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Optimising anti-angiogenic strategies in gastric adenocarcinoma

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INTRODUCTION

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Gastric adenocarcinoma

- Although its overall incidence is constantly decreasing, gastric adenocarcinoma remains the fourth leading cause of cancer death worldwide[1]

- In patients with operable disease, surgery alone results in relatively poor long-term survival. In this situation, patients benefit from perioperative chemotherapy, adjuvant chemotherapy, or post-operative chemoradiation[2-5]

1. Jemal A, *et al.* CA Cancer J Clin 2011;61:69-90;
2. Cunningham D, *et al.* N Engl J Med 2006;355:11-20;
3. Ychou M, *et al*. J Clin Oncol 2011;29:1715-21;
4. GASTRIC Group. JAMA 2010;303:1729-37;
5. Macdonald JS, *et al.* N Engl J Med 2001;345:725-30

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Treatment of HER-2 negative metastatic gastric adenocarcinoma in the first-line setting

- In patients with advanced disease, combination chemotherapy has proven a survival benefit over best supportive care alone and is the corner-stone of the treatment for patients with human epidermal growth factor receptor 2 (HER-2) negative disease

- Although there is no international consensus regarding the optimal first-line chemotherapy regimen, a doublet with a platinum and fluoropyrimidine or a triplet regimen with the addition of docetaxel or epirubicin is frequently used

- The median overall survival of HER-2 negative metastatic patients is between 9 months and 1 year

Cunningham D, *et al*. N Engl J Med 2008;358:36-46;
Van Cutsem E, *et al*. J Clin Oncol 2006;24:4991-7;
Cunningham D, *et al*. N Engl J Med 2008;358:36-46

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Treatment of HER-2 positive metastatic gastric adenocarcinoma in the first-line setting

- For patients with HER-2 positive tumour, trastuzumab has become, in association with platinum and fluoropyrimidine doublet, the standard of care in the first-line metastatic setting, since the randomised phase III ToGA (Trastuzumab for Gastric Cancer) study

- In this study, patients have a significantly increase of their median overall survival with trastuzumab: 13.8 months *versus* 11.1 months with chemotherapy alone
(HR=0.74; [95%CI: 0.60- 0.91] (p=0.0046))

- Continuing trastuzumab beyond progression is still a non answered question

Bang YJ, Lancet 2010;376:687-97

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Angiogenesis in cancer

- Angiogenesis is the formation of new blood vessels from pre-existing vessels and is an essential process in malignant tumour growth, progression and metastasising process

- Vascular Endothelial Growth Factors (VEGF) and VEGF receptors (VEGFRs) are known as a the main part of the angiogenesis signaling pathways since the early 1990s

Kerbel R, Folkman J. Nat Rev Cancer 2002;2:727-39

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Angiogenesis in cancer

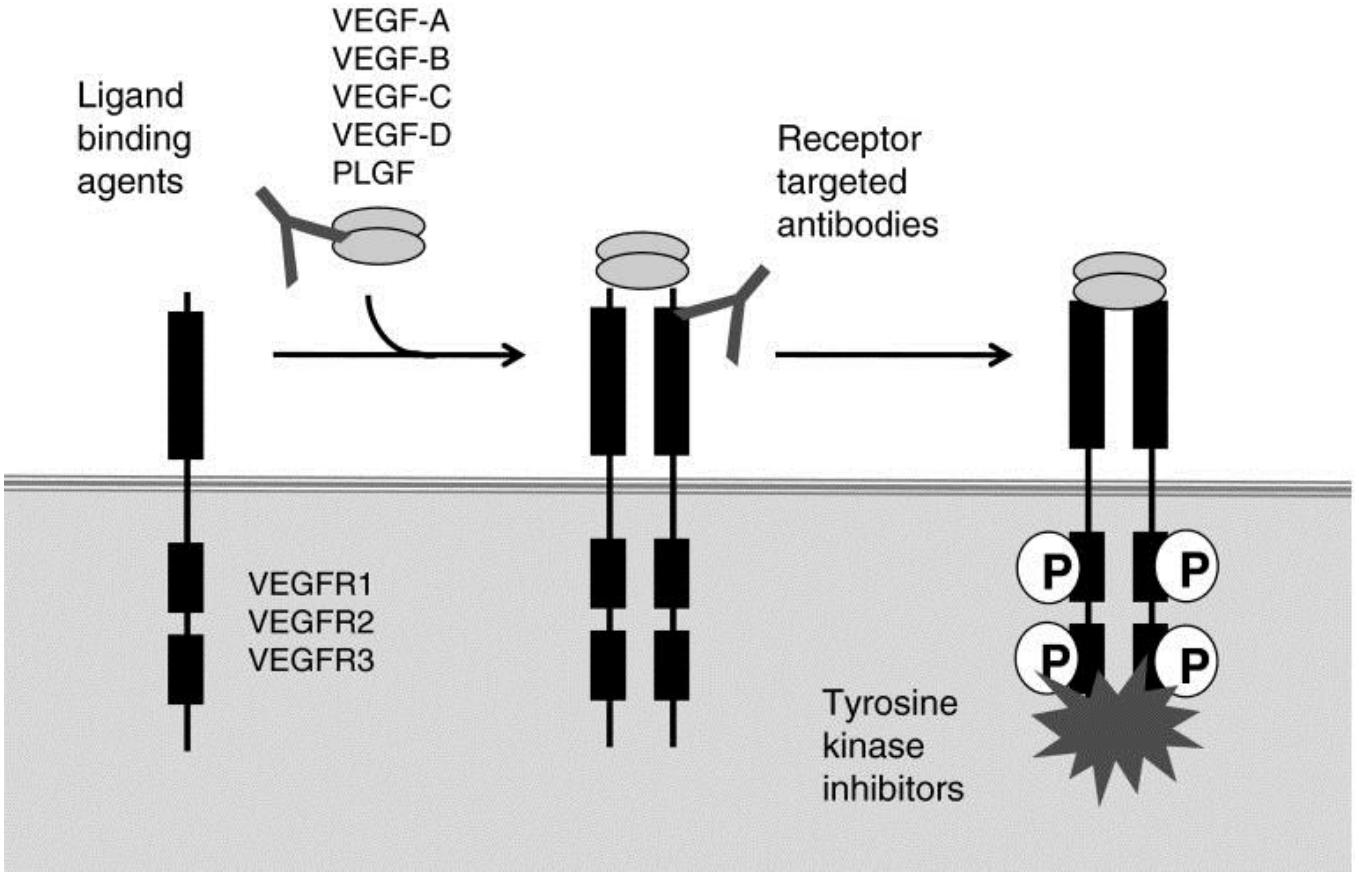
- There are 5 members of the VEGF family (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E), and 2 placental growth factors (PlGF-1,-2)

- There are 3 VEGFRs: VEGFR-1 and -2, mostly expressed in endothelial cells whereas VEGFR-3 has been found mostly associated with lymphangiogenesis

Kerbel R, Folkman J. Nat Rev Cancer 2002;2:727-39

Angiogenesis in cancer

- The majority of anti-angiogenic treatment used in the clinic are based upon the inhibition of VEGF/VEGFR signalling



Angiogenesis in gastric cancer

- Neoplastic angiogenesis and lymphangiogenesis represent a critical process for tumour growth, invasion and metastatic spread
  - Altered or abnormal expression of tumour angiogenesis-related factors is associated with poor prognosis in several tumour types, including gastric cancer

Carmeliet P, Jain RK. Nature 2000;407:249-57
Takahashi Y, *et al*. Clin Cancer Res 1996;2:1679-84
Peng L, *et al.* Mol Biol Rep 2012;39:9473-84
Maeda K., *et al.* Cancer 1996;77:858–863

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Angiogenesis in gastric cancer

- Tumour angiogenesis has also been associated with response or resistance to chemotherapy in several clinical and preclinical models
  - Hypoxic conditions could impair tumour drug penetration thus limiting chemotherapy efficacy
  - VEGF polymorphisms may have predictive role in platinum-based chemotherapy sensitivity

Brown JM, Wilson WR. Nat Rev Cancer 2004;4:437-47;
Van der Veldt AA, *et al*. Cancer Cell 2012 17;21:82-91;
Roberts DL, *et al*. Br J Cancer 2009;101:1290-7;
Kim JG, *et al.* Ann Oncol 2007;18:1030-6

Angiogenesis in gastric cancer preclinical data

- In patients with gastric cancer, circulating VEGF levels are associated with increased tumour aggressiveness and reduced survival[1,2]

- In animal models of gastric adenocarcinoma, VEGF/VEGFR inhibition reduced tumour growth and vascularity[3]

1. Karayiannakis AJ, *et al.* Ann Surg. 2002;236:37-42;
2. Villarejo-Campos P, *et al*. Clin Transl Oncol 2013;15:265-70;
3. Kanai T, *et al*. Int J Cancer 1997;71:838-41

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Angiogenesis in gastric cancer clinical data

- Monoclonal antibodies, soluble receptors, and small-molecule tyrosine kinase inhibitors have been developed to inhibit tumour angiogenesis
- Several of these drugs have been tested in phase II studies in gastric cancer
- Three drugs, bevacizumab, ramucirumab and apatinib, have been evaluated in phase III trials

