Targeting HER 2 and angiogenesis in gastric cancer: What is the impact?

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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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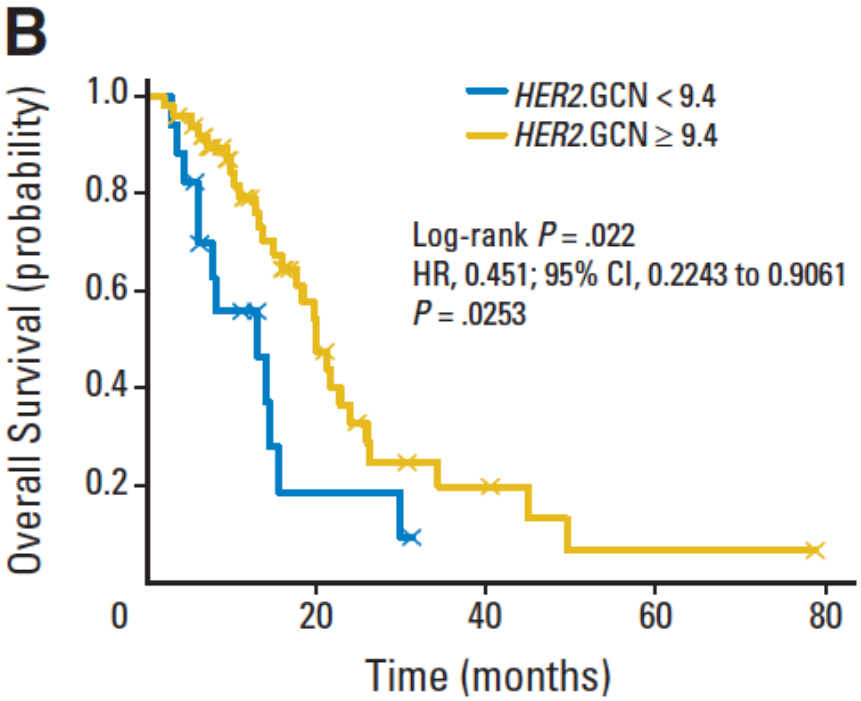
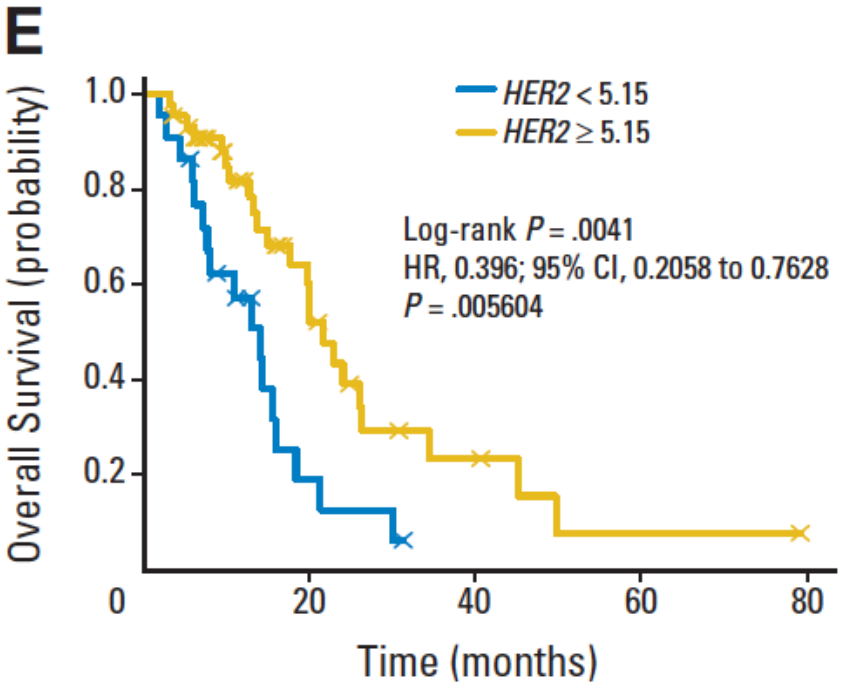
Level of HER2 amplification predicts OS in HER2 amplified advanced gastric cancer patients treated with Trastuzumab





Gómez-Martin C, et al. J Clin Oncol 2013; 31:4445–4452

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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=0.031	+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 2016; 34:443-451.
3. Satoh N, et al. J Clin Oncol 2014; 32:2039–2049.

Targeted therapies against HER2 in advanced gastric cancer: Summary of Phase III Trials on Trastuzumab, Lapatinib and TDM1

TRIAL	Chemotherapy backbone	Line of therapy number	HR OS	P value	Response rate	Increase in median survival
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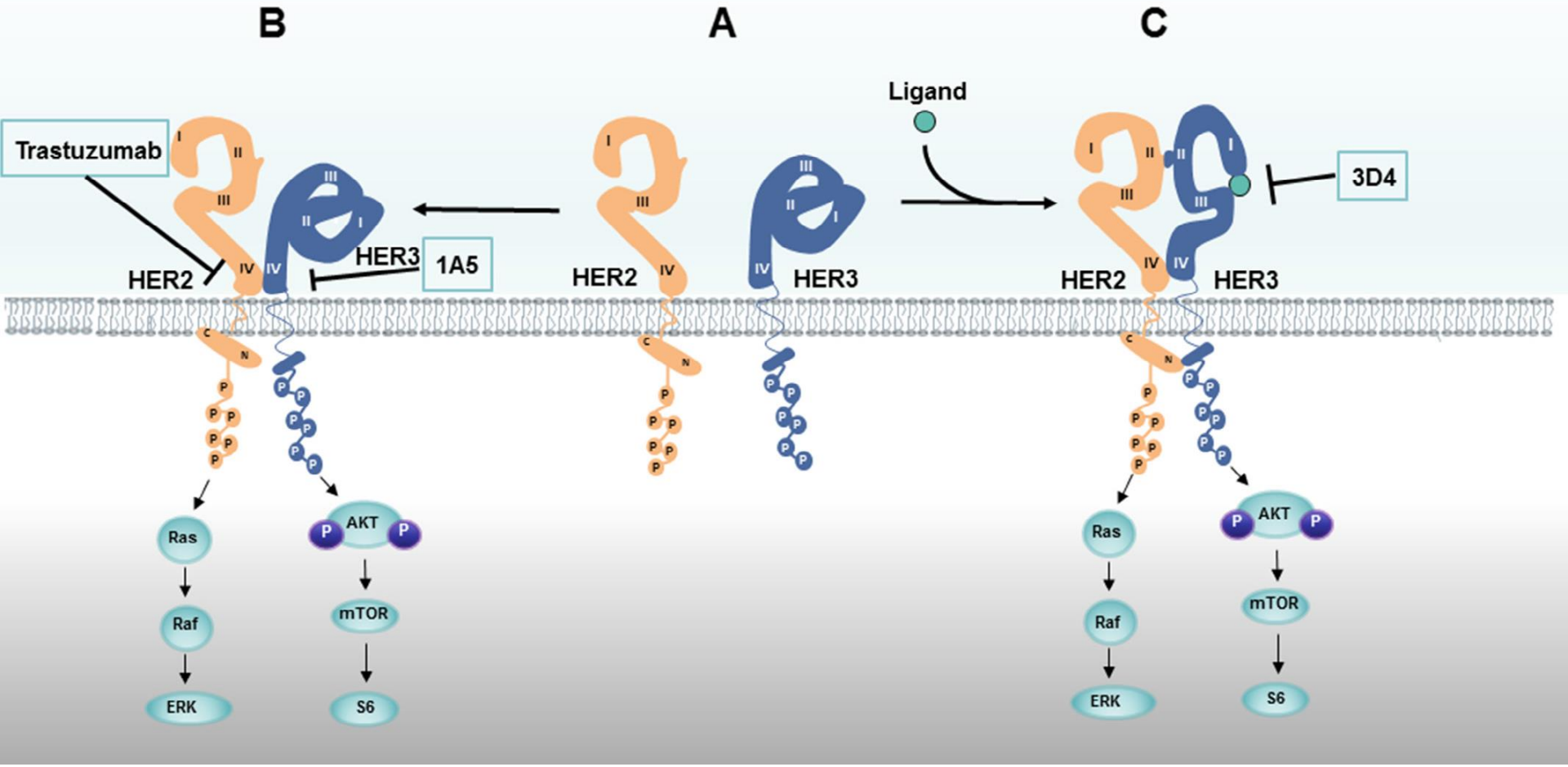
TyTAN[3]	Paclitaxel	Second 261	0.84	0.20	27% vs 9% p=0.001	+2.1 months
GATSBY[4]	TDM-1 vs Taxane	Second 228 vs 117	1.15	0.85	NP	- 0,7 months

