ESMO Preceptorship Program

Gastric Cancer – Multidisciplinary Management, Standards of Care, Therapeutic Targets and Future Perspectives

October 11th – 12th, 2013, Berlin

Biological Targeted Agents in Gastric Cancer

Florian Lordick, MD, PhD

Professor of Oncology

Director of the University Cancer Center UCCL

Leipzig, Germany

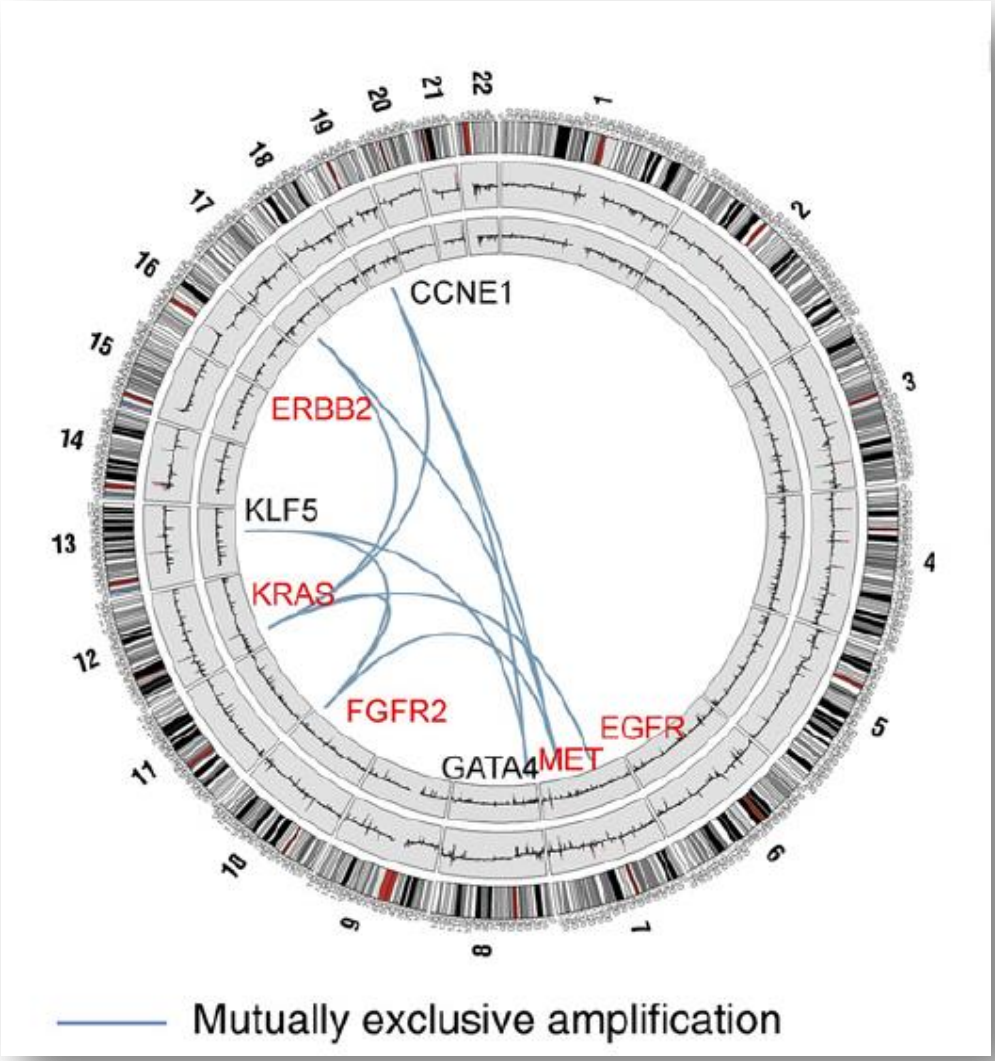
ESMO European Society for Medical Oncology

Universitätsklinikum Leipzig Anstalt öffentlichen Rechts

UCCL UNIVERSITÄRES KREBSZENTRUM

Gastric Cancer Biology

Receptor Tyrosine Kinase Gene Amplification

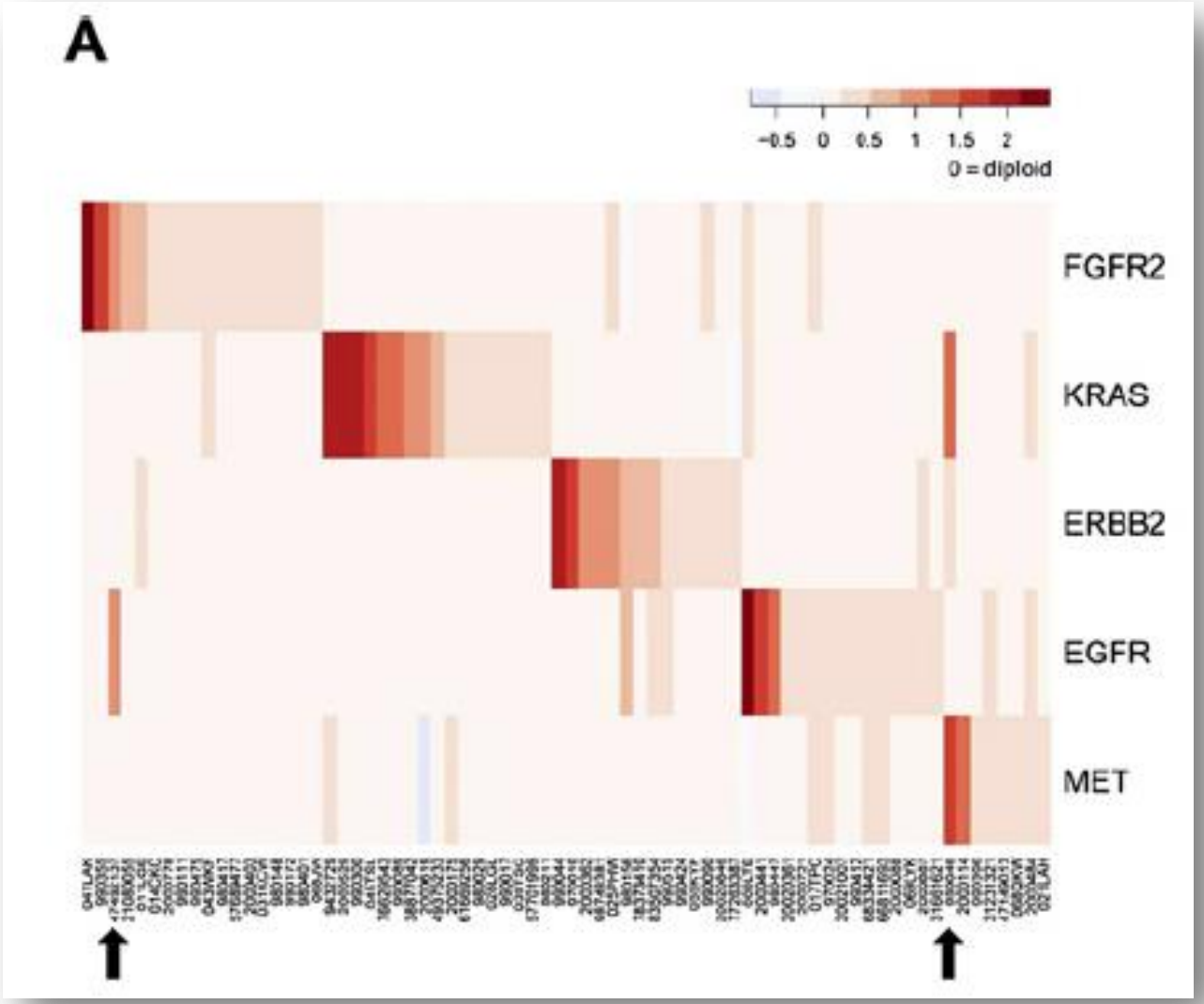


Patrick Tan,
Duke Univ Singapore

Genomic DNA were extracted from flash-frozen tissues or cell pellets using a Qiagen genomic DNA extraction kit (Qiagen, Hilden, Germany), and profiled on Affymetrix SNP 6.0 arrays (Affymetrix, Santa Clara, California, USA)