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BEVACIZUMAB

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Angiogenesis in gastric cancer bevacizumab

- Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF)-A

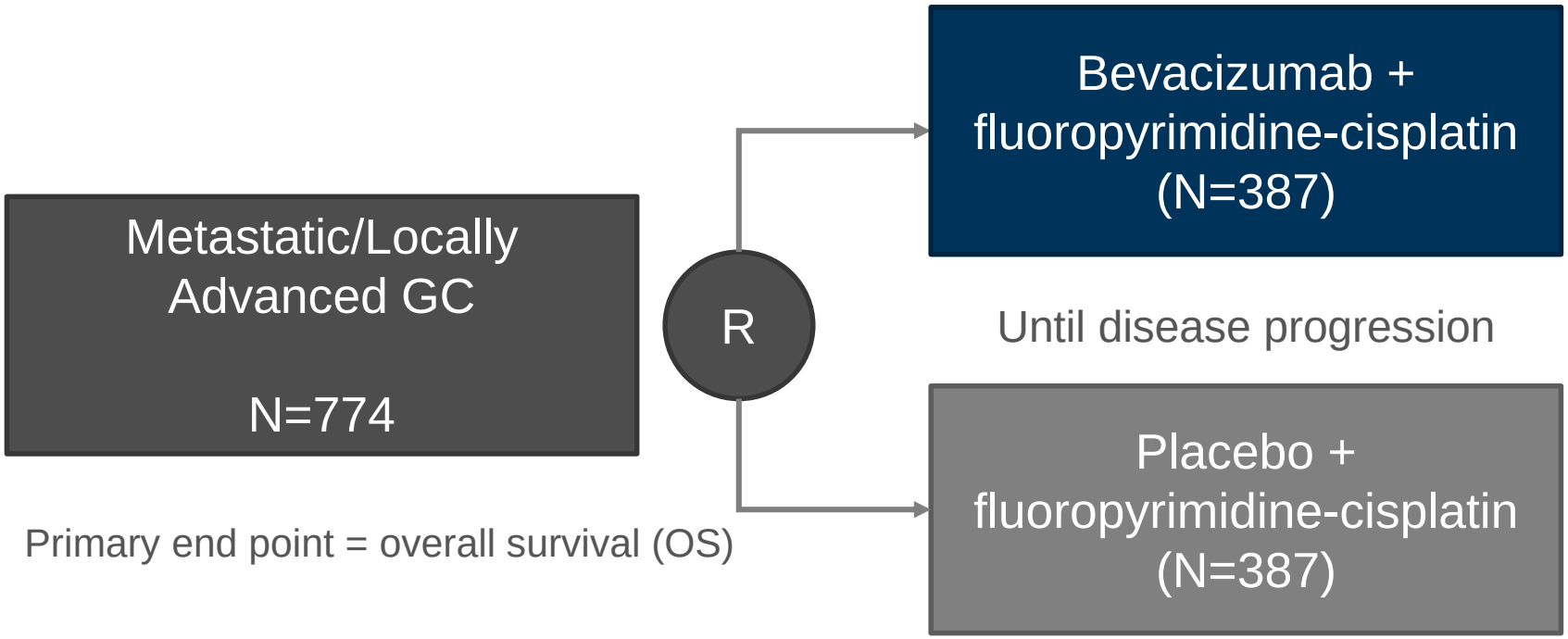
- Encouraging results* were reported in combination with chemotherapy in first-line metastatic setting in phase II studies

Reference	Regimen	N	ORR (%)	Median PFS Months (95%CI)	Median OS Months (95%CI)
Shah MA 2006	Irinotecan-cisplatin BEV	47	65	8.3 (5.5-9.9)	12.3 (11.3-17.2)
El-Rayes BF 2010	Docetaxel-Oxaliplatin BEV	38	42	6.6 (4.4-10.5)	11.1 (8.2-15.3)
Uronis HE 2013	Capecitabine-Oxaliplatin BEV	35	51.4	7.2 (5.4–8.5)	10.8 (8.7–14.5)

* Published results

Angiogenesis in gastric cancer bevacizumab

- **AVAGAST** (Avastin for Advanced Gastric Cancer) study was the randomised phase III clinical trial evaluating the efficacy of bevacizumab in combination with chemotherapy



Ohtsu A, *et al.* J Clin Oncol 2011;29:3968-3976

Angiogenesis in gastric cancer bevacizumab

- **AVAGAST** study: patients profile

	Fluoropyrimidine-cisplatin + bevacizumab (n=387)	Fluoropyrimidine-cisplatin + placebo (n=387)
Geographic region		
Asia-Pacific	188 (49%)	188 (49%)
Europe	125 (32%)	124 (32%)
Pan America	74 (19%)	75 (19%)
Site of primary tumour		
Gastric	333 (86%)	338 (87%)
Gastro-oesophageal junction	54 (14%)	49 (13%)

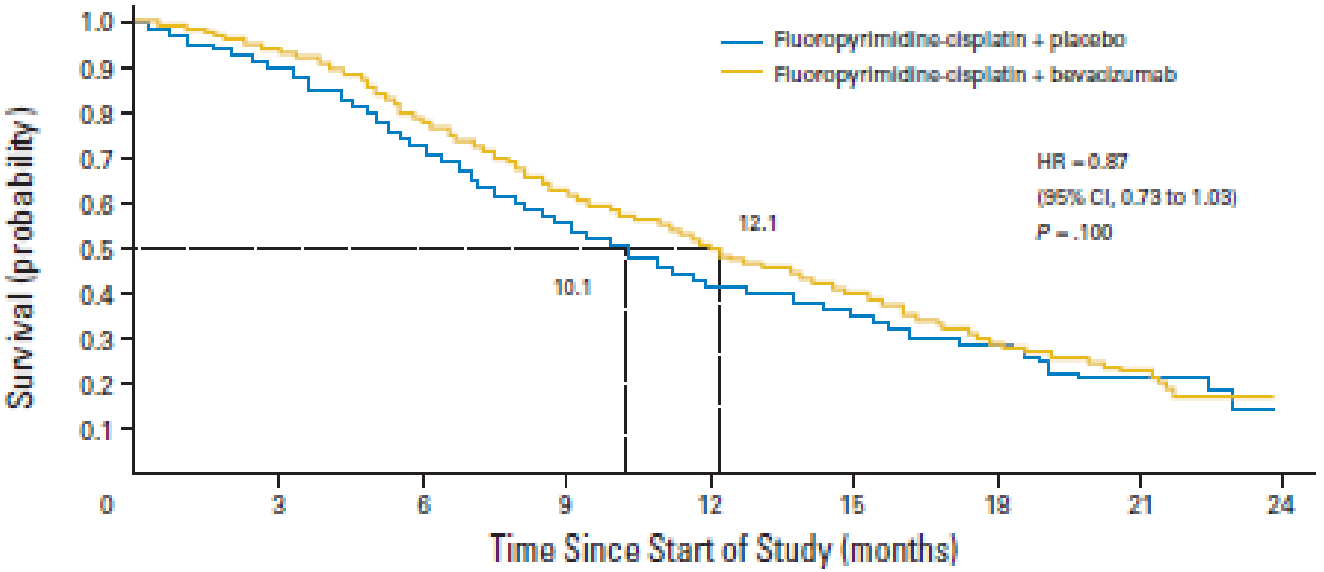
Ohtsu A, *et al.* J Clin Oncol 2011;29:3968-3976

Angiogenesis in gastric cancer bevacizumab

The adjunction of bevacizumab showed no significant increase in overall survival: HR=0.87 (95%CI 0.73-1.03) p=0.1002