1. Bang YJ, et al. Lancet 2010;376:687–697.
2. Hecht JR, et al. j Clin Oncol 2016; 34:443-451.
3. Satoh N, et al. J Clin Oncol 2014; 32:2039–2049.
4. Kang YK et al. ASCO GI 2016

Mechanisms of resistance to Trastuzumab and other anti-HER2 therapies in advanced gastric cancer:

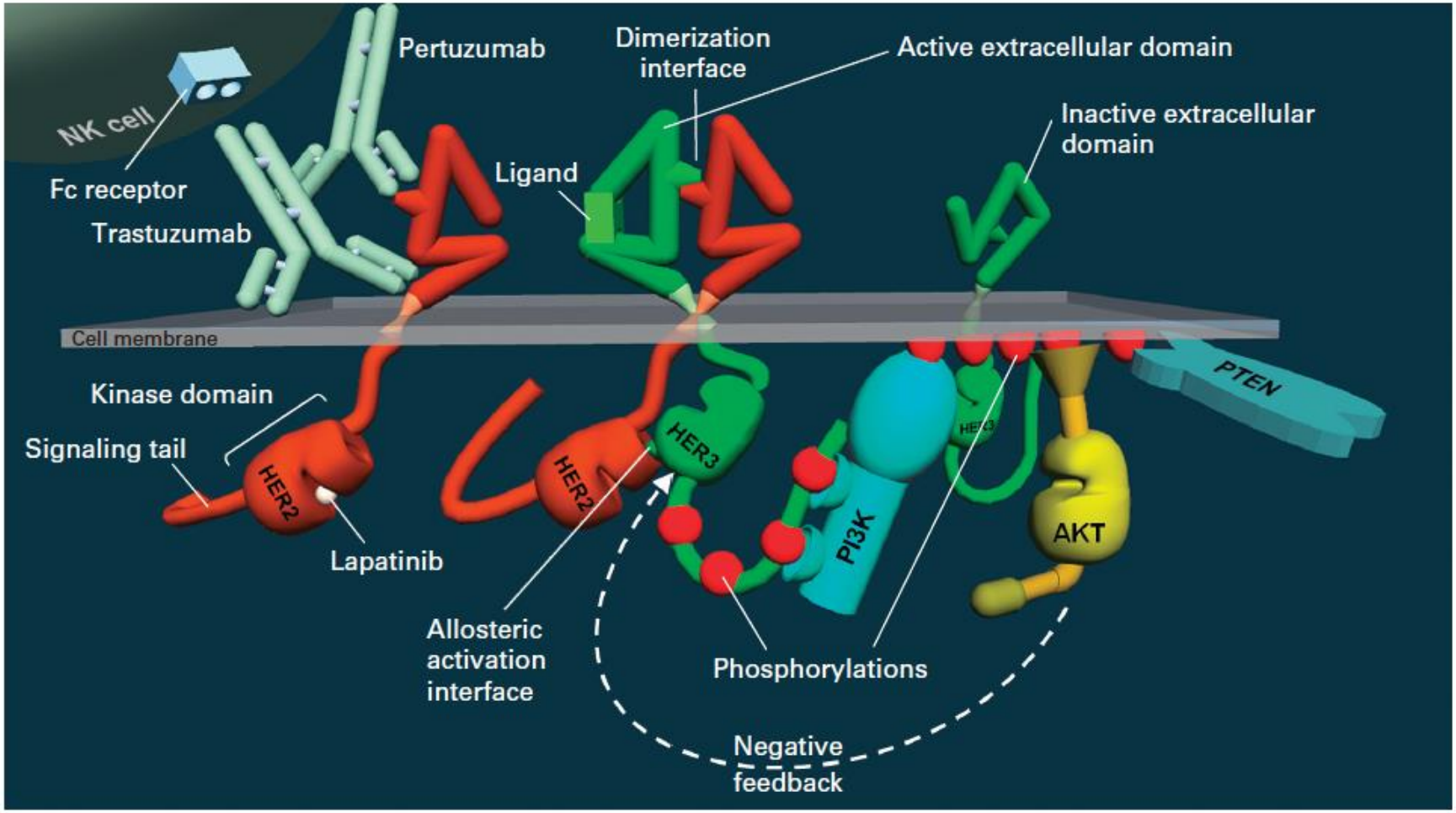
- Co-amplification of HER3 and/or EGFR
- Heterodimerization with HER3
- HER3 mutations
- Co-amplification of MET
- FGFR autocrine loops

Heterodimerization HER2 and HER3



1.Wang Q, et al. Cancer Letters 2016; 380:20-30.

Structure and activation of the HER2 and HER3 receptors



Moasser MM. *et al.* J Clin Oncol 2014;32:2014–2077. Reprinted with permission © 2014 American Society of Clinical Oncology. All rights reserved.

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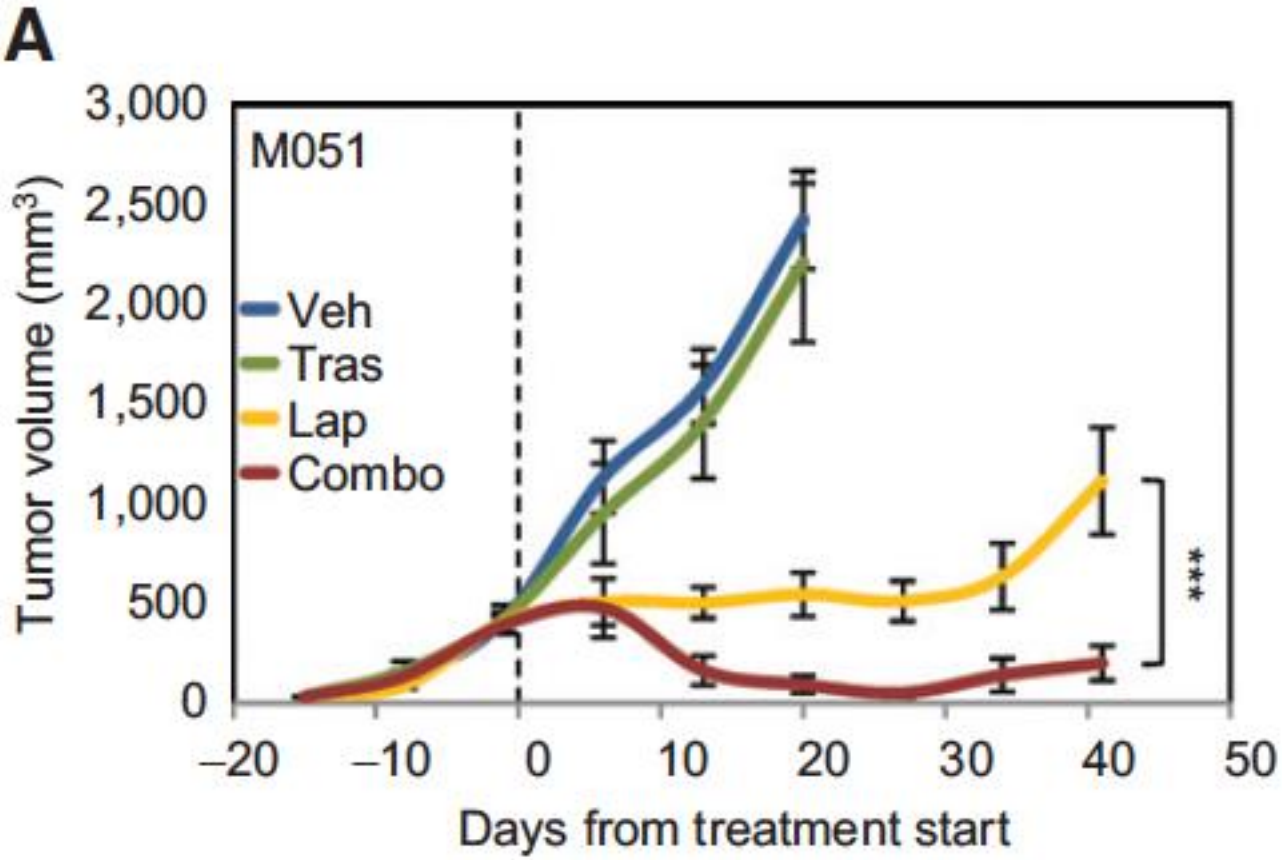
Sustained Inhibition of HER3 and EGFR Is Necessary to Induce Regression of *HER2*-Amplified Gastrointestinal Carcinomas