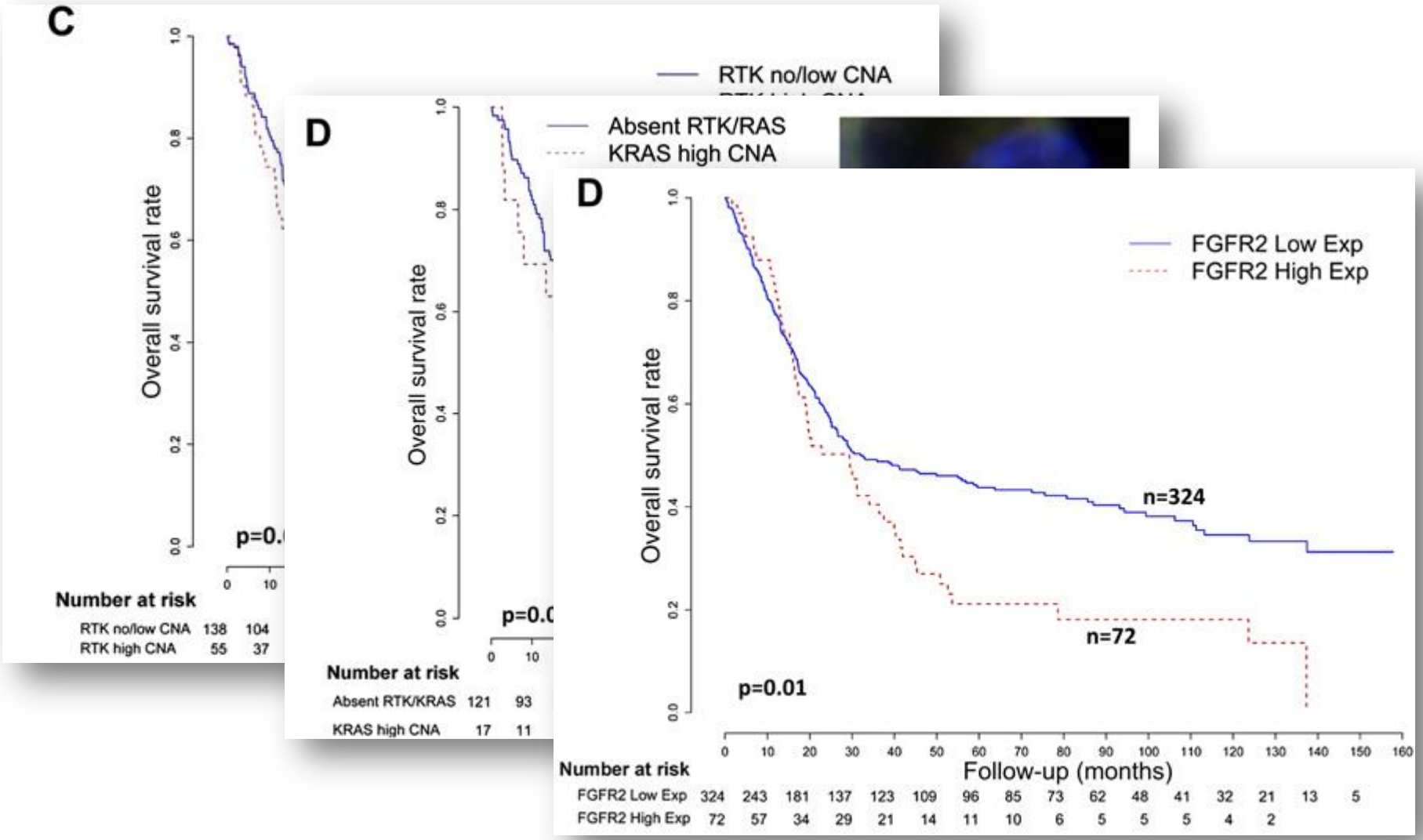
Deng et al. *Gut* 2012; 61: 673-684

Gastric Cancer Biology



Deng et al. *Gut* 2012; 61: 673-684

Gastric Cancer Biology



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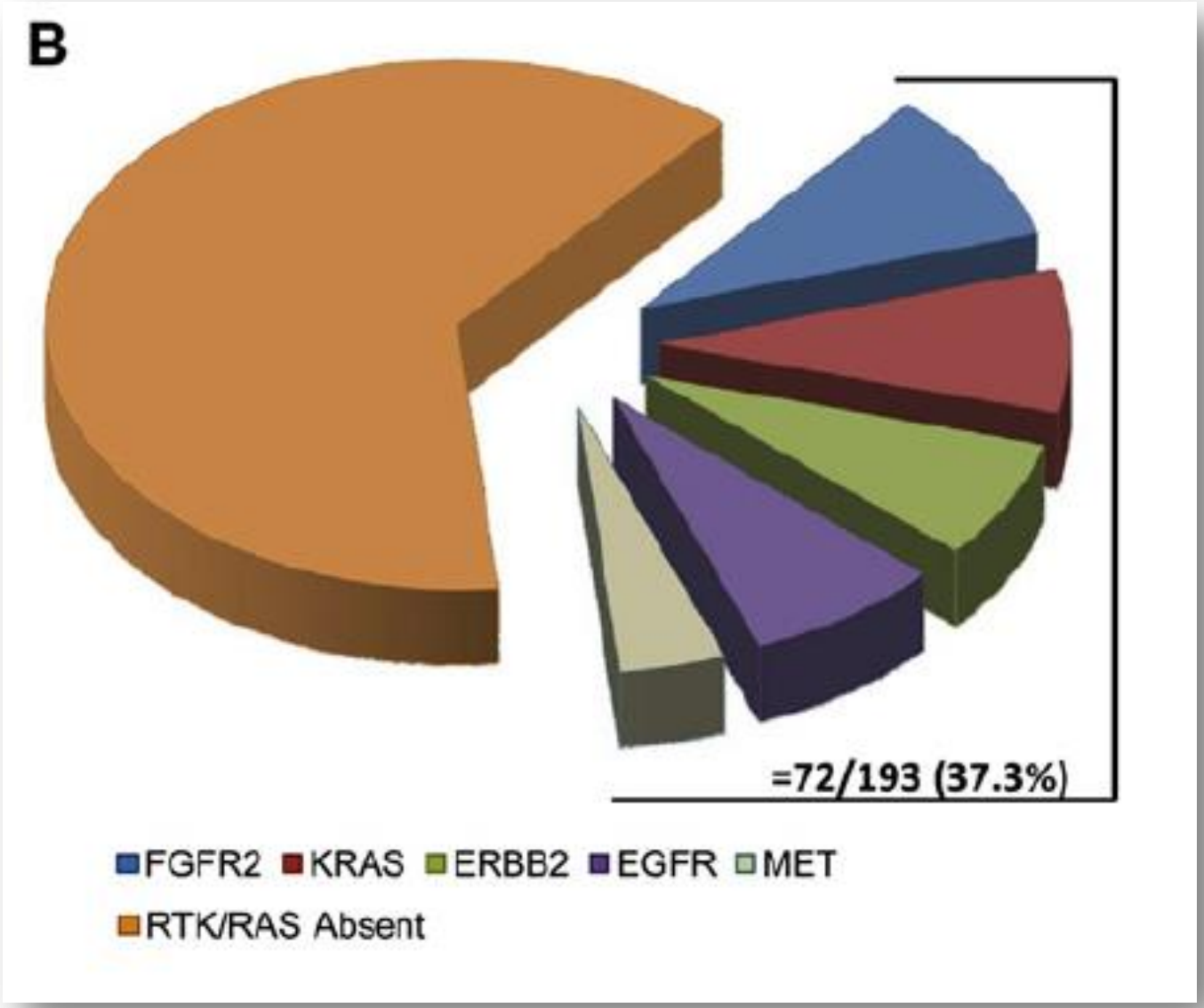
Gastric Cancer Biology