Median Overall Survival: 12.1 *vs.* 10.1 months

Primary end point

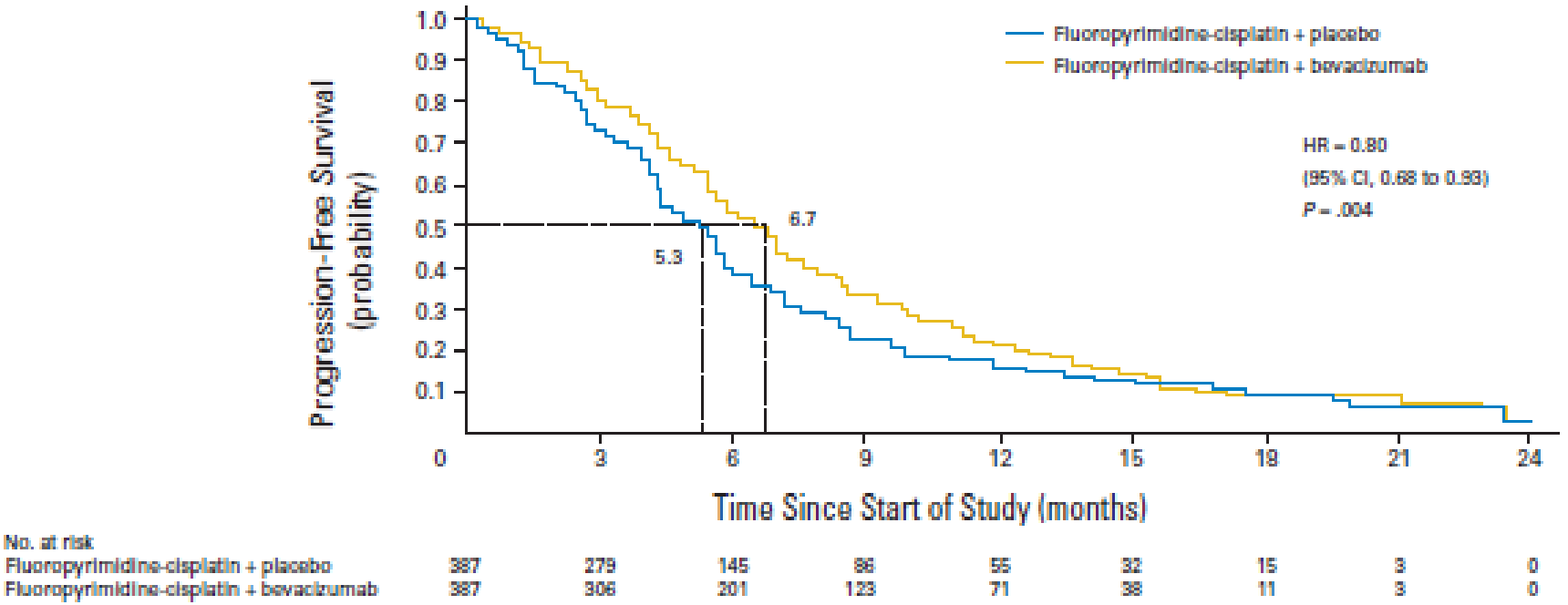


No. at risk									
Fluoropyrimidine-cisplatin + placebo	387	343	271	204	146	98	54	15	0
Fluoropyrimidine-cisplatin + bevacizumab	387	355	291	232	178	104	50	19	0

Ohtsu A, *et al*. J Clin Oncol 2011;29:3968-3976. Reprinted with permission.

Angiogenesis in gastric cancer bevacizumab

The adjunction of bevacizumab significantly increased the progression-free survival: HR=0.80 (95%CI 0.68-0.93) p=0.0037; Median PFS: 6.7 *vs.* 5.3 months



Angiogenesis in gastric cancer bevacizumab

The adjunction of bevacizumab significantly increased the response rate

Response	Bevacizumab	Placebo	p
Overall response rate	46% 40.3 to 51.7	37.4% 31.9 to 43.1	0.0315
Complete response	1.6%	1%	
Partial response	44.4%	36.4	
Stable disease	29.9%	30.3%	

Unadjusted analysis of efficacy (intention-to-treat population)

Ohtsu A, *et al*. J Clin Oncol 2011;29:3968-3976

Angiogenesis in gastric cancer bevacizumab

Adverse events

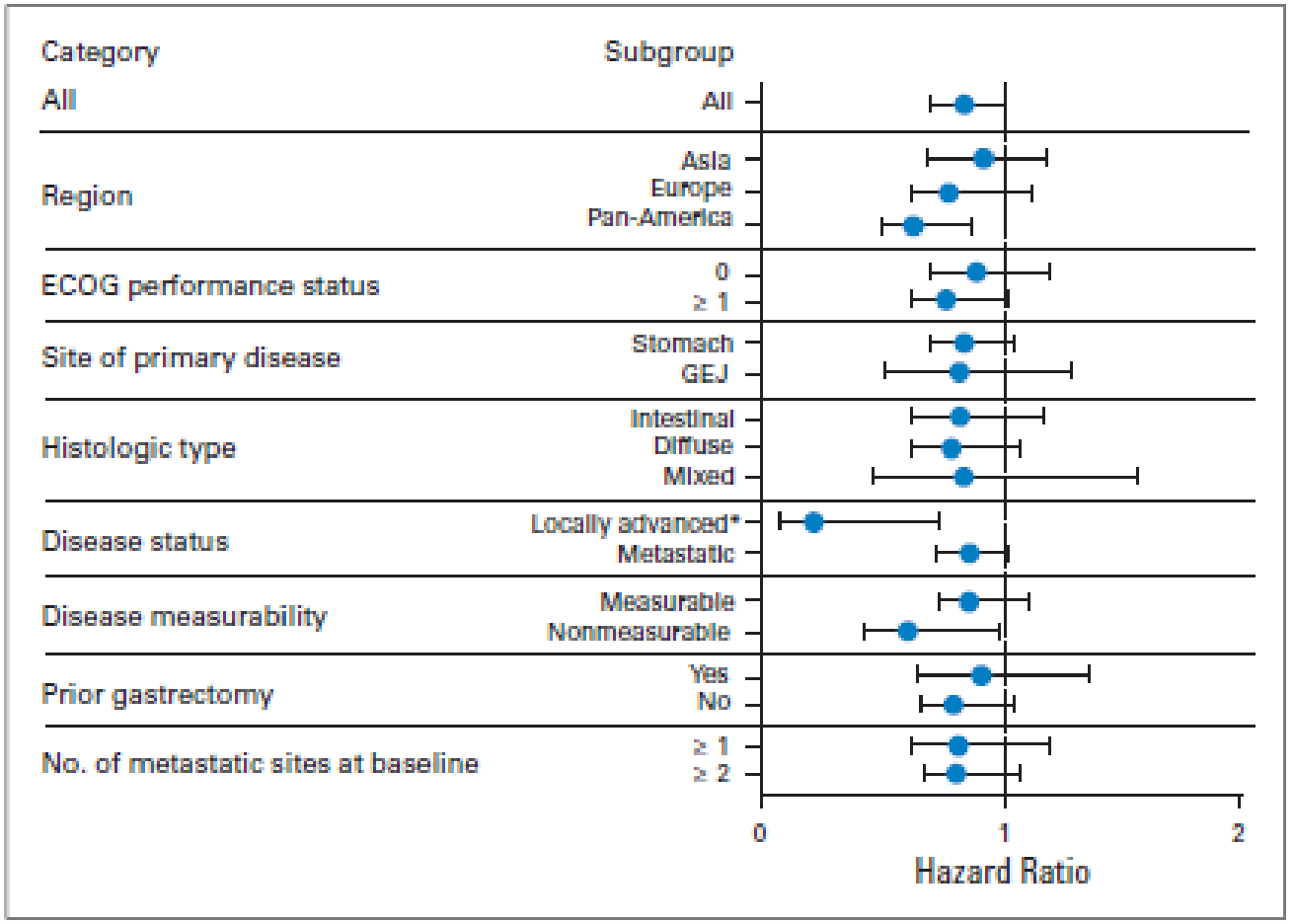
- The overall incidence of grade 3 to 5 adverse events was 76% in the bevacizumab group and 77% in the placebo group
- **Diarrhea** (D) and **hand-foot syndrome** (HFS) incidences were increased in the bevacizumab arm (D: 8% *vs.* 4%) (HFS 6% *vs.* 3%)
- As expected, a higher incidence of **hypertension** (HTN) and **GI perforation** were noted in the bevacizumab group (g3 HTN 6% *vs.* 1%) (GI perforation 2% *vs.* 1%)
- Venous/Arterial thromboembolic events and bleeding were both similar in the 2 treatment arms

Ohtsu A, *et al*. J Clin Oncol 2011;29:3968-3976

Angiogenesis in gastric cancer bevacizumab

Possible regional variation in efficacy?

A greater benefit in South America, North America and Europe (*vs.* Asia) ?



Angiogenesis in gastric cancer bevacizumab

Possible regional variation in efficacy?

- Differences in efficacy results between Asian and Non-Asian patients were not explained by significant difference in bevacizumab pharmacokinetics[1]

- The phase III AVATAR study recently showed no improvement in OS or PFS in Chinese patients treated with bevacizumab plus capecitabine and cisplatin[2]

1. Han K, *et al*. AAPS J. 2014;16:1056-63;
2. Shen L, *et al*. Gastric Cancer 2015;18:168-76

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Angiogenesis in gastric cancer bevacizumab: Biomarkers study

- In AVAGAST, **high baseline plasma levels of VEGF-A and low neuropilin-1 tumour expression (IHC)** seemed to have both prognostic and predictive roles in **non-Asian** patients treated with bevacizumab

- **On the contrary**, patients from **Asia-Pacific** had:
  - Lower baseline VEGF-A levels and those with high baseline VEGF-A levels did not demonstrate benefit from bevacizumab
  - A lower Neuropilin-1 expression score (maybe confounded by the tissue acquisition)

Van Cutsem E, *et al.* J Clin Oncol 2012;30:2119-27

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Angiogenesis in gastric cancer bevacizumab in perioperative setting

- **ST03 (MAGIC-B)** was a multicentre, randomised, phase II/III study comparing perioperative ECX with or without bevacizumab (ECX-B)
  - 1063 patients were recruited in the phase III

- 200 eligible patients with histologically proven gastric or oesophago-gastric junction (OGJ) adenocarcinoma (Siewert type II or III), stage Ib-IV (T4N1-2M0) has been randomised in the phase II part of the trial. In the first analysis, wound-healing complications and tumour perforations were not increased by bevacizumab[1]

