in a Phase III Study design *vs.* placebo

- Design: Multicenter, randomized, double-blind, placebo-controlled clinical trial



- 1 treatment cycle = 28 days
- Stratification factor: Number of metastatic sites (≤ 2 vs. >2)

Qin S, *et al.* J Clin Oncol 2014:32(5 suppl):Abstract 4008.

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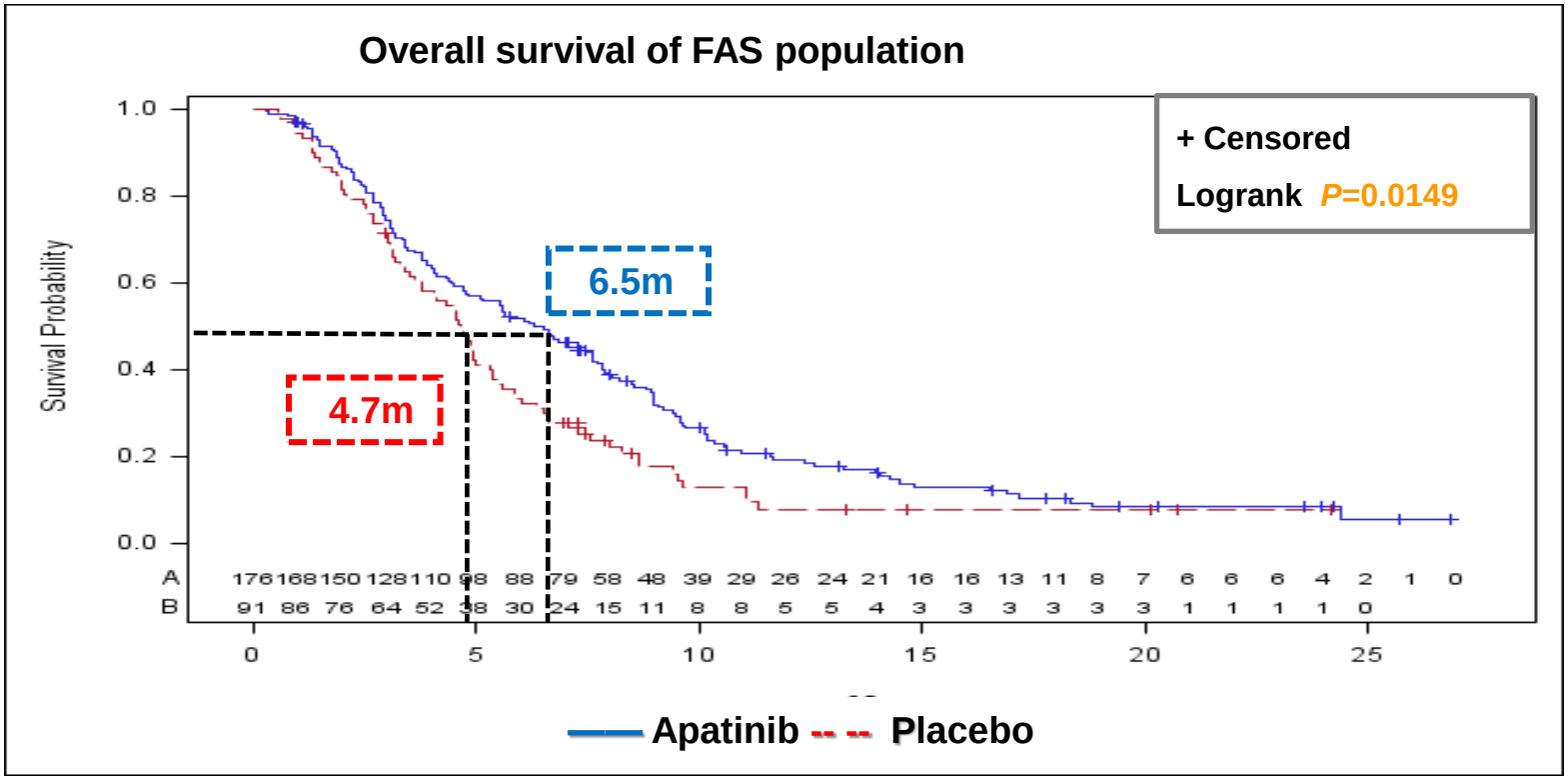
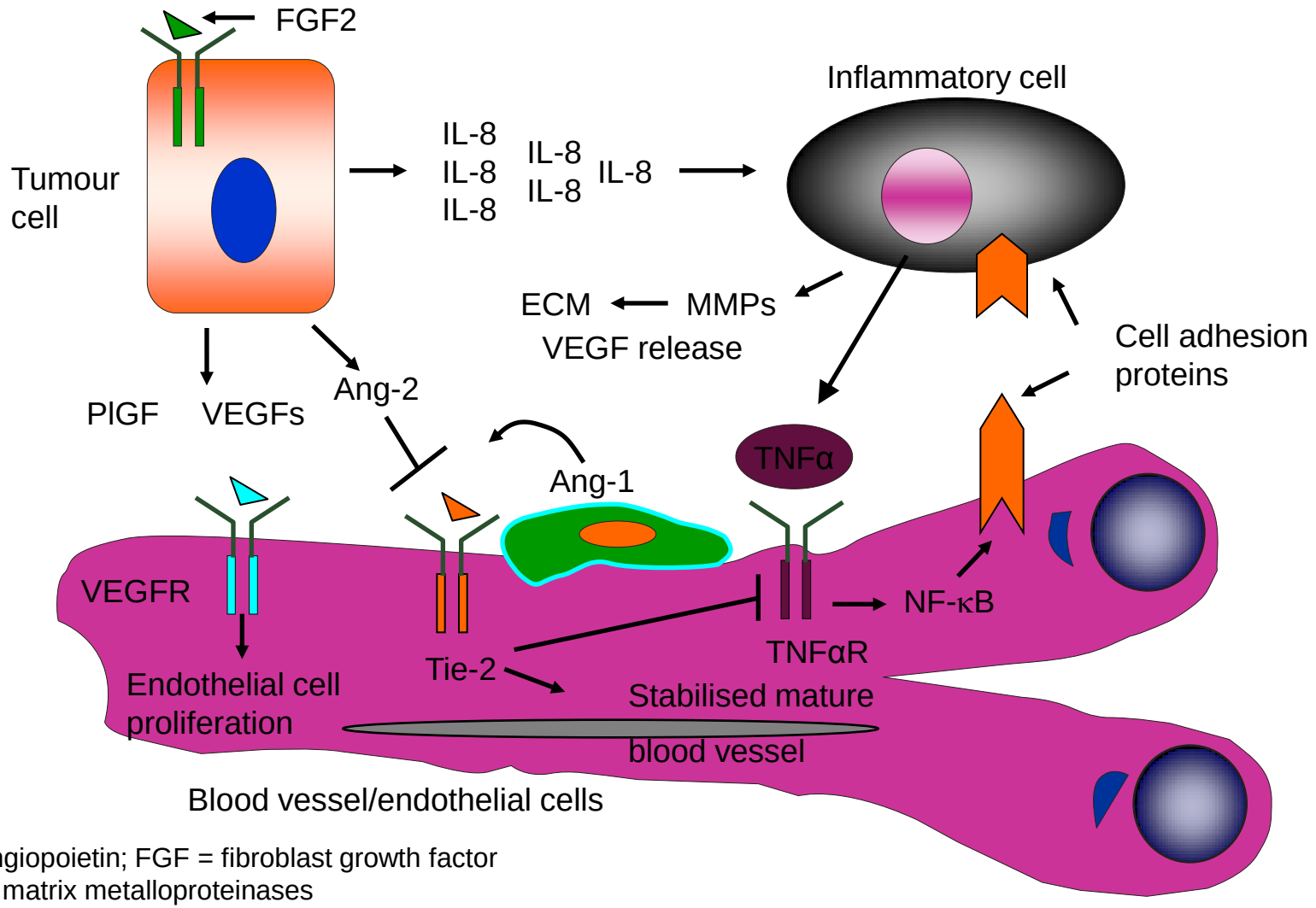
Apatinib improves survival in third line for advanced gastric cancer