Deng et al. *Gut* 2012; 61: 673-684

Targeted Therapy

„Personalized Treatment“

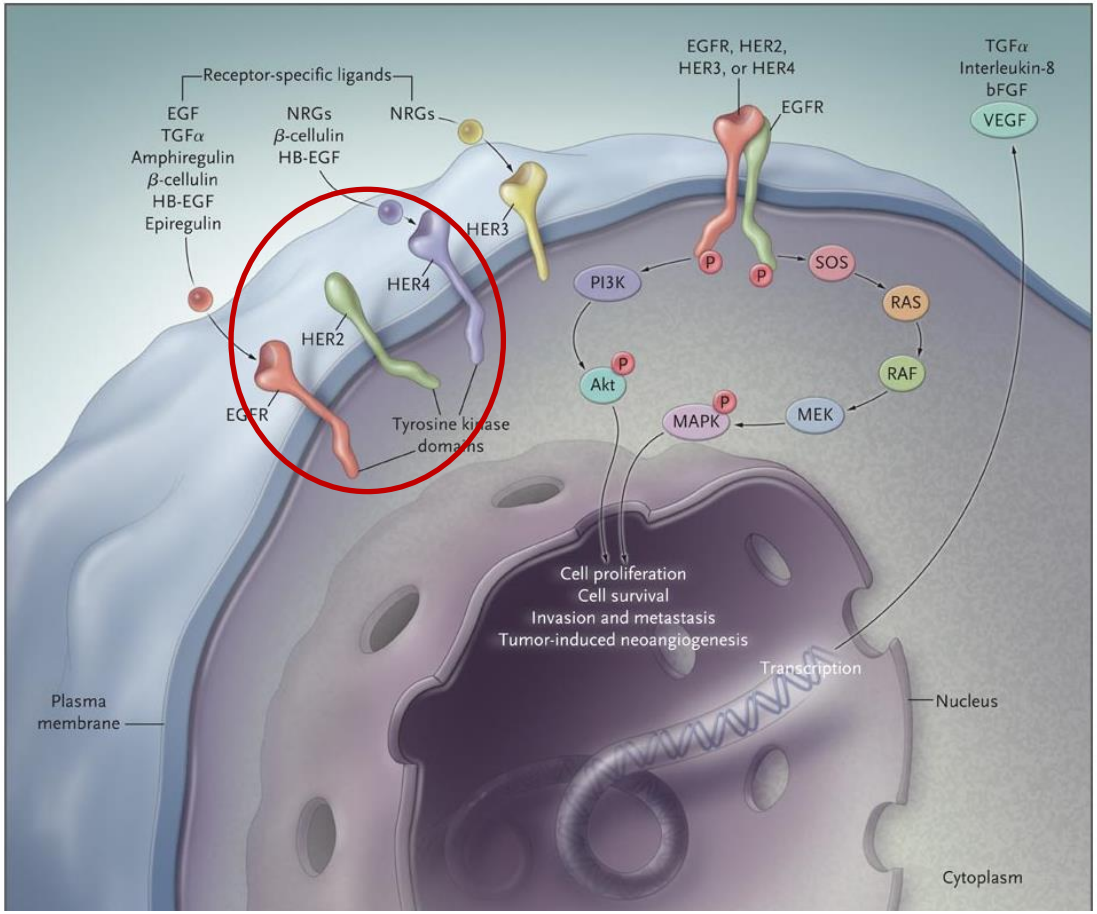
Select the right treatment for every individual patient

Biological Treatment Selection

Premisses & Hurdles

- Do we know the relevant target structures?
- Is the detection of these structures reliable?
- Is a targeted treatment/drug available?
- Is the response to this specific treatment predictable?
- Is the targeted treatment feasible and tolerable?

Is the Target Expressed and is it Relevant?
Epidermal Growth Factor Receptor Signalling