- Final results showed no improvement in overall, disease-free or progression-free survival with bevacizumab and suggest an increased risk of post-operative anastomotic leak [2]

1. Okines AF, *et al*. Ann Oncol 2013;24:702–709
2. Cunningham D, *et al.* Abstract 2201, European Cancer Congress 2015

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Optimising anti-angiogenic strategies in gastric adenocarcinoma

RAMUCIRUMAB

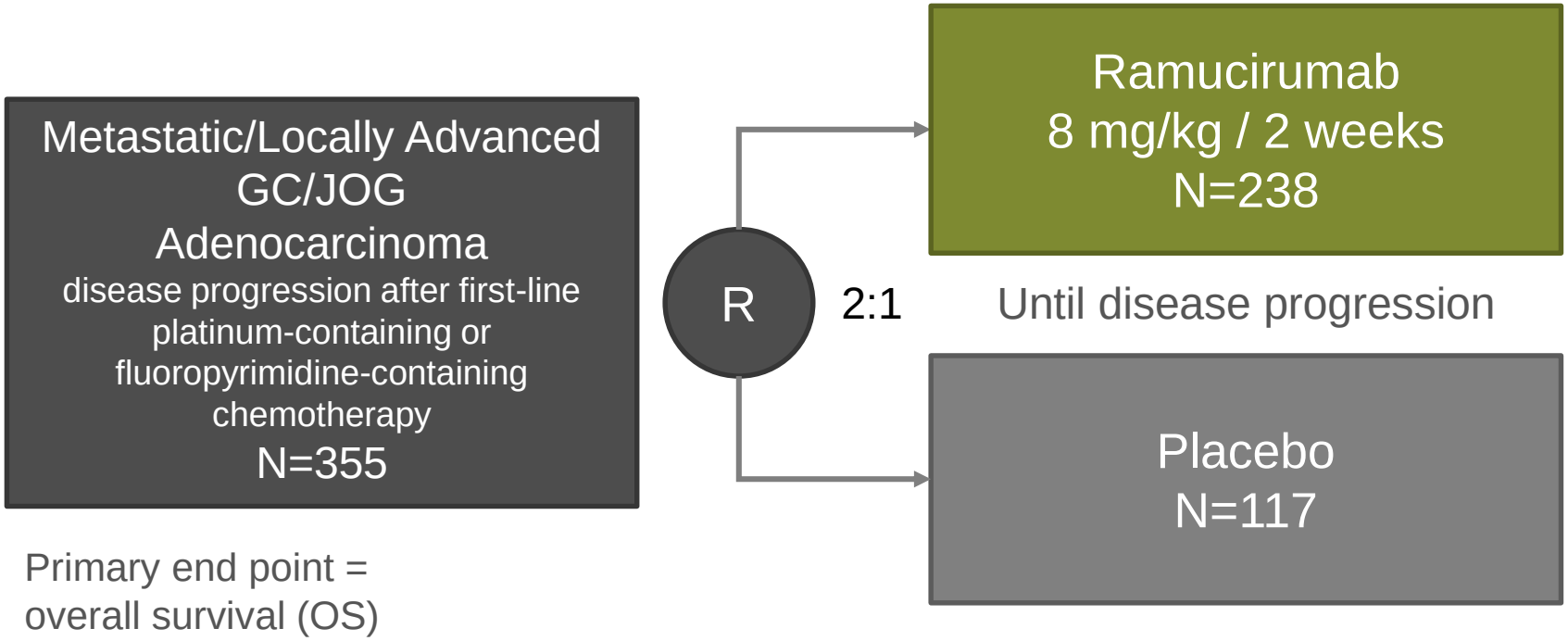
Angiogenesis in gastric cancer ramucirumab

- Ramucirumab (IMC-1121B, LY3009806) is a fully humanised monoclonal antibody directed against the extracellular domain of VEGFR-2
- In a phase I study of 37 patients, 4 partial responses (11%) were observed, including one with previously treated gastric cancer
  - The safety profile was similar to that of bevacizumab, with serious adverse events including dose-related hypertension, venous thromboembolism and proteinuria
- Two phase III studies were designed in GC: REGARD and RAINBOW trials

Spratlin J, *et al*. J Clin Oncol 2010;28:780-7

Angiogenesis in gastric cancer ramucirumab

- **REGARD** study was an international, randomised, double-blind, placebo-controlled phase 3 trial evaluating ramucirumab monotherapy in second-line setting



Primary end point = overall survival (OS)

Fuchs CS, *et al.* Lancet 2014;383:31-9

Angiogenesis in gastric cancer ramucirumab

- **REGARD** study: patients profile

	Ramucirumab (n=238)	Placebo (n=117)
Race (by self report)		
White	181 (76%)	91 (78%)
Asian	39 (16%)	17 (15%)
Black	4 (2%)	2 (2%)
Other	14 (6%)	7 (6%)
Geographic region		
▪ North America, Europe, Australia, New Zealand	165 (69%)	80 (68%)
▪ Asia	18 (8%)	8 (7%)
▪ South/Central America, India, South-Africa, Middle East	55 (23%)	29 (25%)
Site of primary tumour		
Gastric	178 (75%)	87 (74%)
Gastro-oesophageal junction	60 (25%)	30 (26%)

Fuchs CS, *et al*. Lancet 2014;383:31-9

Angiogenesis in gastric cancer ramucirumab

- **REGARD** study: patients profile

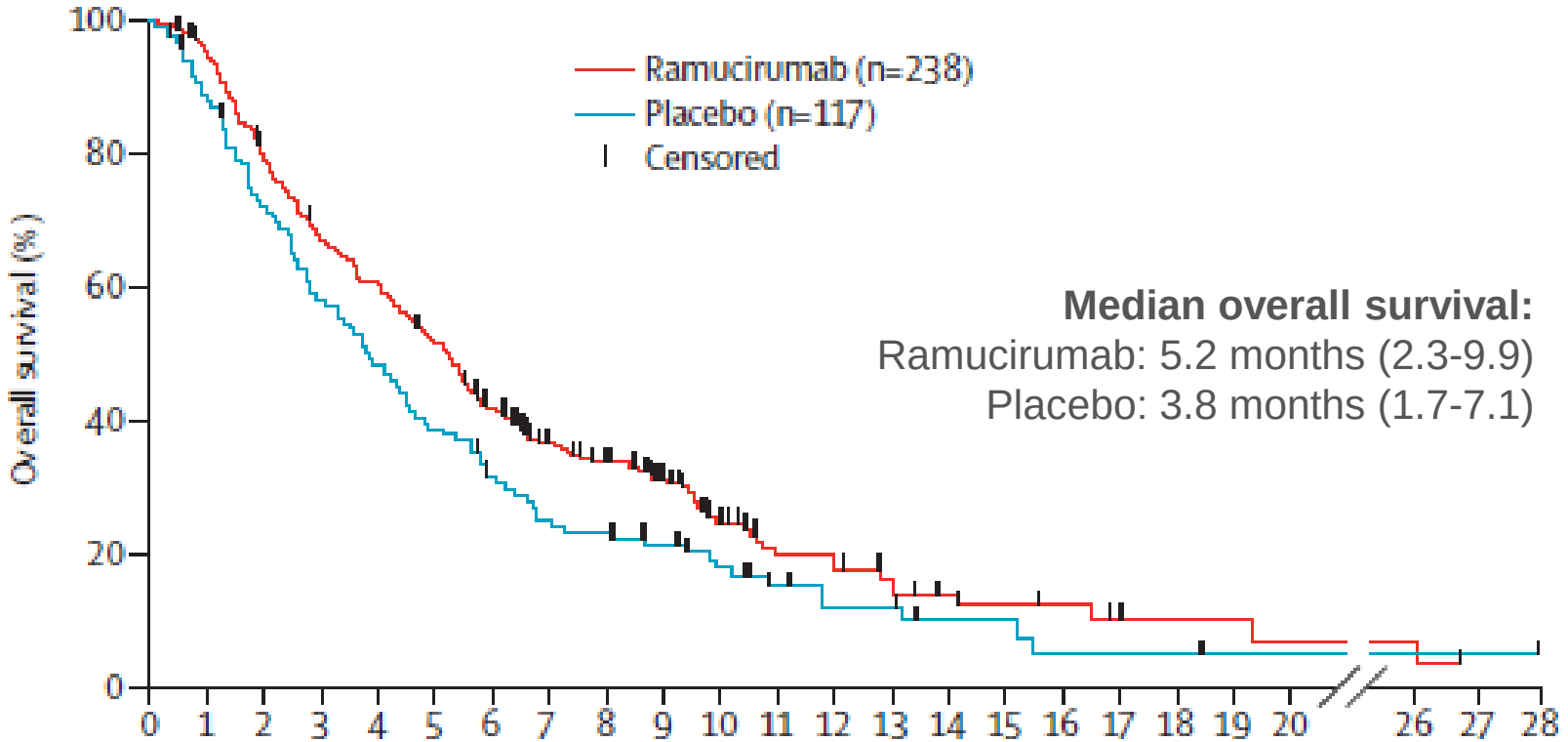
	Ramucirumab (n=238)	Placebo (n=117)
Histological subtype (Lauren classification)		
Intestinal	52 (22%)	35 (30%)
Diffuse	96 (40%)	44 (38%)
Unknown or not available	90 (38%)	38 (32%)
Primary tumour present	174 (73%)	86 (74%)
Number of metastatic sites		
0–2	163 (68%)	71 (61%)
≥3	75 (32%)	46 (39%)
Peritoneal metastases	64 (27%)	45 (38%)