Group	n	mOS (95% CI), months	P value	HR (95%CI)
Apatinib	176	6.5 (4.8–7.6)	0.0149	0.709 (0.537–0.937)
Placebo	91	4.7 (3.6–5.4)		

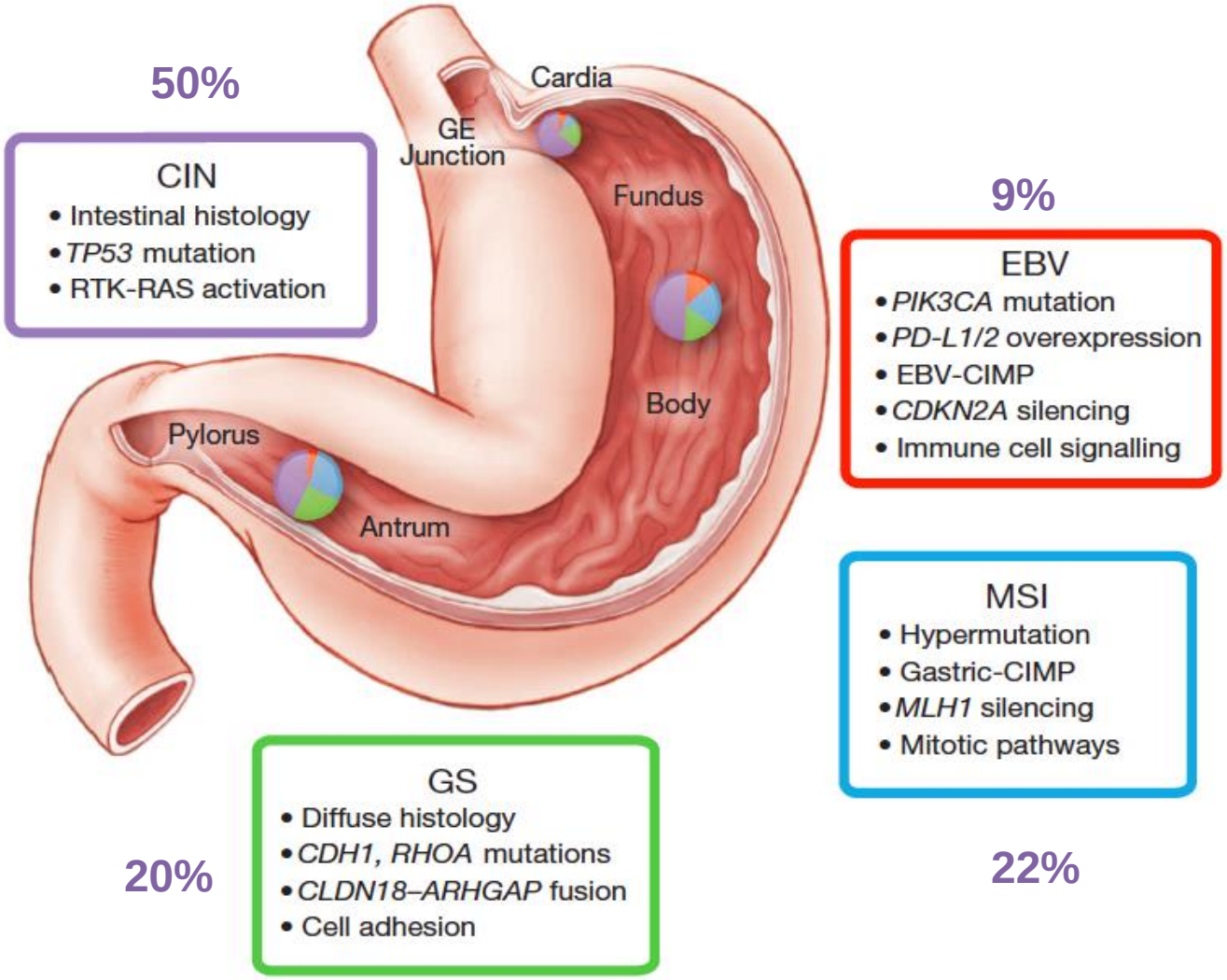
Qin S, *et al*. J Clin Oncol 2014:32(5 suppl):Abstract 4008.

Angiogenesis: a multiple signalling process



Ang = angiopoietin; FGF = fibroblast growth factor
MMPs = matrix metalloproteinases
TNF = tumour necrosis factor; VEGFR = VEGF receptor
PlGF = placental growth factor

Modified from Acevedo, et al. Cell Cycle 2009



Cancer Genome Atlas Research Network. Nature 2014;513:202–209. Available under a CC BY-NC 4.0 licence

Conclusions

- Gastric cancer remains difficult to treat
- Not all gastric cancers the same
- 4 active classes of cytotoxics: fluoropyrimidines, platins, taxanes, irinotecan. Most frequently as doublet used.
- Trastuzumab is the first biological to show a survival benefit in gastric cancer.
  - Selected population: HER2 +
- **Ramucirumab has shown a survival benefit in the 2nd line setting**
  - **Unselected population**
- Other targeted agents under investigation
  - PI3K pathway, angiogenesis, new HER-2 blockers, HGF-c-Met, FGFR, ….
- **Additional research for molecular characterization and prognostic/predictive markers is important**

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