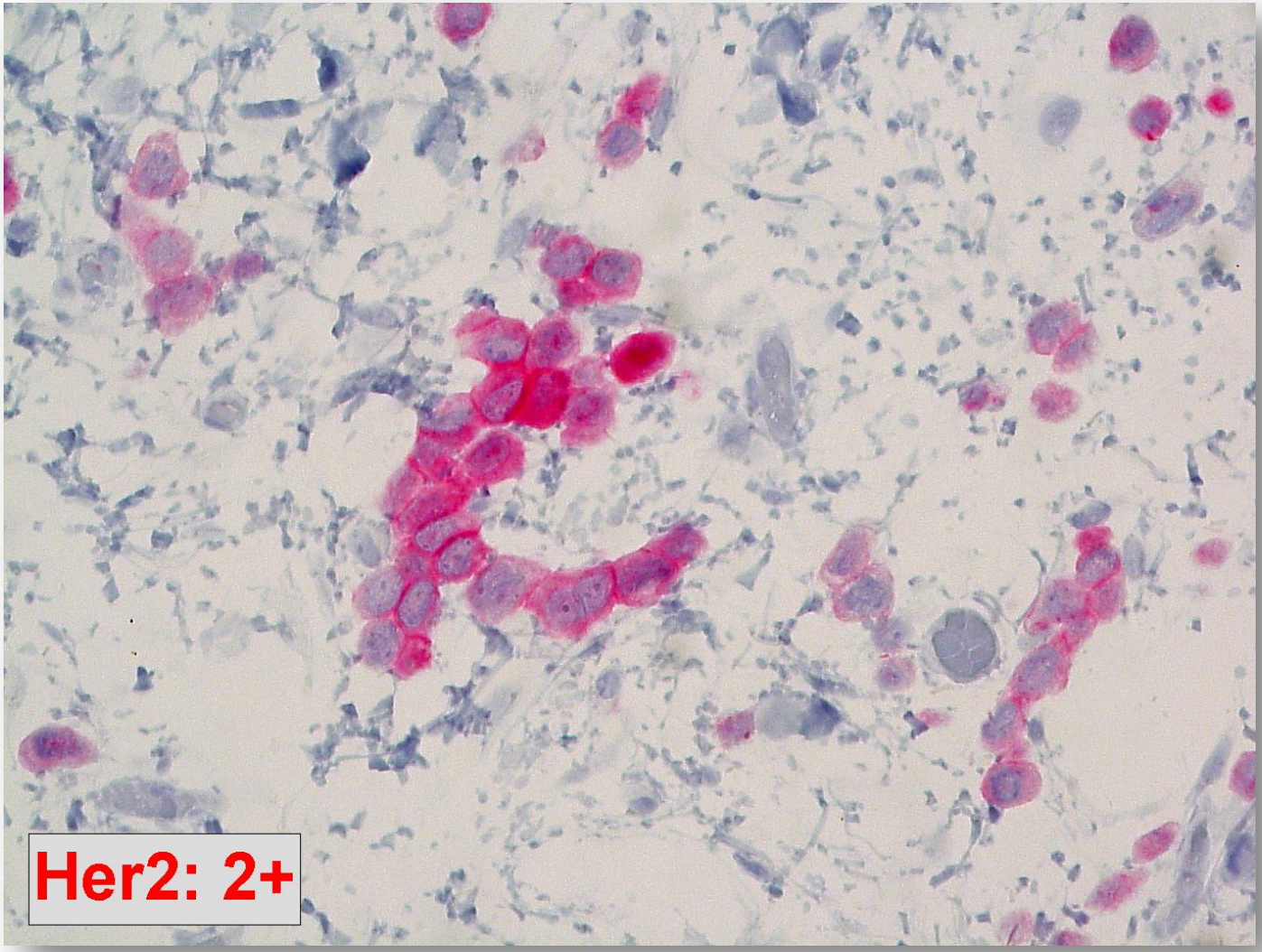
EGFR family

EGFR:
Epidermal Growth Factor Receptor

HER-1 (EGFR)
HER-2
HER-3
HER-4

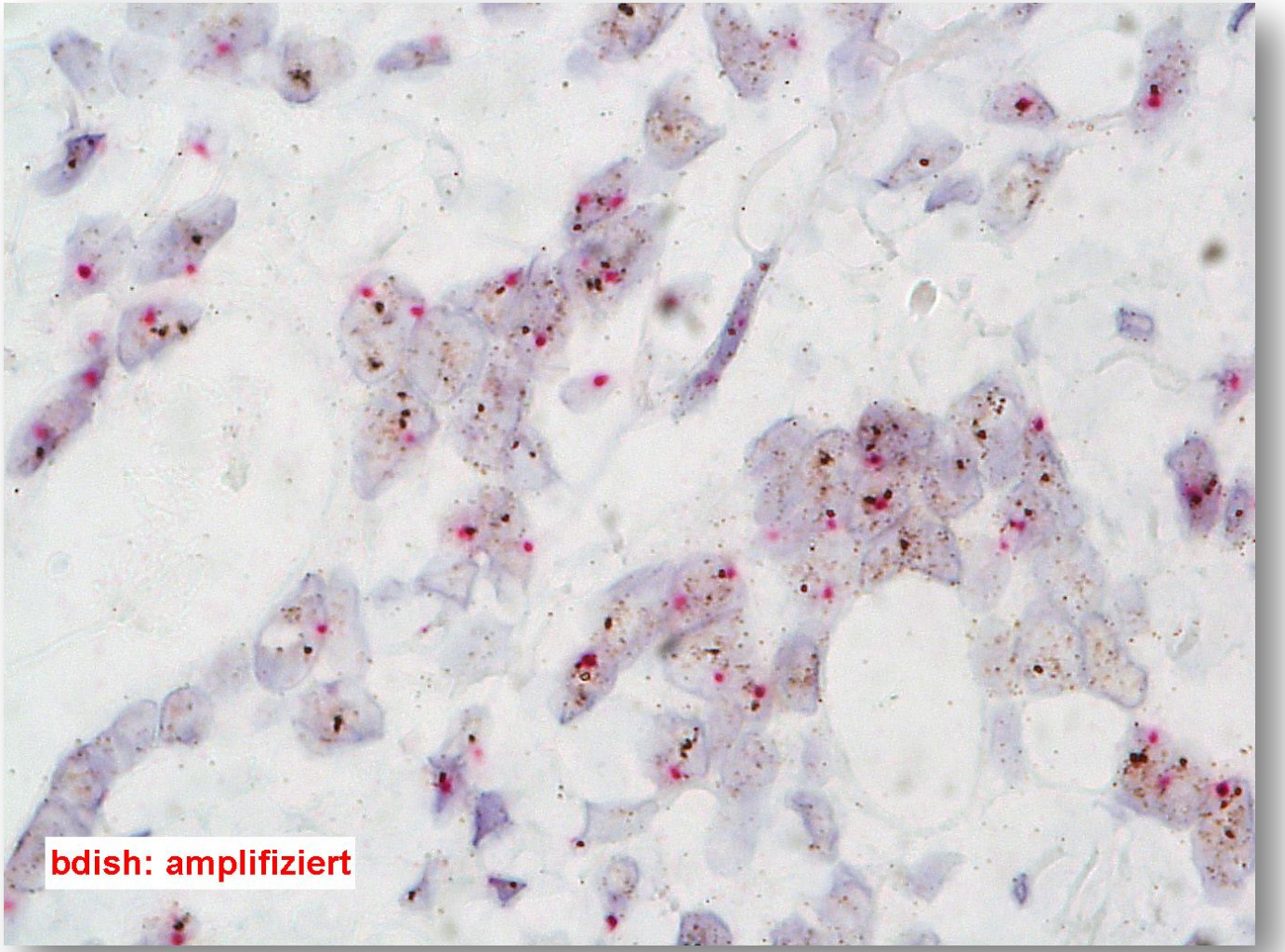
from: **Ciardello F, Tortora G.** *N Engl J Med.* 2008; 358: 1160-1174

Reliable Detection of a Target?
e.g. HER2 Immunohistochemistry (IHC)



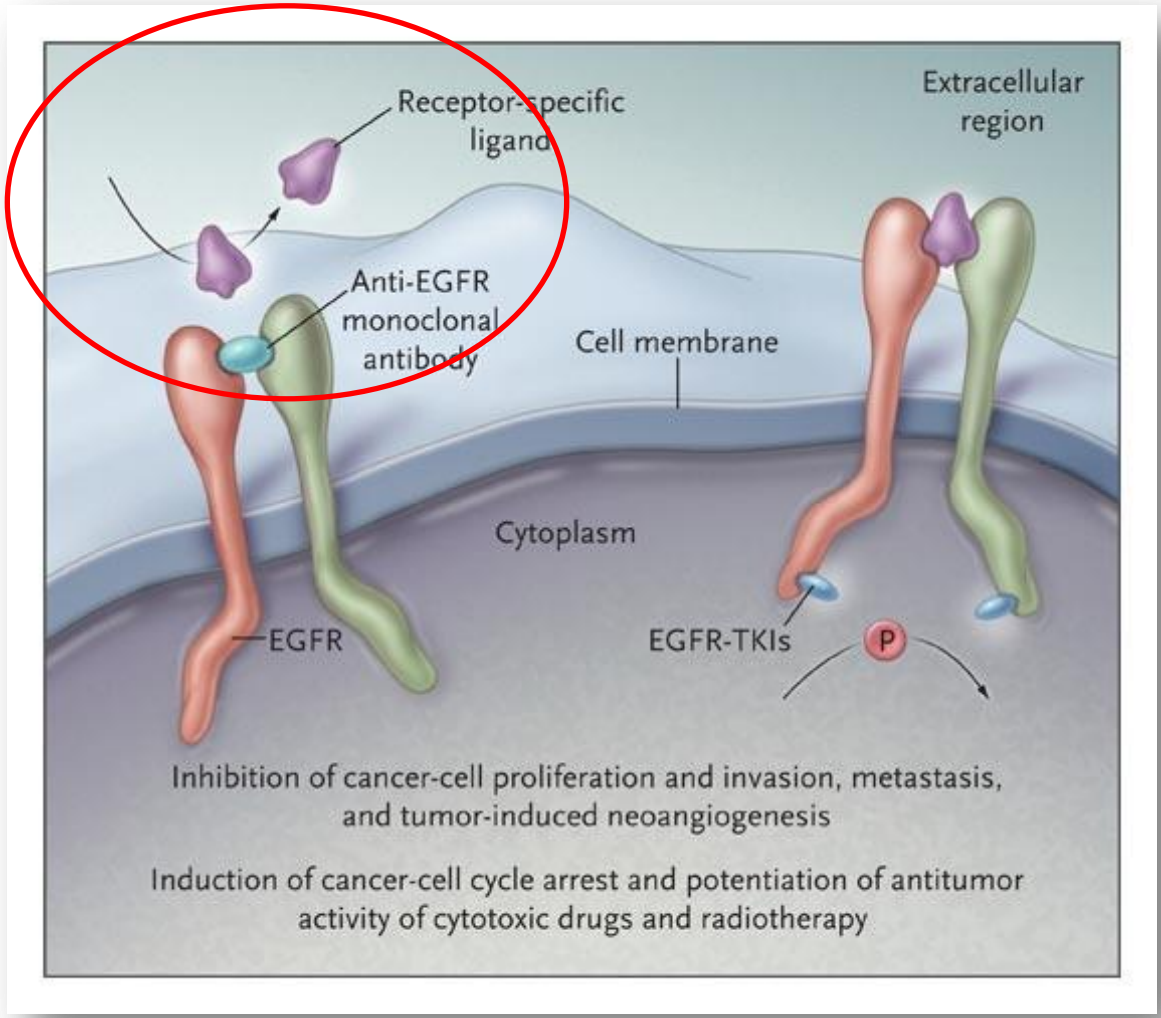
With courtesy of Prof. Donhuijsen, Pathologie Braunschweig

Reliable Detection of a Target?
e.g. HER2 in situ hybridization (ISH)