Fuchs CS, *et al*. Lancet 2014;383:31-9

Angiogenesis in gastric cancer ramucirumab

Overall survival was significantly increased by ramucirumab

HR=0.776 95%CI [0.603-0.998]; p=0.047



Median overall survival:
Ramucirumab: 5.2 months (2.3-9.9)
Placebo: 3.8 months (1.7-7.1)

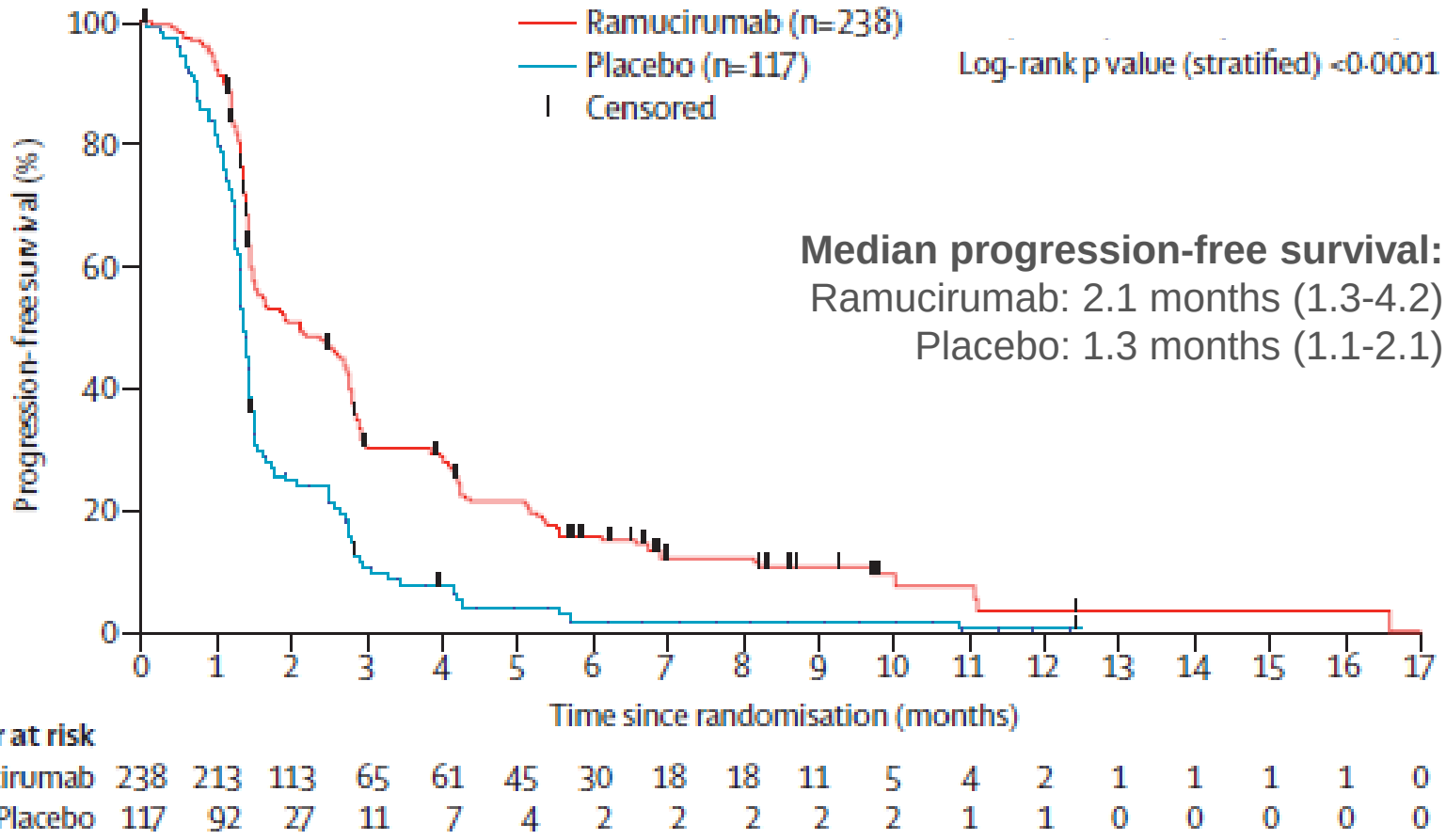
Number at risk

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

Fuchs CS, *et al.* Lancet 2014;383:31-9. Reprinted from The Lancet, Vol. 383(9911) Copyright (2014), with permission from Elsevier

Angiogenesis in gastric cancer ramucirumab

Progression-free survival was significantly increased by ramucirumab: HR=0.483 95%CI [0.376-0.620]; p<0.0001

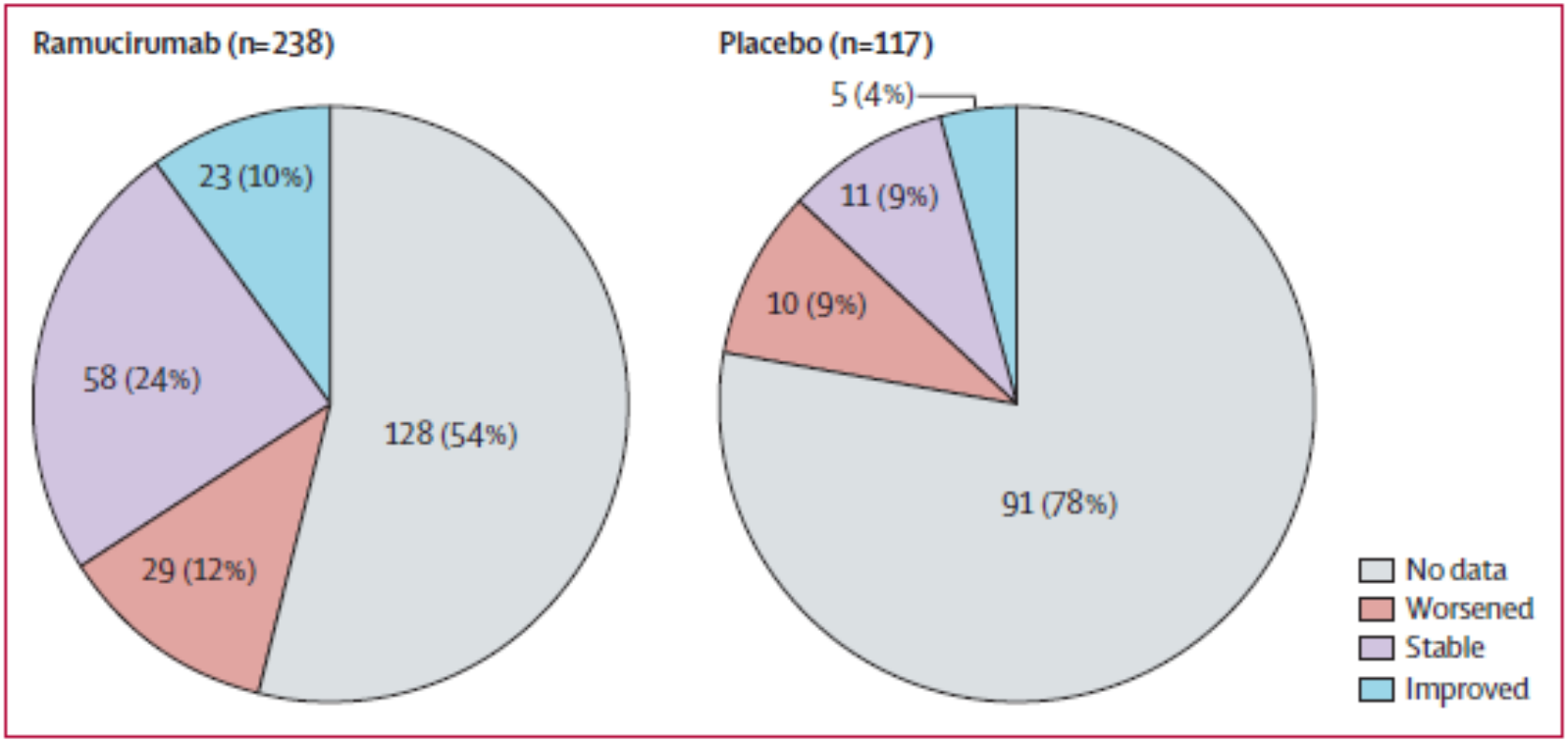


Median progression-free survival:
Ramucirumab: 2.1 months (1.3-4.2)
Placebo: 1.3 months (1.1-2.1)

Fuchs CS, *et al.* Lancet 2014;383:31-9. Reprinted from The Lancet, Vol. 383(9911) Copyright (2014), with permission from Elsevier

Angiogenesis in gastric cancer ramucirumab

More patients reported an improvement of their quality of life (6 weeks after treatment initiation)