1.Letto SM, et al. Clin Cancer Res 2015; 21:5519-5531.

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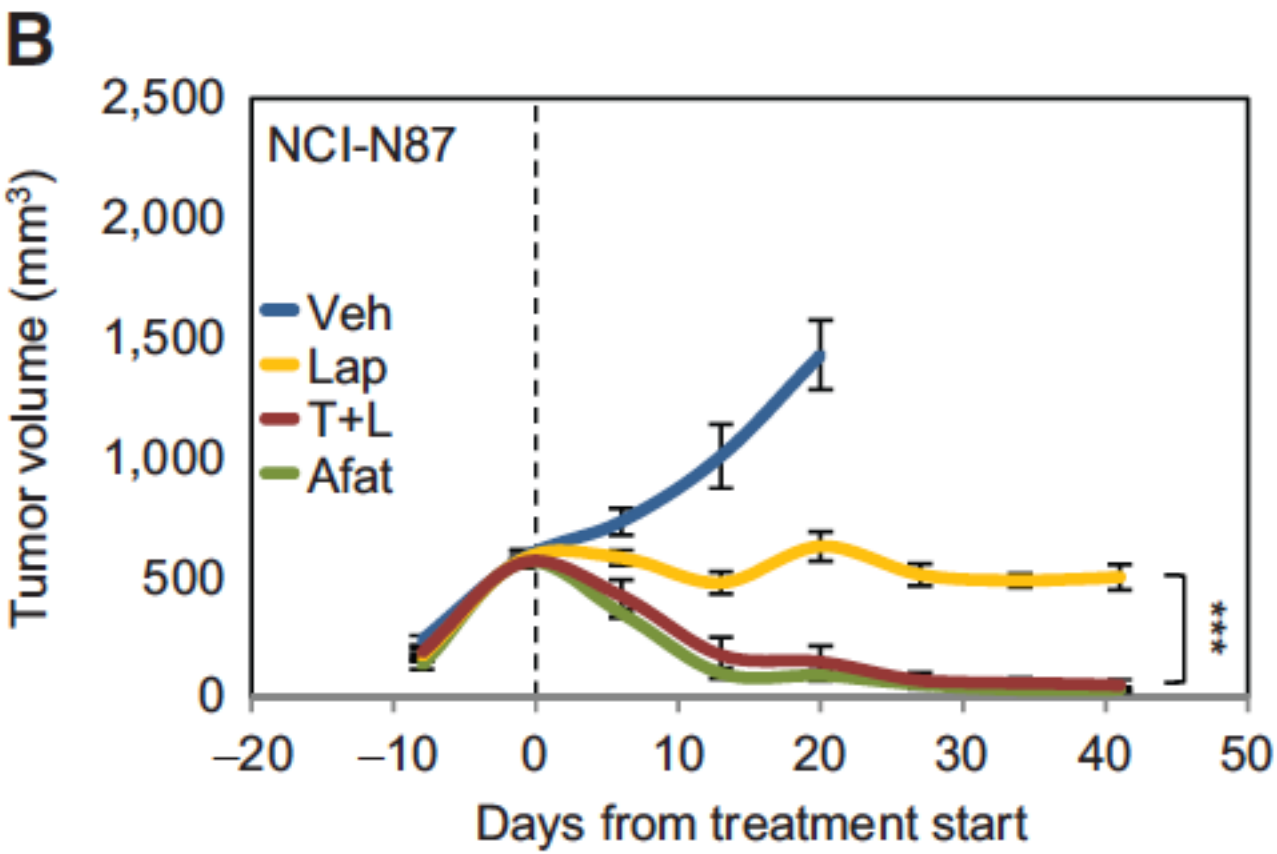
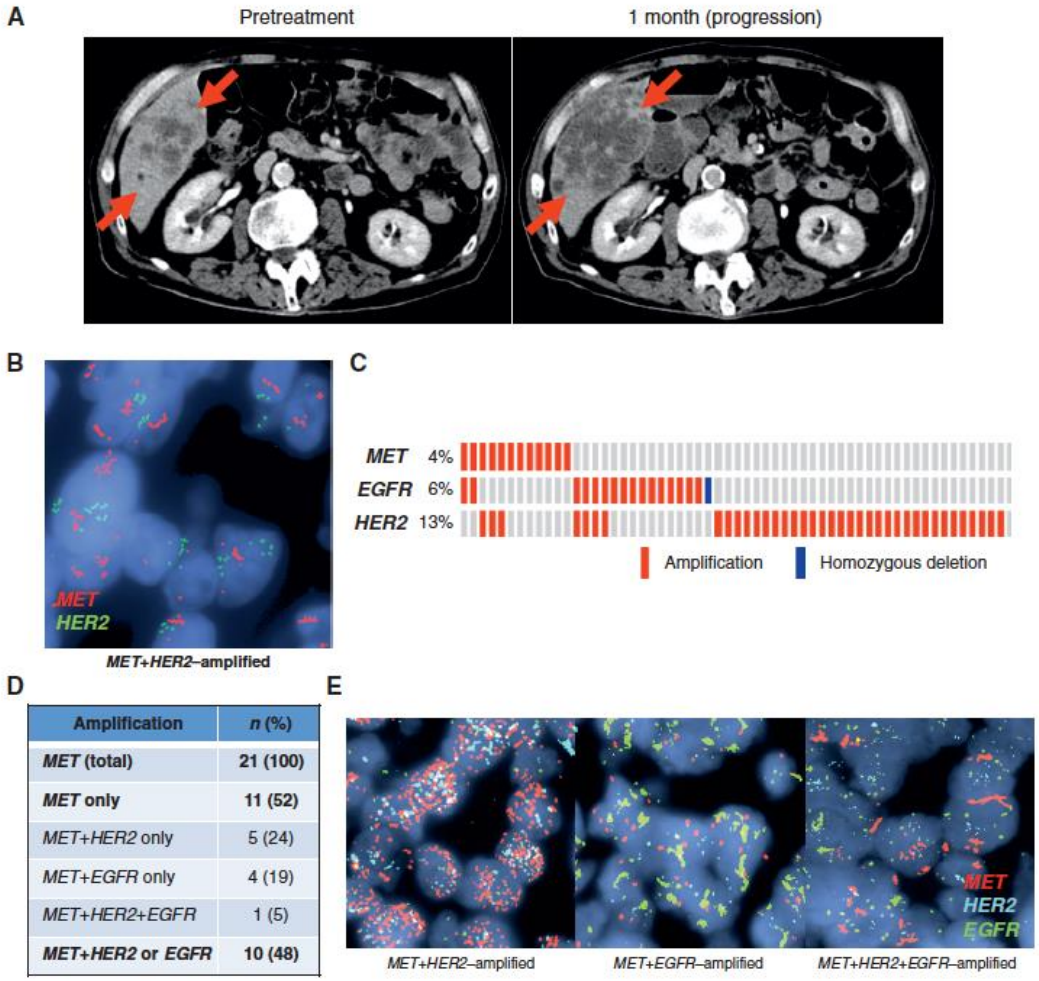
Sustained Inhibition of HER3 and EGFR Is Necessary to Induce Regression of *HER2*-Amplified Gastrointestinal Carcinomas



1.Letto G, et al. Clin Cancer Res 2015; 21:5519-5531.