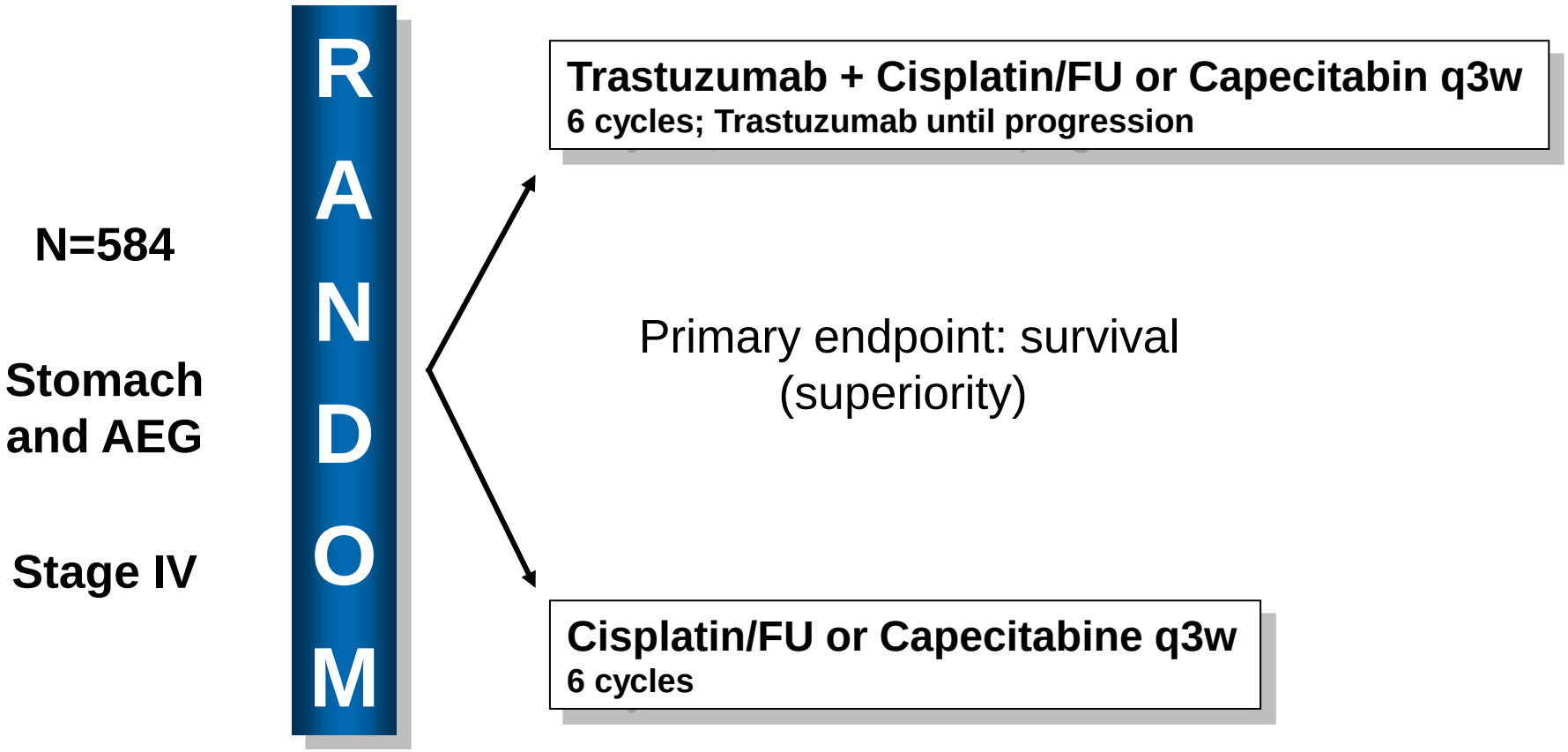
With courtesy of Prof. Donhuijsen, Pathologie Braunschweig

Is a targeted treatment available? HER-antibodies and HER-kinase-inhibitors



aus: **Ciardello F, Tortora G.** *N Engl J Med.* 2008; 358: 1160-1174

Trastuzumab (Herceptin®) in Her2+ Gastric Cancer: ToGA Study



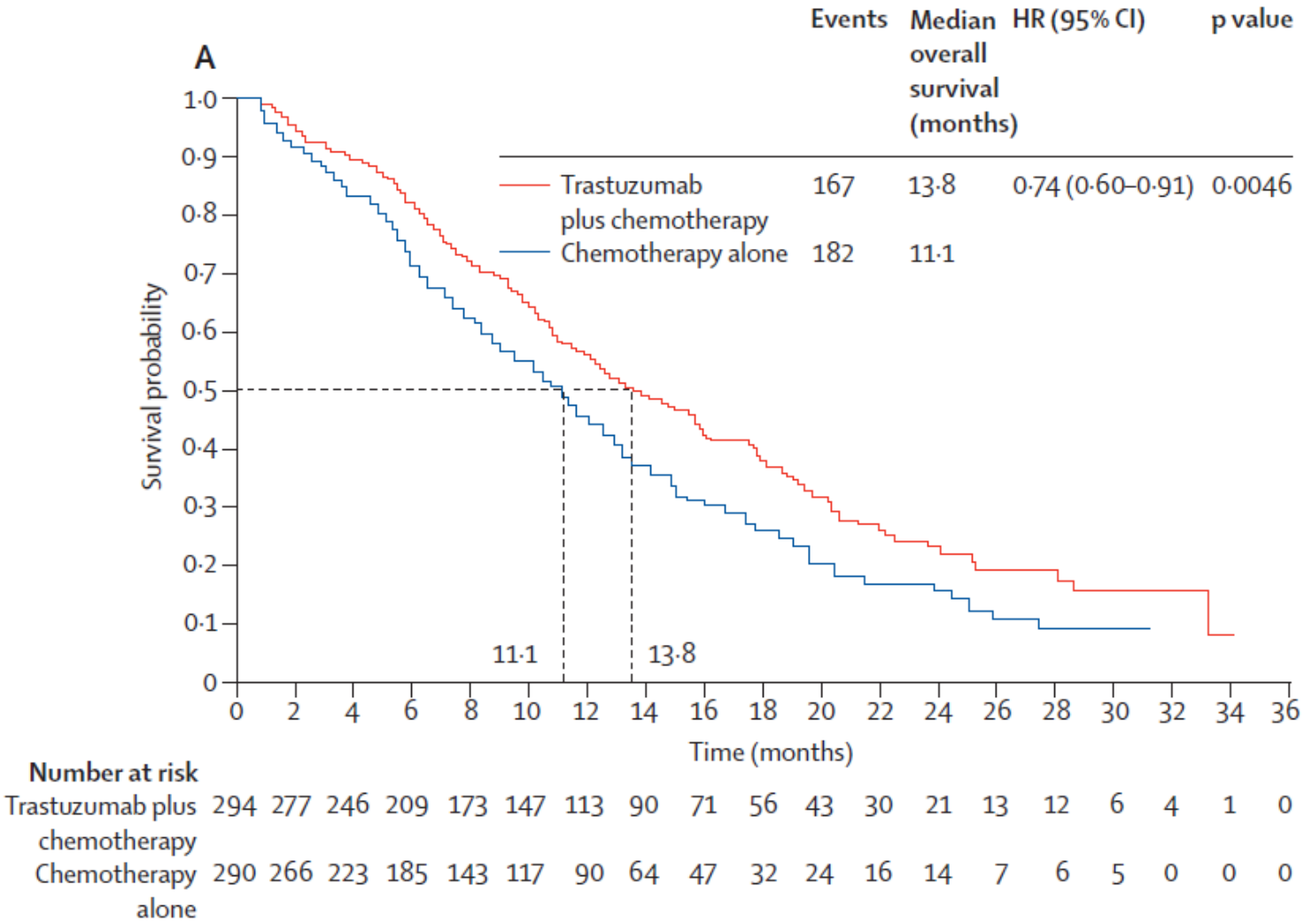
Bang Y et al. *Lancet* 2010; 376: 687-697

ToGA Response Data

	Trastuzumab plus chemotherapy (n=294)	Chemotherapy alone (n=290)
Overall tumour response rate	139 (47%)	100 (35%)
Complete response	16 (5%)	7 (2%)
Partial response	123 (42%)	93 (32%)
Stable disease	93 (32%)	101 (35%)
Progressive disease	35 (12%)	53 (18%)
Missing	27 (9%)	36 (12%)