Fuchs CS, *et al.* Lancet 2014;383:31-9. Reprinted from The Lancet, Vol. 383(9911) Copyright (2014), with permission from Elsevier

Angiogenesis in gastric cancer ramucirumab

Adverse events

- Ramucirumab was associated with increased rates of hypertension (HTN) including grade 3 or more HTN: 8% in the ramucirumab arm *versus* 3% in the placebo arm
- Bleeding, proteinuria, venous thrombotic events or gastrointestinal perforation were not increased by ramucirumab
- Only arterial thrombotic events were slightly more common in the ramucirumab arm (4 events (2%) including 3 grade ≥3 events *versus* 0; p=0.55)

Fuchs CS, *et al*. Lancet 2014;383:31-9

Angiogenesis in gastric cancer ramucirumab: Discussion

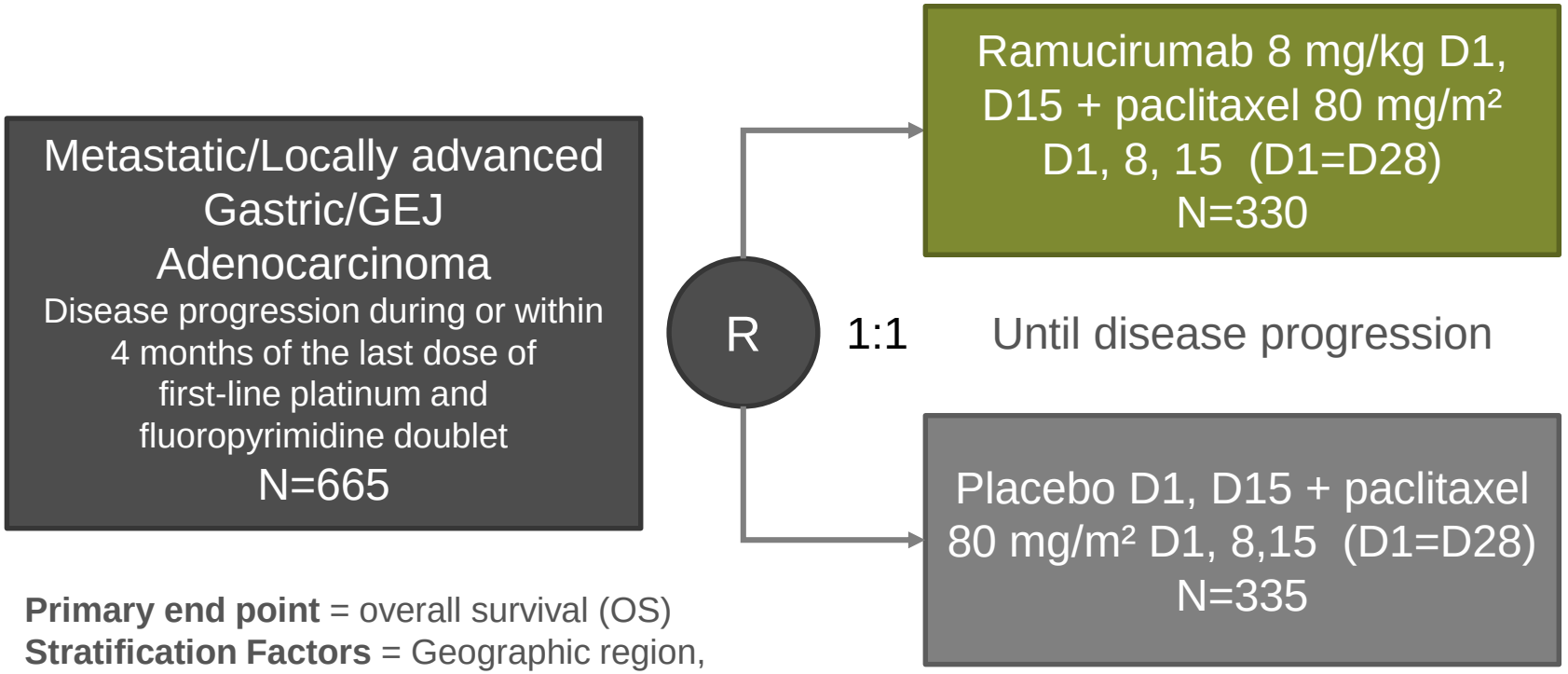
- The survival benefit for ramucirumab *versus* placebo, although small[1], is similar to that reported in the phase 3 trials comparing second-line cytotoxic chemotherapy with best supportive care (median 5.3 months *vs.* 3.8 months (HR 0.657)[2] and 5.2 months *vs.* 3.6 months (HR 0.67)[3]

- The survival benefit associated with ramucirumab was similar between Asian patients and the rest of the world (ROW) although relatively few Asian patients were enrolled

1. Fuchs CS, *et al*. Lancet 2014;383:31-9
2. Kang JH, *et al.* J Clin Oncol 2012;30:1513–18
3. Ford HE, *et al*. Lancet Oncol 2014;15:78-86

Angiogenesis in gastric cancer ramucirumab + paclitaxel

- **RAINBOW** study was an international, randomised, double-blind, placebo-controlled phase 3 trial in second-line setting evaluating ramucirumab in combination with chemotherapy



Primary end point = overall survival (OS)
Stratification Factors = Geographic region, time to progression after first dose of first-line therapy and disease measurability

Wilke H, *et al*. Lancet Oncol 2014;15:1224-35

GEJ = gastroesophageal junction

Angiogenesis in gastric cancer ramucirumab + paclitaxel

- **RAINBOW** study: patients profile

	Ramucirumab plus paclitaxel (n=330)	Placebo plus paclitaxel (n=335)
Ethnic Origin (by self report)		
White	208 (63%)	199 (59%)
Asian	110 (33%)	121 (36%)
Black or other	12 (4%)	15 (4%)
Geographic region		
1. (Europe, Israel, Australia, USA)	198 (60%)	200 (60%)
2. (Argentina, Brazil, Chile, Mexico)	23 (7%)	21 (6%)
3. (Japan, South Korea, Hong Kong, Singapore, Taiwan)	109 (33%)	114 (34%)
Site of primary tumour		
Gastric	264 (80%)	264 (79%)
Gastroesophageal junction (GEJ)	66 (20%)	71 (21%)

Wilke H, *et al.* Lancet Oncol 2014;15:1224-35

Angiogenesis in gastric cancer ramucirumab + paclitaxel

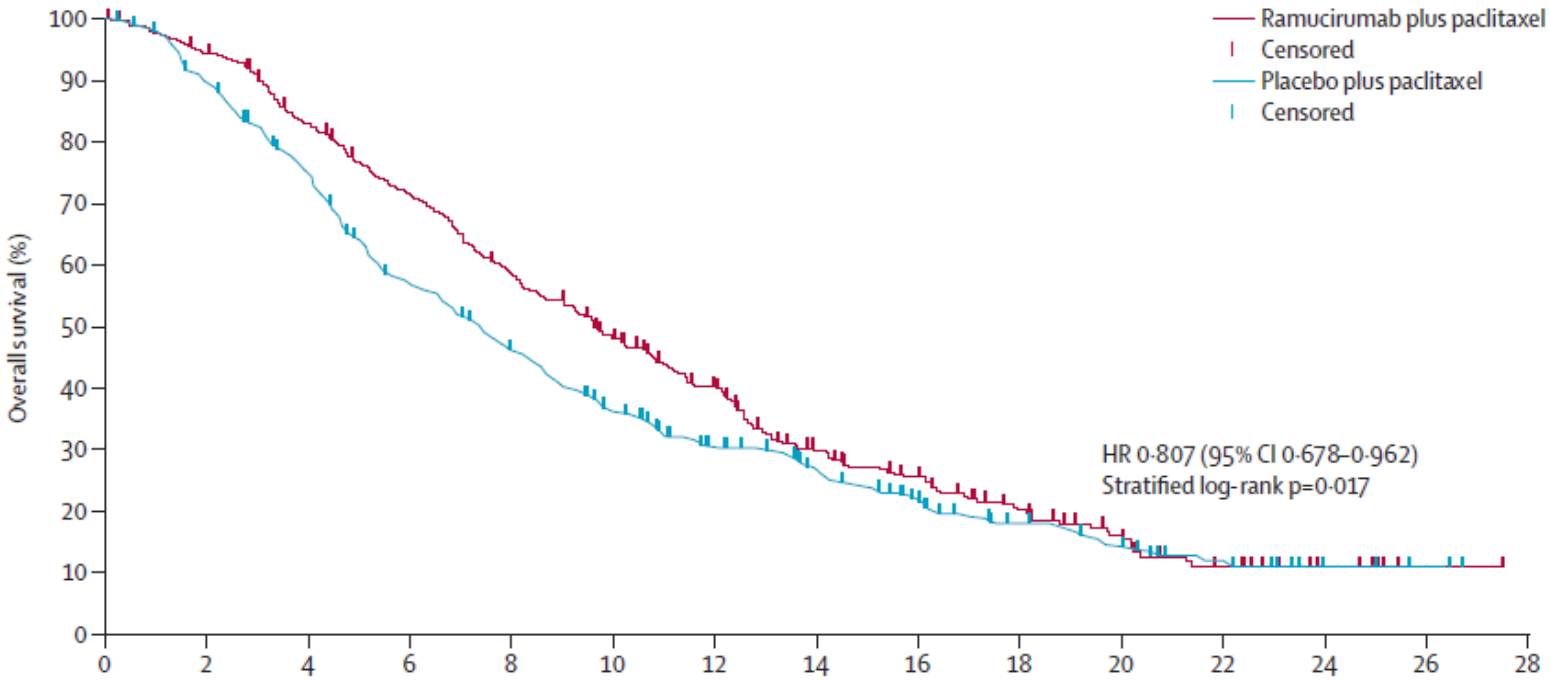
- **RAINBOW** study: patients profile

	Ramucirumab plus paclitaxel (n=330)	Placebo plus paclitaxel (n=335)
Histological subtype (Lauren classification)		
Intestinal	145 (44%)	135 (40%)
Diffuse	115 (35%)	133 (40%)
Mixed	21 (6%)	14 (4%)
Unknown or not available	49 (15%)	53 (16%)
Primary tumour present	209 (63%)	209 (62%)
Number of metastatic sites		
0–2	209 (63%)	232 (69%)
≥3	121 (37%)	103 (31%)
Peritoneal metastases	163 (49%)	152 (45%)