Molecular Heterogeneity and Receptor Coamplification Drive Resistance to Targeted Therapy in *MET*-Amplified Esophagogastric Cancer

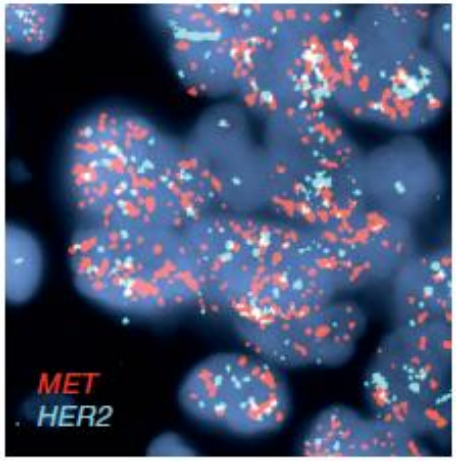


Amplification	*n* (%)
***MET* (total)**	**21 (100)**
***MET* only**	**11 (52)**
MET+HER2 only	5 (24)
MET+EGFR only	4 (19)
MET+HER2+EGFR	1 (5)
MET+HER2* or *EGFR	**10 (48)**

Kwak EL, et al. Cancer discov 2015; 5:1271–1281

Molecular Heterogeneity and Receptor Coamplification Drive Resistance to Targeted Therapy in *MET*-Amplified Esophagogastric Cancer

E



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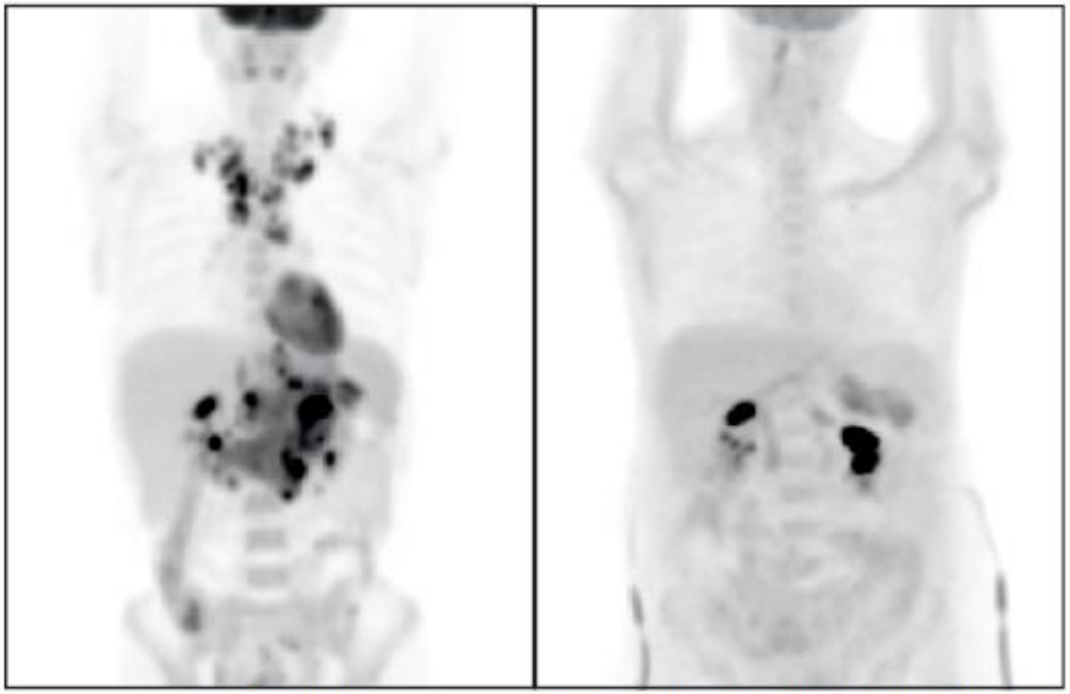
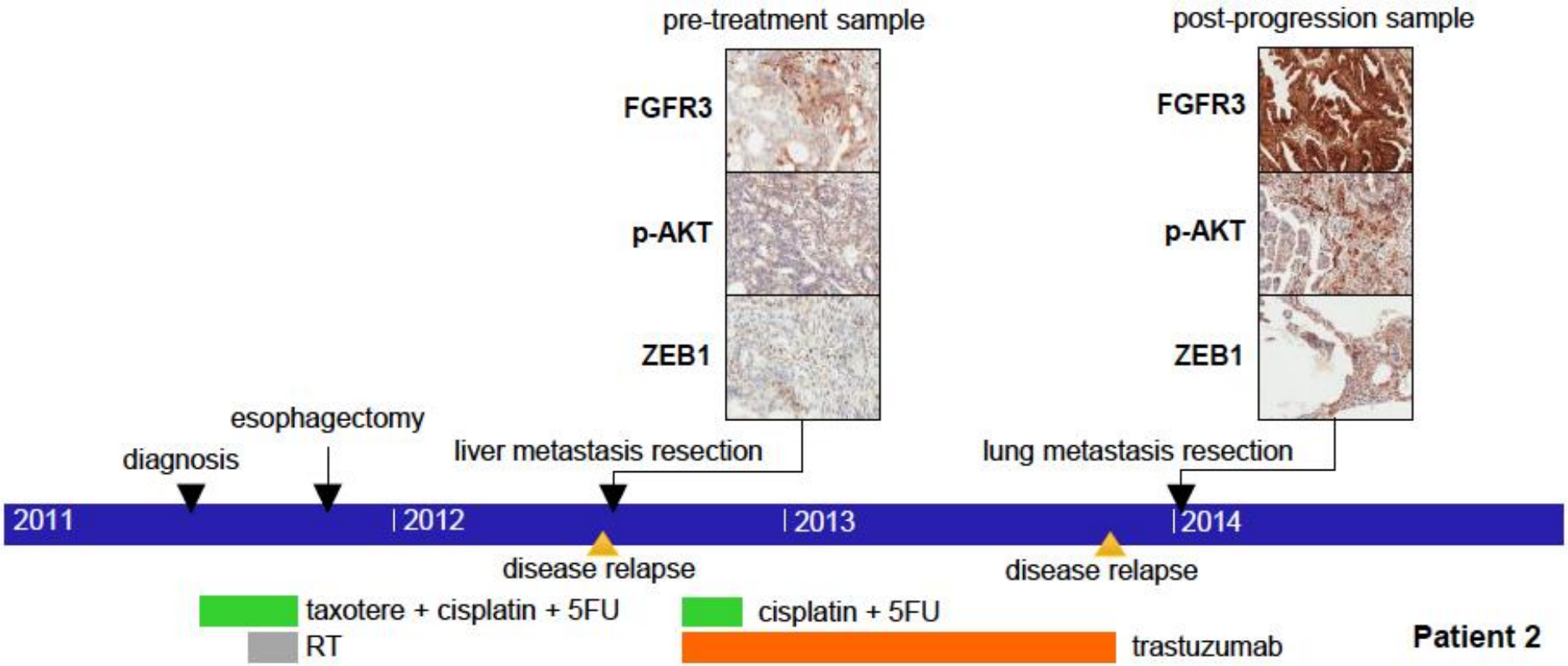


Pretreatment | Trastuzumab + crizotinib (2 months)

Kwak EL, et al. Cancer Discov 2015; 5:1271–1281

An FGFR3 autocrine loop sustains acquired resistance to trastuzumab in gastric cancer patients



1.Piro G, et al. Clin Cancer Res 2016; 23:ahead of print.