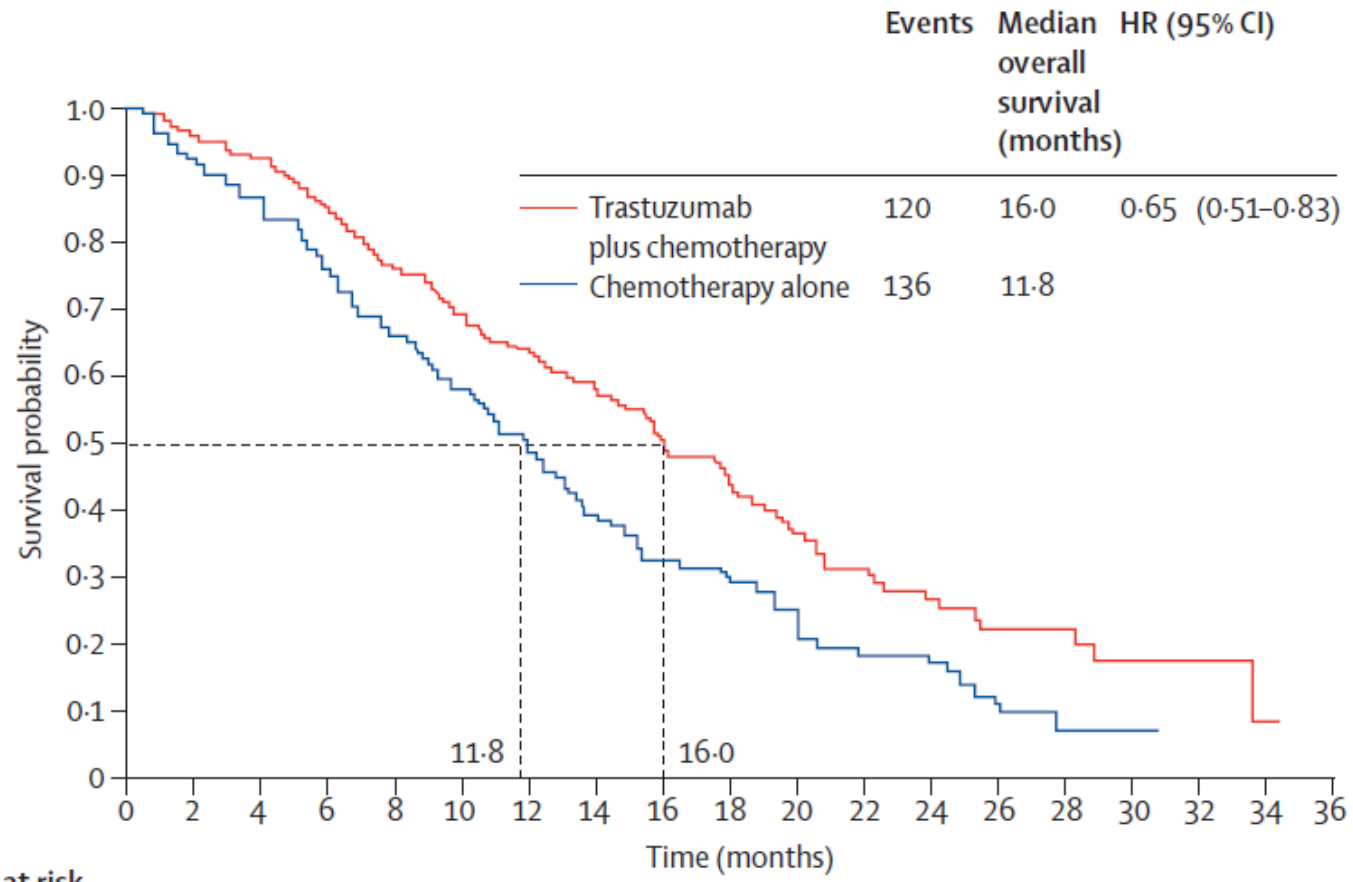
Bang Y et al. *Lancet* 2010; 376: 687-697

ToGA Survival



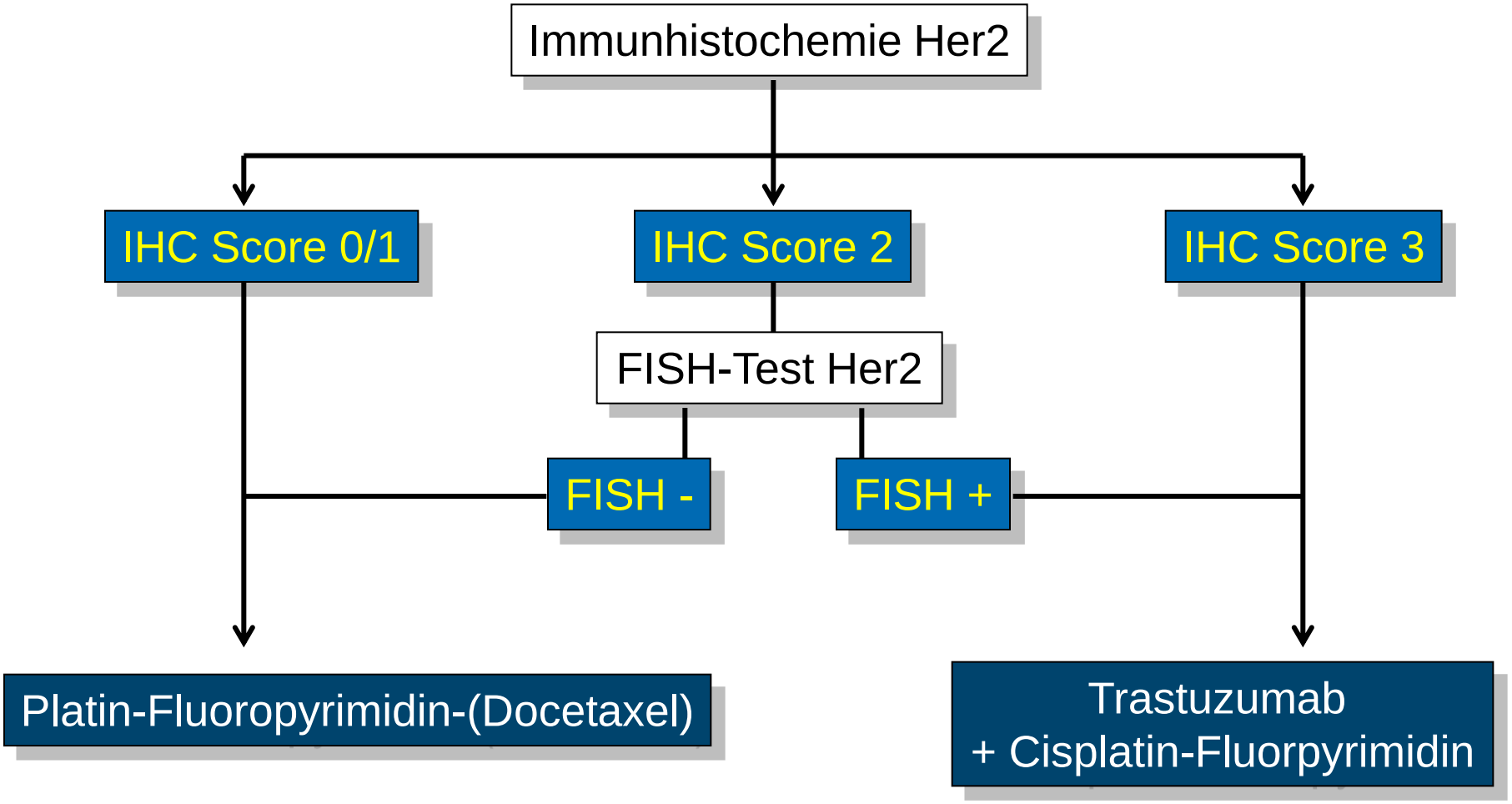
Bang Y et al. *Lancet* 2010; 376: 687-697