Wilke H, *et al*. Lancet Oncol 201;15:1224-35

Angiogenesis in gastric cancer ramucirumab + paclitaxel

Ramucirumab with paclitaxel significantly improved overall survival (OS) over paclitaxel + placebo: HR 0.807; p=0.017
Median OS 9.6 months *versus* 7.4 months



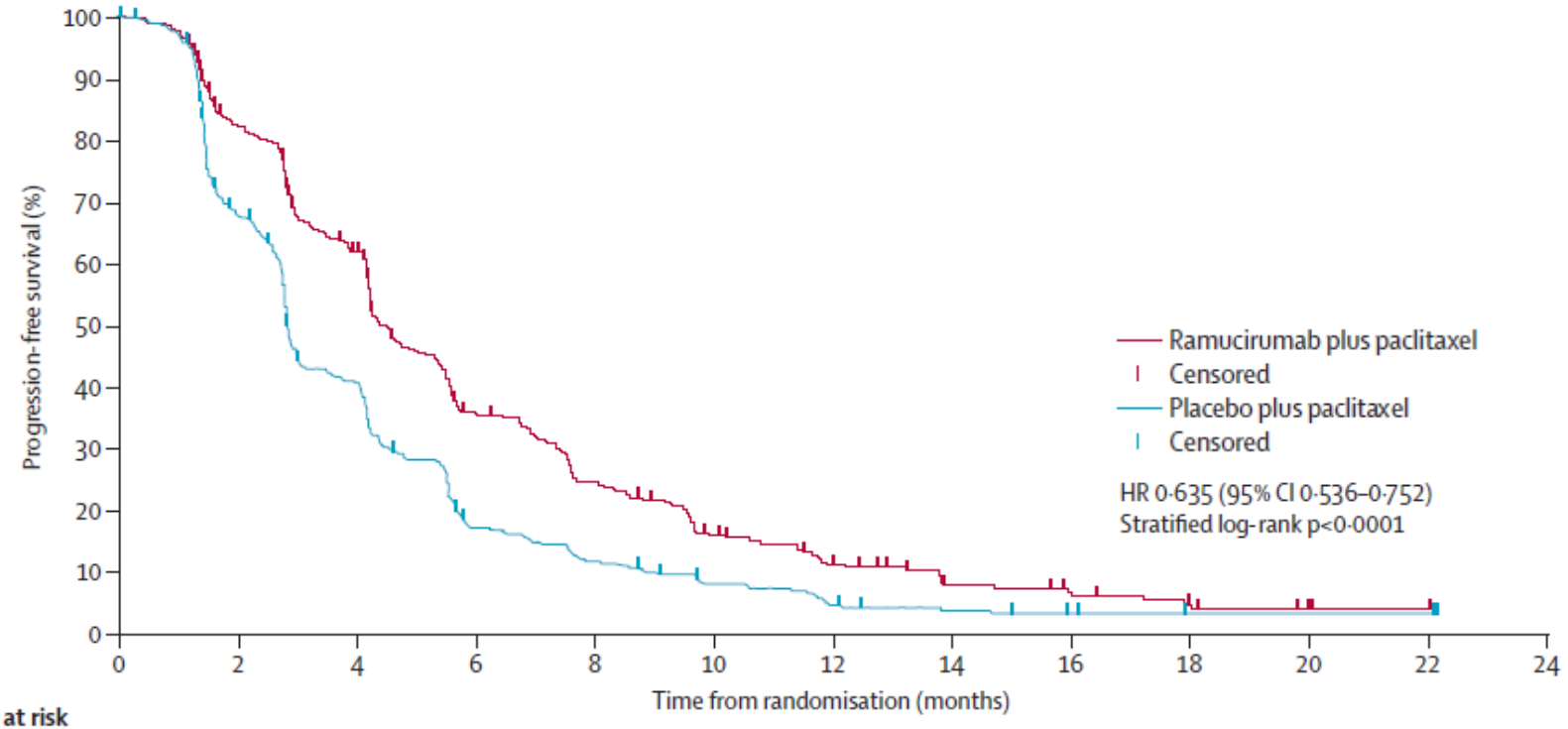
Number at risk															
Ramucirumab plus paclitaxel	330	308	267	228	185	148	116	78	60	41	24	13	6	1	0
Placebo plus paclitaxel	335	294	241	180	143	109	81	64	47	30	22	13	5	2	0

Wilke H, *et al.* Lancet Oncol 2014;15:1224-35. Reprinted from The Lancet, Vol. 15(11)

Angiogenesis in gastric cancer ramucirumab + paclitaxel

Ramucirumab with paclitaxel significantly improved progression-free survival over paclitaxel + placebo: HR 0.635; p<0.0001

Median PFS 4.4 months *versus* 2.9 months



Number at risk													
Ramucirumab plus paclitaxel	330	259	188	104	70	43	28	15	11	7	3	1	..
Placebo plus paclitaxel	335	214	124	50	34	21	12	8	5	3	3	3	..

Wilke H, *et al.* Lancet Oncol 2014;15:1224-35. Reprinted from The Lancet, Vol. 15(11) Copyright (2014), with permission from Elsevier

Angiogenesis in gastric cancer ramucirumab + paclitaxel

The efficacy may be different according to geographic regions?

	Ramucirumab plus paclitaxel	Placebo plus paclitaxel	Hazard ratio (95% CI)	Odds ratio (95% CI)
Median overall survival				
Regions 1 (n=398) and 2 (n=44)	8·5 months (7·4–9·8)	5·9 months (5·2–7·1)	0·732 (0·591–0·907)	
Region 3 (n=223)	12·1 months (10·0–13·3)	10·5 months (7·8–14·1)	0·986 (0·727–1·337)	
Median progression-free survival				
Region 1 (n=398) and 2 (n=44)	4·2 months (3·9–4·9)	2·9 months (2·6–3·5)	0·639 (0·518–0·788)	
Region 3 (n=223)	5·5 months (4·2–5·7)	2·8 months (2·8–4·1)	0·628 (0·473–0·834)	
Proportion of patients achieving an objective response				
Regions 1 (n=398) and 2 (n=44)	55 (25%)	31 (14%)		2·087 (1·278–3·409)
Region 3 (n=223)	37 (34%)	23 (20%)		2·235 (1·177–4·244)

Region 1 = Europe, Israel, Australia, USA
Region 2 = Argentina, Brazil, Chile, and Mexico
Region 3 = Japan, South Korea, Hong Kong, Singapore, and Taiwan

Angiogenesis in gastric cancer ramucirumab + paclitaxel

Adverse events

- The **incidence of grade 3-4 adverse events** was higher in the ramucirumab plus paclitaxel group:
  - Neutropenia (55%) (similar incidence of febrile neutropenia: 3% *vs.* 2%)
  - Neuropathy (46%)
  - Abdominal pain (36%)
  - Leucopenia (35%)
  - Hypertension (15%)
  - Fatigue (12%)
  - Gastrointestinal perforation (1.2%)

- **Treatment-related deaths** were comparable between the two arms

Wilke H, *et al.* Lancet Oncol 2014;15:1224-35

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Angiogenesis in gastric cancer ramucirumab + paclitaxel

Discussion

- The preplanned subgroup analysis showed that Asian patients (region 3) have no overall survival benefit from ramucirumab (region 3: HR 0.986) whereas their median progression-free survival was increased compared with placebo plus paclitaxel (similarly to the entire population)

- The higher use of post-progression therapy in Asia (69%) than in the non-Asian regions (38%) may explain these results[1]

- A post-hoc analysis showed similar OS and PFS in Japanese *vs.* Western patients[2]

1. Wilke H, *et al.* Lancet Oncol 2014;15:1224-35
2. Shitara K, *et al*. Gastric Cancer 2015 Oct 28

Angiogenesis in gastric cancer ramucirumab in first-line metastatic setting

- One phase II study in combination with FOLFOX (*versus* FOLFOX + placebo) with negative results:
  - Progression-free survival: 6.4 *vs.* 6.7 months - HR 0.98, 95%CI [0.69-1.37], p=0.89
  - Overall survival: 11.7 *vs.* 11.5 months (HR=1.08)

- The sub-group analysis questioned about a potential benefit for gastric/GEJ but not for oesophageal adenocarcinomas?