Anti-HER2 therapies in advanced gastric cancer:

- HER2 amplificaction to be determined in all M1 cases
- Trastuzumab plus CDDP-FU or Cap improves outcomes in HER2 amplified cases
- Its role in perioperative or adjuvant therapy under investigation
- Gastric cancer behaves differently from breast cancer
- Mechanisms of resistance are diverse and require better understanding
- A role for personalized medicine

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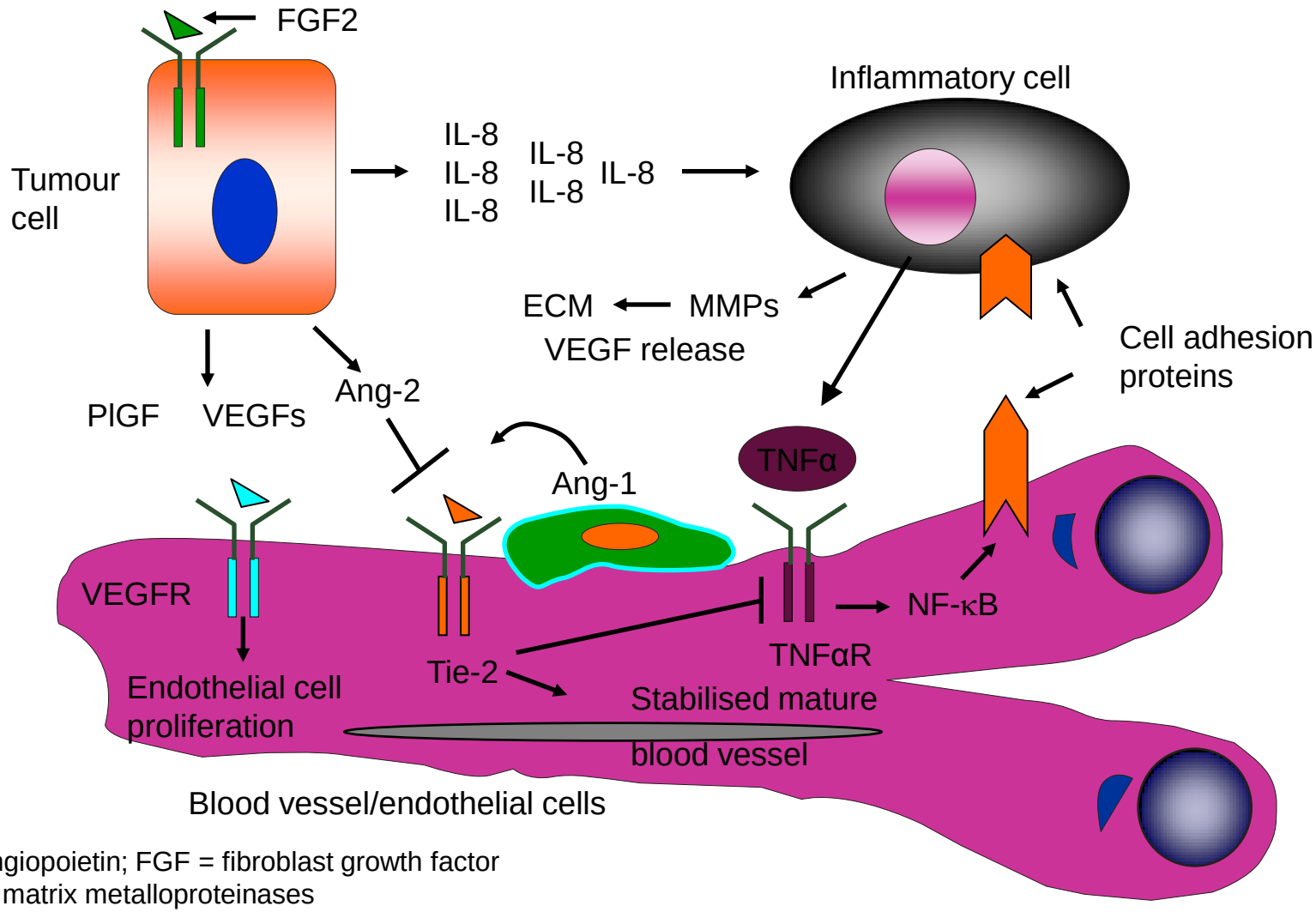
Angiogenesis: a multiple signalling process



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

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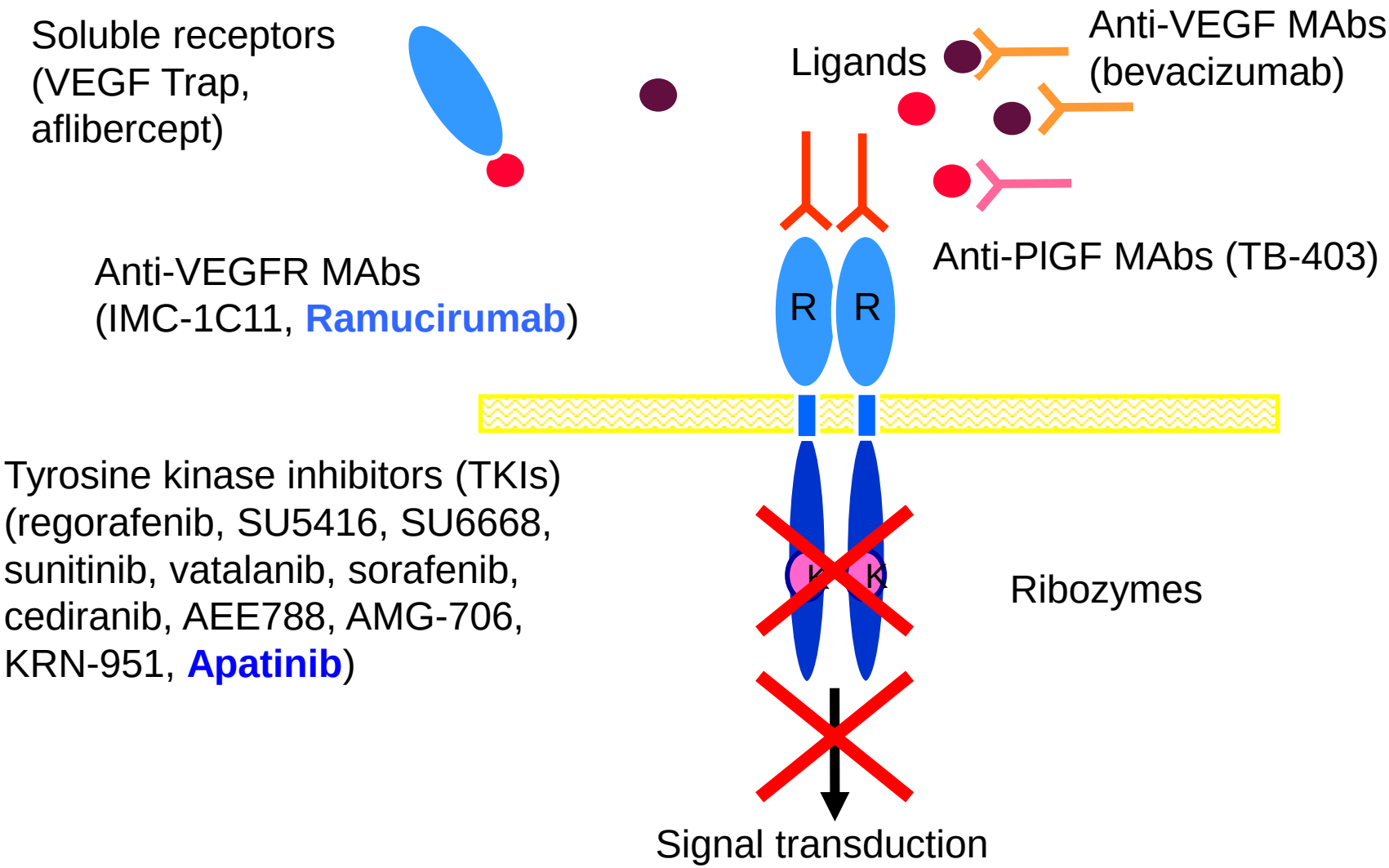
Gastric cancer: Second line chemotherapy trials comparing BSC versus active treatment