ToGA: Survival
Her2 Status: IHC 3+ or IHC 2+/FISH+



Bang Y et al. *Lancet* 2010; 376: 687-697

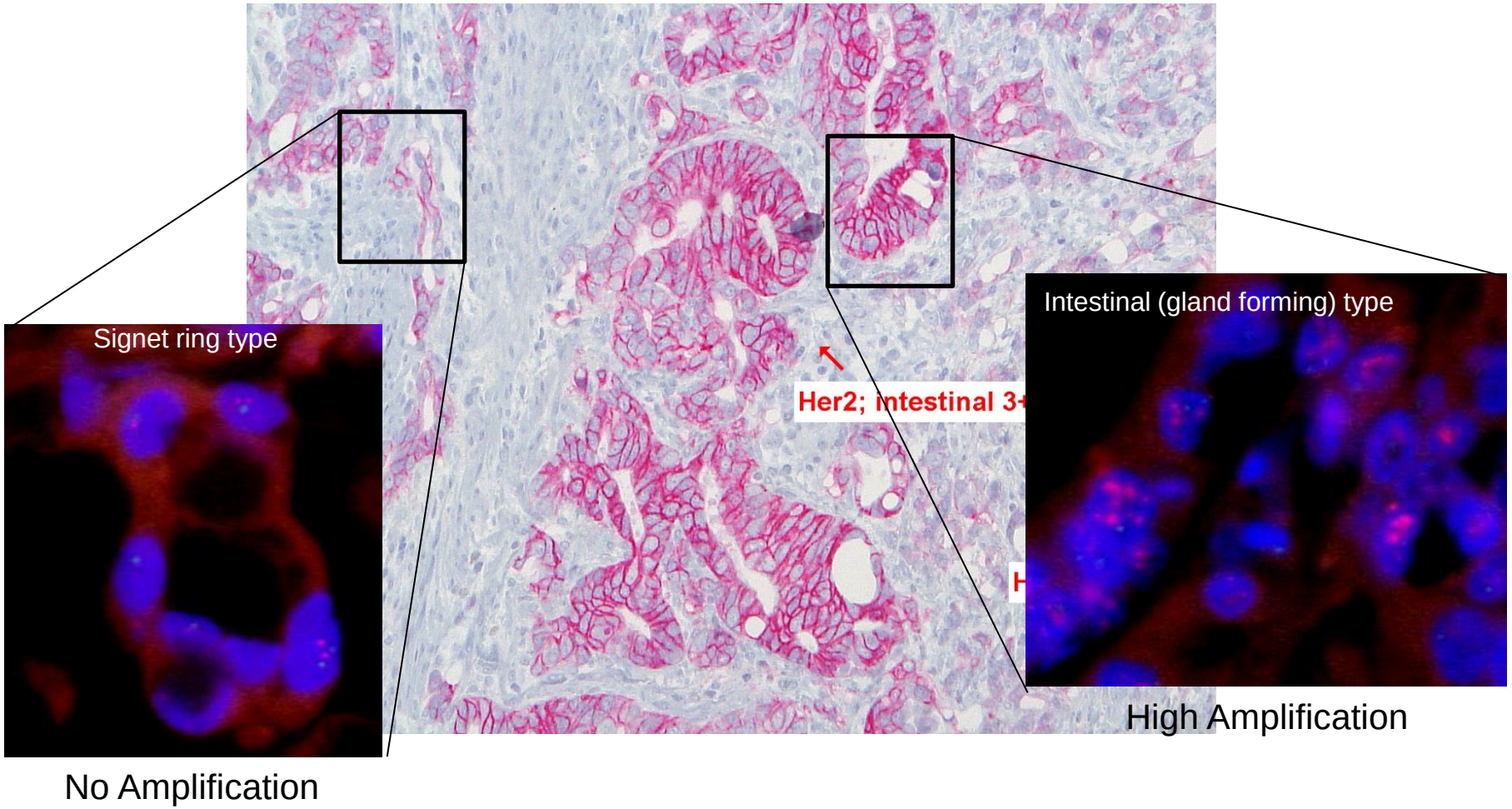
1st-line Treatment Algorithm 2013 Advanced Stomach Cancer



Lordick F et al. *Clin Transl Oncol* 2011; 13: 597-598

HER2 Quality Assurance and Problems

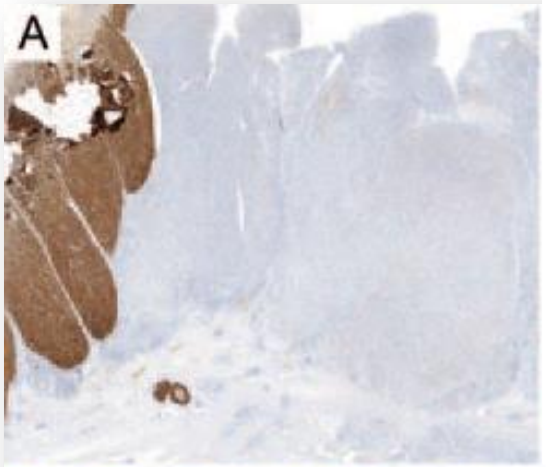
Focal staining in 33% of gastric cancers!

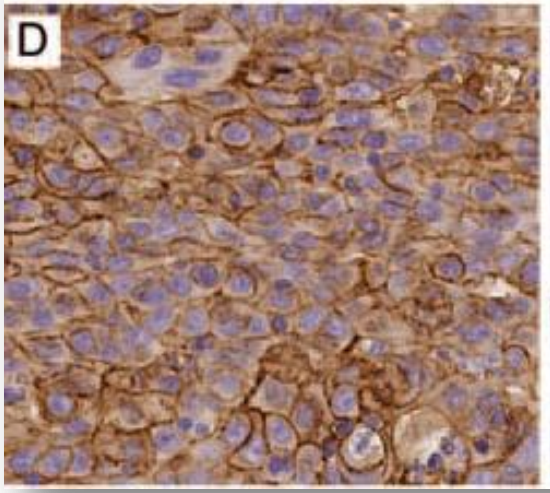


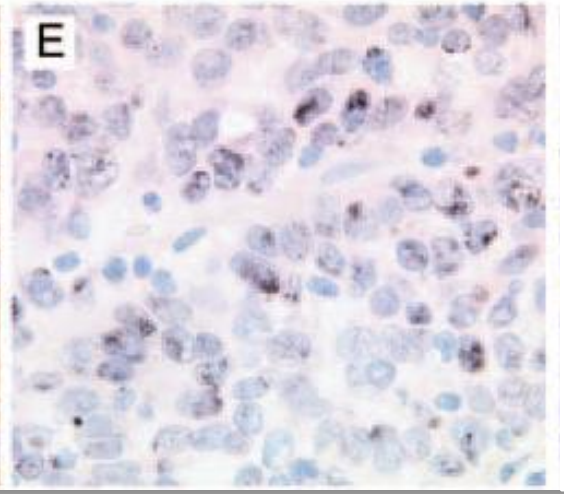
With courtesy of Professor Rüschoff

Heterogeneity and Sampling Errors

2230 Core biopsies from TMA‘s of 454 resection specimens



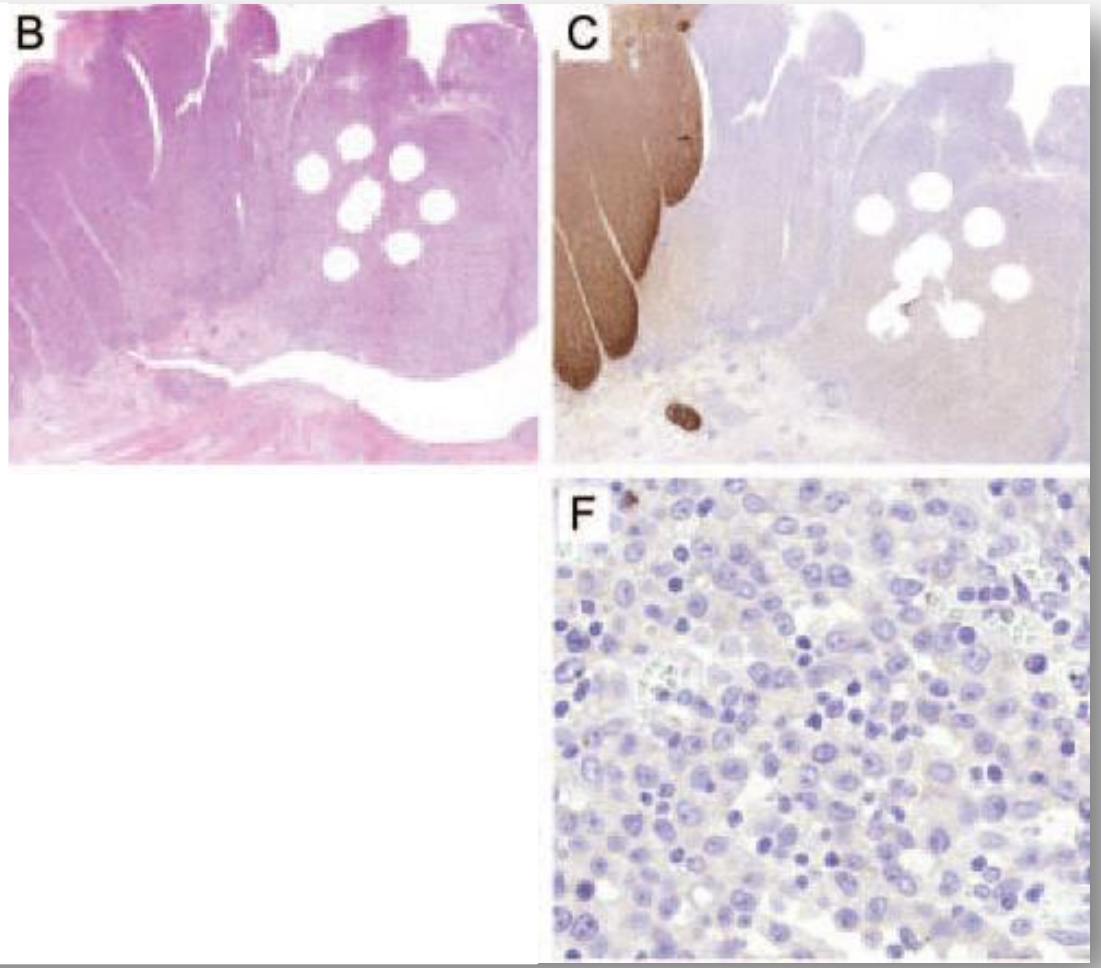




Warneke VS… Röcken C. *Ann Oncol* 2013 Mar;24(3):725-33

Heterogeneity and Sampling Errors

2230 Core biopsies from TMA‘s of 454 resection specimens



Warneke VS… Röcken C. *Ann Oncol* 2013 Mar;24(3):725-33

Heterogeneity and Sampling Errors

2230 Core biopsies from TMA‘s of 454 resection specimen

Core biopsies (from TMA‘s) were compared with whole tissue sections by two indepenedent investigators