- The question remains unanswered due to the small size of the sub-groups

Yoon HH, *et al*. ASCO 2014, Abstr. 4004

Angiogenesis in gastric cancer ramucirumab in first-line metastatic setting

- A Phase III study with ramucirumab in combination with capecitabine and cisplatin in participants with stomach cancer (RAINFALL) is currently ongoing in first-line metastatic setting (NCT02314117)

https://clinicaltrials.gov

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Angiogenesis in gastric cancer ramucirumab / bevacizumab discussion

- GC is a heterogeneous disease
- Inherent differences exist in disease biology, genetic factors, histology that may influence patient and treatment outcome
- The management of gastric cancer patients differs between Asia and the rest of the world (ROW) and can also explain the differences in efficacy results

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Angiogenesis in gastric cancer ramucirumab / bevacizumab discussion

- The absence of benefit from bevacizumab in the AVAGAST study may be due to an important part of Asian patients (49%)
- A lesser proportion of Asian patients were included in the ramucirumab trials (REGARD 16%, RAINBOW 33-36%)

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Optimising anti-angiogenic strategies in gastric adenocarcinoma

APATINIB

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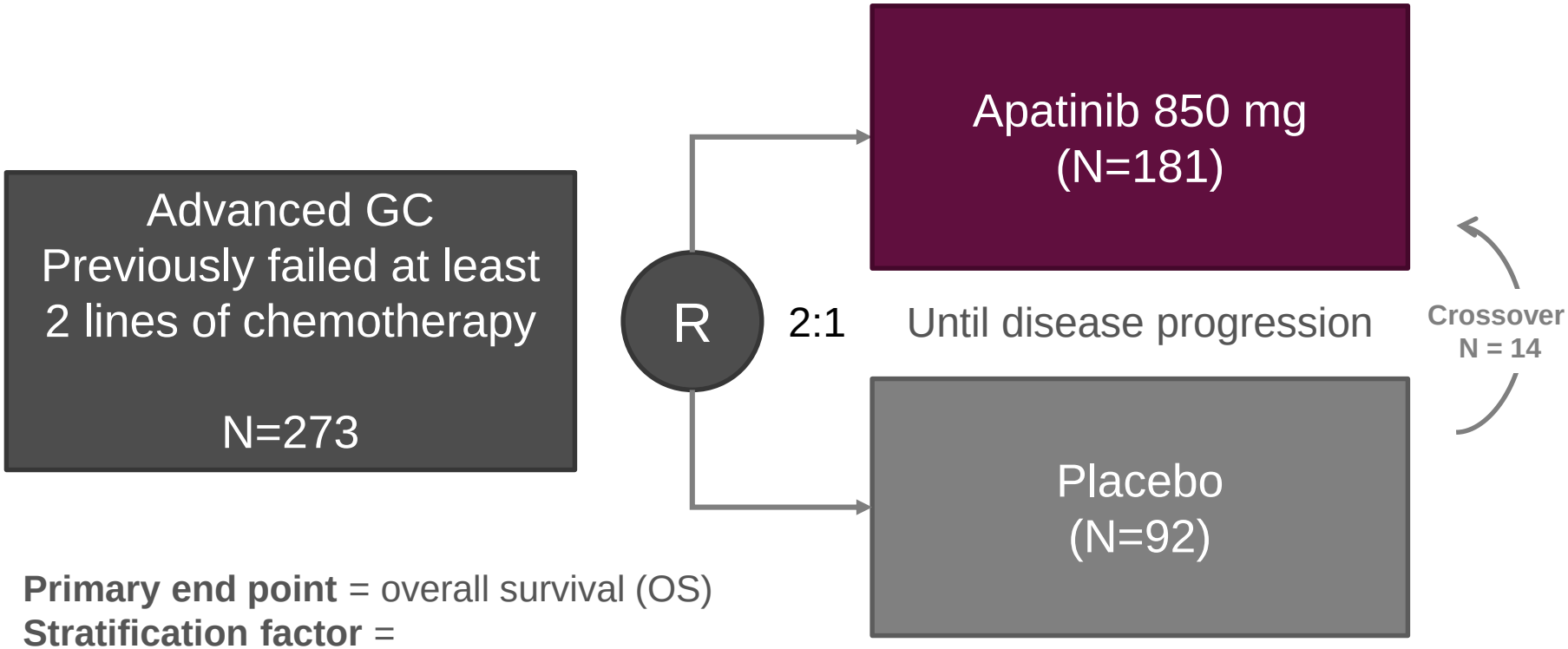
Angiogenesis in gastric cancer apatinib

- Apatinib (YN968D1) is a small-molecule VEGFR-2 tyrosine kinase inhibitor. It could also inhibit Ret, c-kit and c-src
- A phase I clinical trial showed antitumour activity in Chinese patients with metastatic gastric cancer
- A randomised placebo-controlled phase II study showed an improvement in PFS and OS in heavily pretreated Chinese patients (failure after two or more chemotherapy regimens)

Li J, *et al.* BMC Cancer 2010;10:529;
Li J, *et al*. J Clin Oncol 2013;31:3219-25

Angiogenesis in gastric cancer apatinib

- Multicentre, randomised, double-blind, placebo-controlled phase III trial in multi-treated patients



Primary end point = overall survival (OS)
Stratification factor =
Number of metastatic sites (≤2 or >2)

Qin S. 2014 ASCO Annual Meeting. J Clin Oncol 2014;32(Suppl):5S. Abstr 4003

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Angiogenesis in gastric cancer apatinib

- Apatinib induced a significant improvement of overall survival,
  - Median overall survival: 6.5 *vs.* 4.7 months, HR=0.709 95%CI [0.537-0.937] p=0.0149
- A significant improvement of progression-free survival
  - Median progression-free survival: 2.6 *vs.* 1.8 months, HR 0.444 95%CI [0.331-0.595] p<0.0001
- A significant increase in disease control rate
  - Disease control rate 31.82% *vs.* 10.99% (p=0.002)

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Angiogenesis in gastric cancer apatinib

Adverse events

- The incidence of adverse events was higher in the apatinib group:
  - All adverse events: 98.30% in the apatinib arm *vs.* 90.11% in the placebo arm (p=0.0038)
  - Grade 1-2 events: 88.07% *vs.* 67.03% (p=0.0001)
  - Grade 3-4 events: 60.23% *vs.* 41.76% (p=0.0045)

- Similar rate of serious adverse events: 15.34% *vs.* 16.48% (p=0.8598)

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Angiogenesis in gastric cancer apatinib

Grade 3/4 adverse events (incidence ≥5%)

	Apatinib N=176	Placebo N=91	P value
Hand-Foot syndrome	8.52%	0.00%	0.0032
Elevation of transaminases	7.95%	4.40%	0.3155
Hyperbilirubinemia	7.39%	6.59%	1.0000
Hypochromia	6.25%	4.40%	0.7799
Elevation of GGT	6.25%	6.59%	1.0000
Neutropenia	5.68%	1.10%	0.1045
Hypophosphatemia	5.11%	2.2.%	0.3417

Qin S. 2014 ASCO Annual Meeting. J Clin Oncol 2014;32(Suppl):5S. Abstr 4003

Angiogenesis in gastric cancer apatinib: Conclusion

- The data on apatinib in Chinese patients are highly significant and call for a confirmation in Caucasian patients

- Apatinib is under evaluation in several situations in GC:
  - Maintenance therapy after first line treatment in locally advanced or metastatic gastric cancer (NCT02537171 and NCT02509806)
  - Compared to docetaxel treatment in patients with advanced gastric cancer after one prior chemotherapy regimen (NCT02409199)
  - In combination with S-1 as first-line treatment in patients with advanced gastric cancer (NCT02525237)
  - In combination with S1 and paclitaxel chemotherapy for unresectable untreated gastric cancer (NCT02529878)

https://clinicaltrials.gov

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Optimising anti-angiogenic strategies in gastric adenocarcinoma

CONCLUSION

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Conclusion

- Angiogenesis plays a major role in gastric cancer development and progression
- Clinical data, despite some contradictory results, suggest that the inhibition of angiogenic signaling pathways has an important therapeutic potential
- Based on the positive results of the REGARD and RAINBOW trials, ramucirumab is the first anti-angiogenic treatment having FDA and EMA approval in advanced GC
- Ramucirumab is indicated as second line treatment alone or in combination with paclitaxel, in patients with advanced or metastatic gastric or oesophagogastric junction cancers who progressed on fluoropyrimidine-or platinum-containing first-line chemotherapy

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Conclusion

- Apatinib has been approved by the China Food and Drug Administration and will be certainly evaluated in Western countries. Its results are exciting

- Other antiangiogenic treatments (Ziv-Aflibercept, pazopanib, dovitinib…) are currently evaluated in phase II studies and may represent new tools in the future management of GC

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Thank you!