Trial author	Year	Patients random (n)	Treatment	HR OS	P value	Gain in median survival
Thuss-Patience, et al.[1]	2011	40 1:1	Irinotecan	0.48	0.0023	2.4 months
Kang, et al.[2]	2012	193 2:1	Irinotecan Docetaxel	0.65	0.004	1.3 months
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

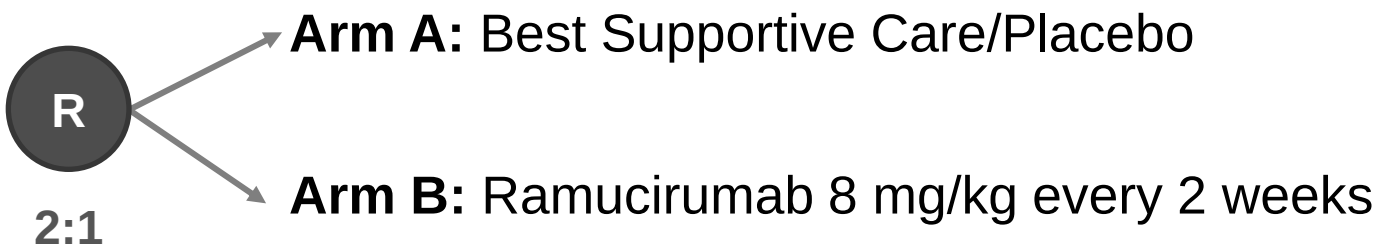
1. Thuss-Patience PC, et al. Eur J Cancer 2011;47:2306–2314. 2. Kang JH, et al. J Clin Oncol 2012;30:1513–1518.
3. Ford HE, et al. Lancet Oncol 2014;15:78–86. 4. Otshu A. et al. J Clin Oncol 2013;31:3935–3943. 5. Fuchs CS, et al. Lancet 2014;383:31–39.

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)

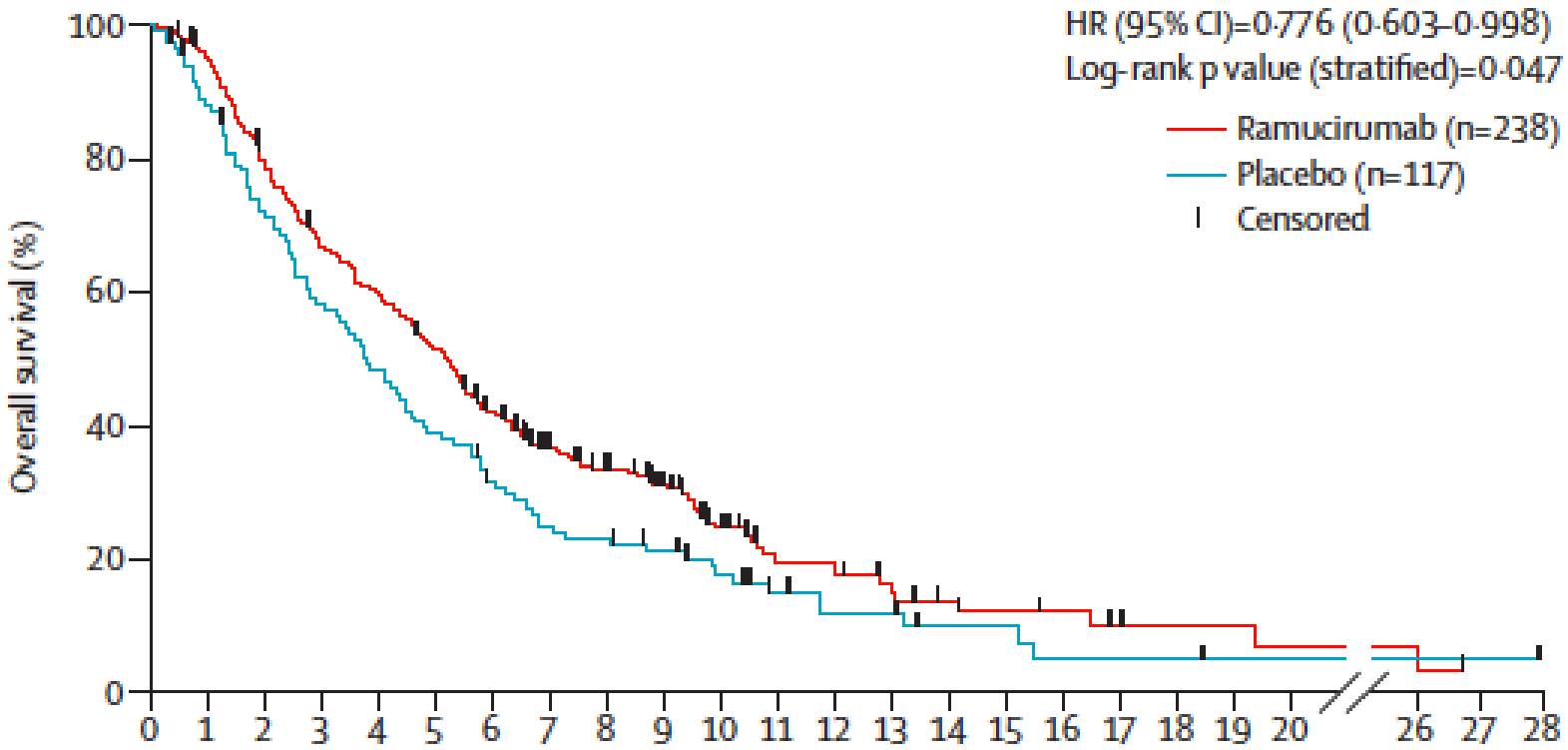


Main aim: Overall survival

- 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.

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

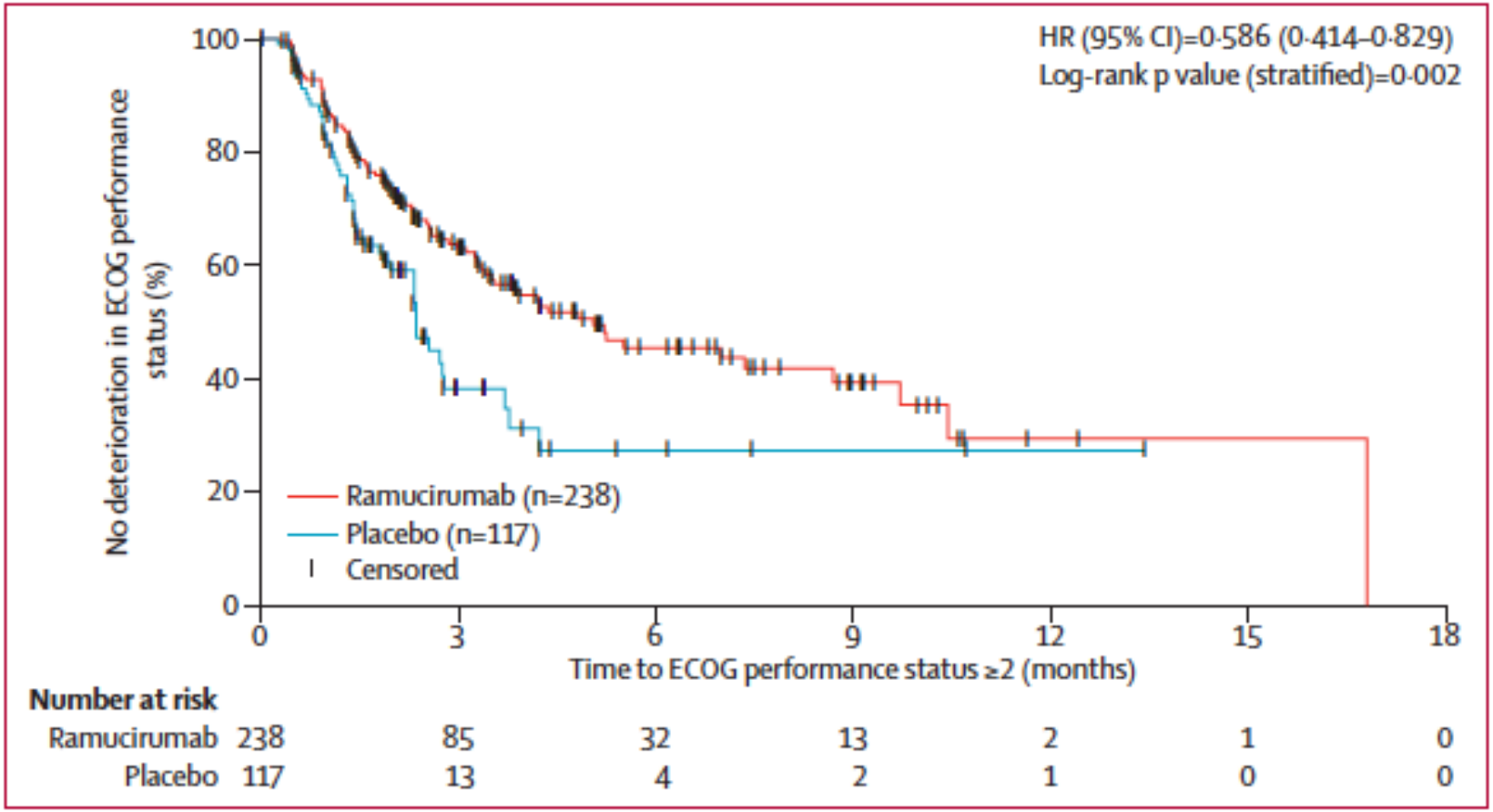

Figure 6: **Time to deterioration in ECOG performance status to a score of 2 or worse**
HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group.

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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)

R

1:1

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

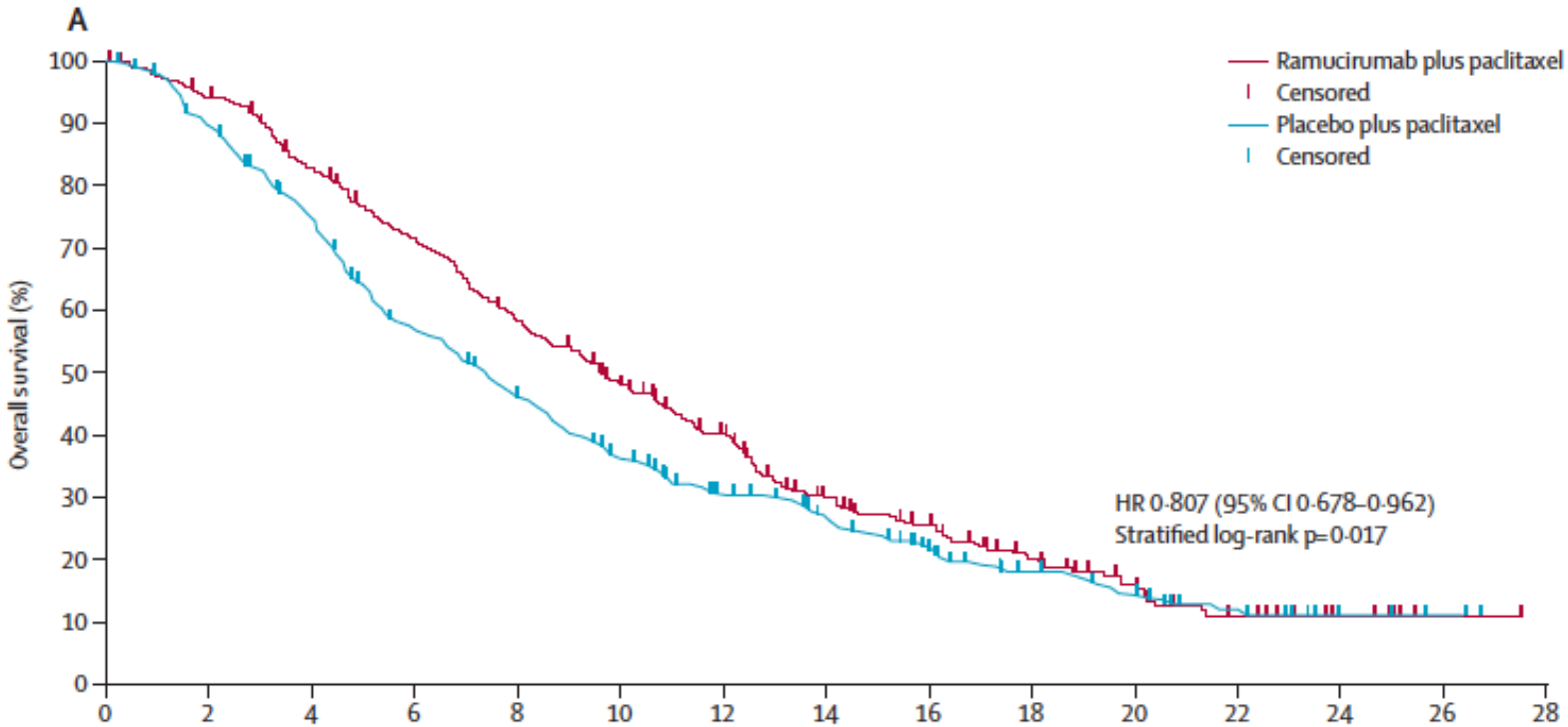
Arm B: Paclitaxel 80 mg/m^2 day 1, 8, 14 every 28 days
Ramucirumab 8 mg/kg every 2 weeks

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.

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)

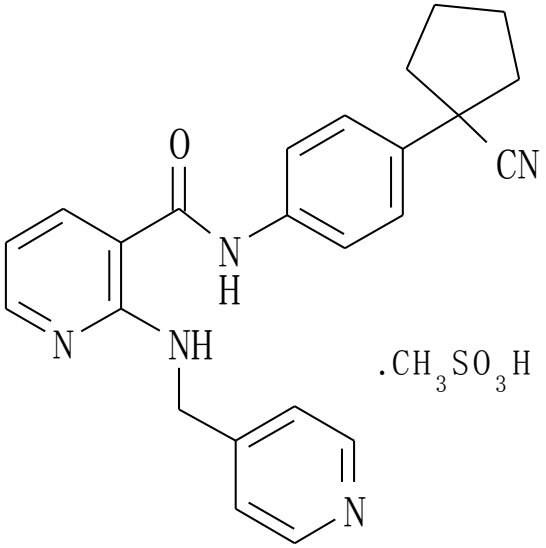
	Ramucirumab plus paclitaxel (n=327)				Placebo plus paclitaxel (n=329)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Bleeding or haemorrhage	123 (38%)	12 (4%)	1 (<1%)	1 (<1%)	51 (16%)	4 (1%)	2 (<1%)	2 (<1%)
Proteinuria	51 (16%)	4 (1%)	0	0	20 (6%)	0	0	0
Liver injury or failure	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.

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Gastric cancer: Second line and third line trials comparing BSC versus active treatment

Trial author	Year	Patients random (n)	Treatment	HR OS	P value	Gain in median survival
Thuss-Patience, et al.[1]	2011	40 1:1	Irinotecan	0.48	0.0023	2.4 months
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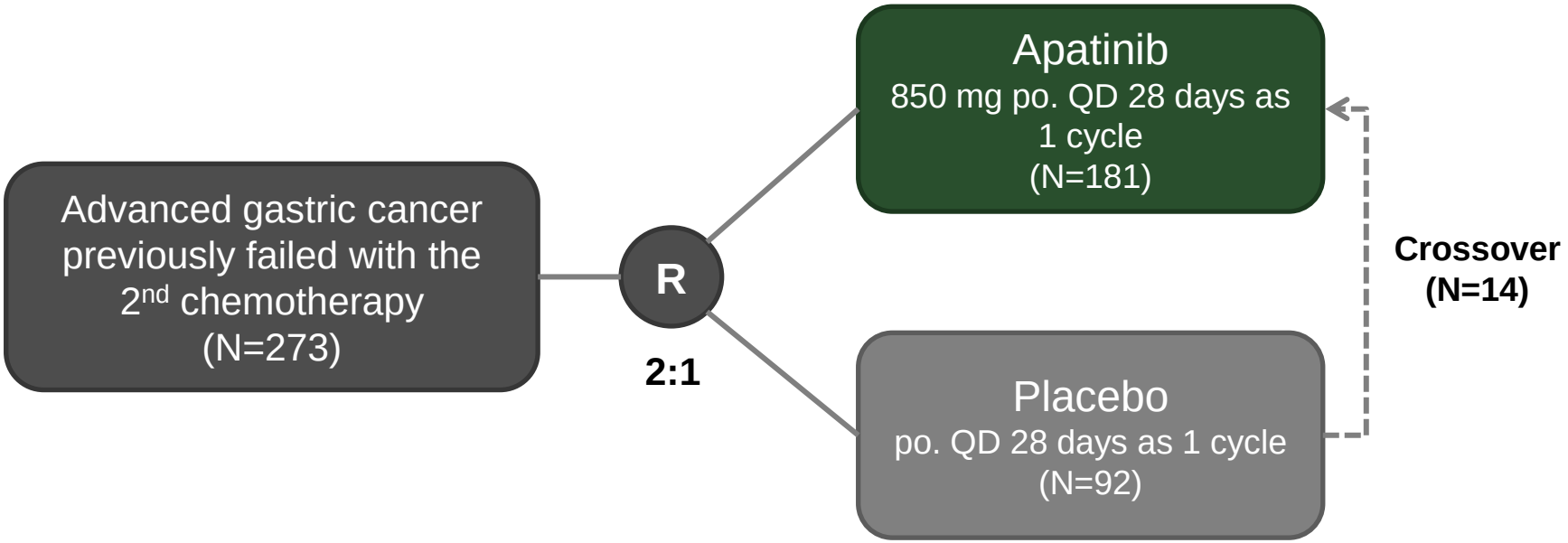
Fuchs, et al[5]	2014	355 2:1	Ramucirumab	0.77	0.047	1.4 months
Li, et al[6]	**2016**	**273 2:1**	**Apatinib**	**0.70**	**0.015**	**1.8 months**

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. 6. Li J, et al. J Clin Oncol 2016; 34:1448-1454.

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

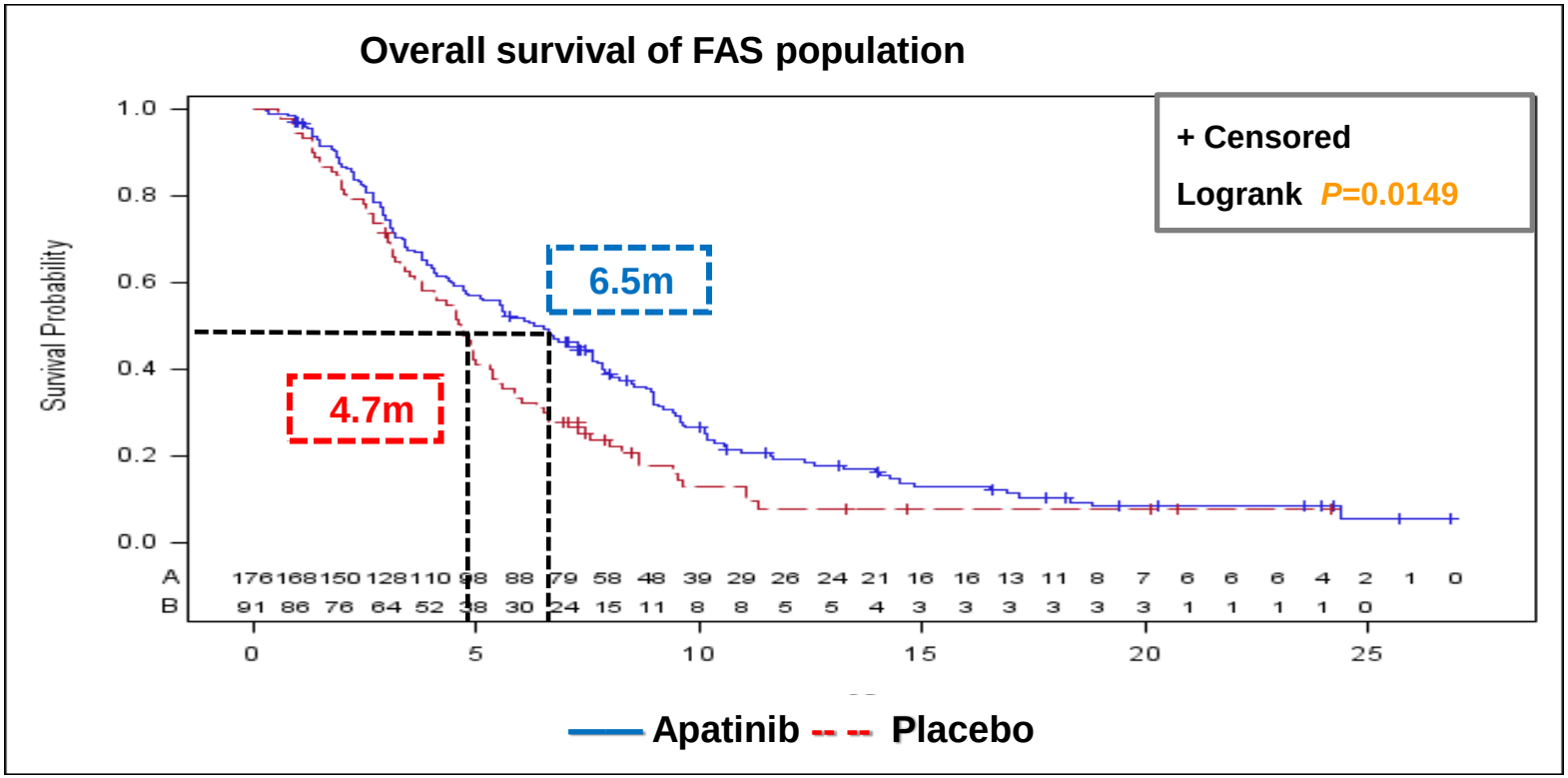
- Design: Multicenter, randomized, double-blind, placebo-controlled clinical trial



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

Li J, *et al.* J Clin Oncol 2016:34:1458-1464.

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)		

Li J, *et al.* J Clin Oncol 2016:34:1458-1464.

Anti-angiogenic treatment in gastric cancer:

- Only anti-VEGF or anti-VGEFR therapies
- Bevacizumab improves and RR and PFS, but not OS in advanced disease
- Bevacizumab of no value when added to perioperative treatment in localized disease
- Ramucirumab prolongs OS in second line as single agent and in combination with weekly pacltaxel
- Apatinib prolongs OS in 2nd and 3rd line
- Studies in early lines underway