HER-2 from whole tissue sections:	8.1 und 8.4% positivity
HER-2 from core biopsies:	6.3 und 6.3% positivity

False negative rate of core biopsies:	**24%**
False positive rate of core biopsies:	**3%**

Warneke VS… Röcken C. *Ann Oncol* 2013 Mar;24(3):725-33

Heterogeneity and Sampling Errors

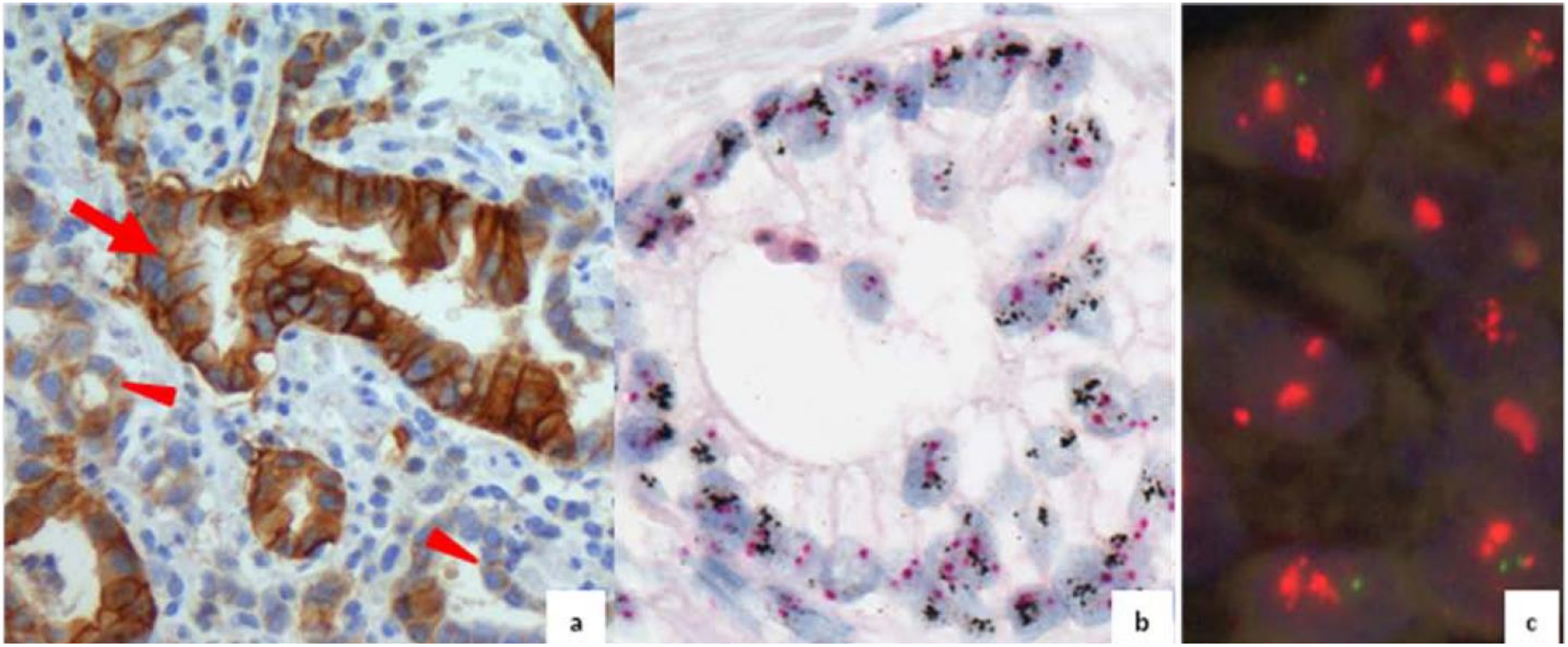
Practical consequence

When selecting patients for anti-HER2 treatment,…

- Don‘t rely on one negative endoscopic biopsy (false-negative rate: 24%)
- Investigate whole tissue sections from resection specimens in addition to endoscopic biopsies (if available)
- Take new biopsies from metastatic sites (if feasible)

Warneke VS… Röcken C. *Ann Oncol* 2013 Mar;24(3):725-33

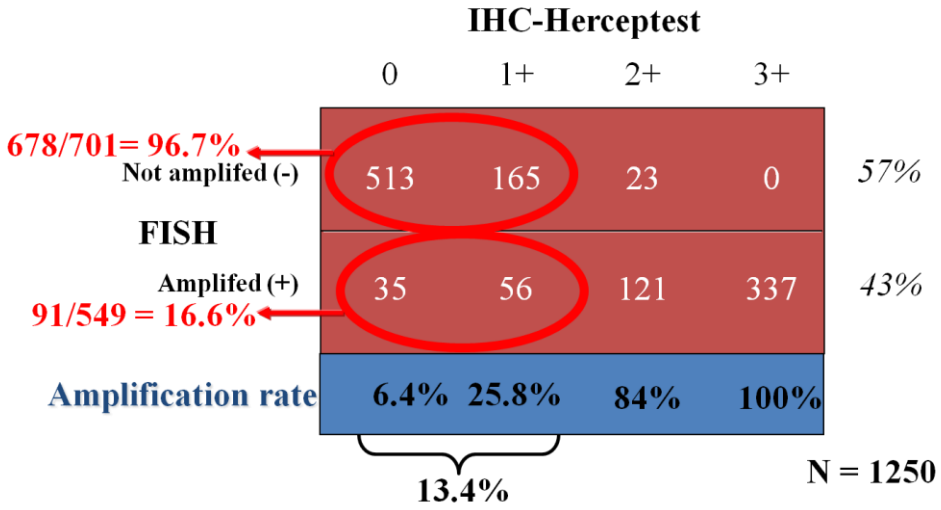
FISH, CISH, BDISH or IHC



Rüschoff et al., 2010

Warneke VS… Röcken C. *Ann Oncol* 2013 Mar;24(3):725-33

HER2 Results from LoGIC



	HER2 /CEP 17 Ratio				
IHC, n (%)	<2	2-5	5-10	>10	Total
0	518 (73)	29 (18)	4 (2)	0 (0)	551
1+	167 (23)	45 (28)	12 (6)	1 (<1)	225
2+	24 (3)	57 (35)	45 (24)	18 (9)	144
3+	0 (0)	31 (19)	124 (67)	181 (91)	336
Total	709	162	185	200	1256

Overall concordance between FISH and IHC results was 90.9% (95% CI: 89.2%, 92.5%)

Press. *ECCO* 2013

HER2 Results from ToGA

	Trastuzumab plus chemotherapy (n=294)	Chemotherapy alone (n=290)
FISH positive/IHC 0	23 (8%)	38 (13%)
FISH positive/IHC 1+	38 (13%)	32 (11%)
FISH positive/IHC 2+	80 (27%)	79 (27%)
FISH positive/IHC 3+	131 (45%)	125 (43%)
FISH negative/IHC 3+	9 (3%)	6 (2%)
FISH positive/IHC no result	5 (2%)	2 (1%)
FISH no result/IHC 3+	8 (3%)	8 (3%)

Bang Y et al. *Lancet 2010*; 28: 487-497

HER2 Results from ToGA

	Trastuzumab plus chemotherapy (n=294)	Chemotherapy alone (n=290)
FISH positive/IHC 0	23 (8%)	38 (13%)
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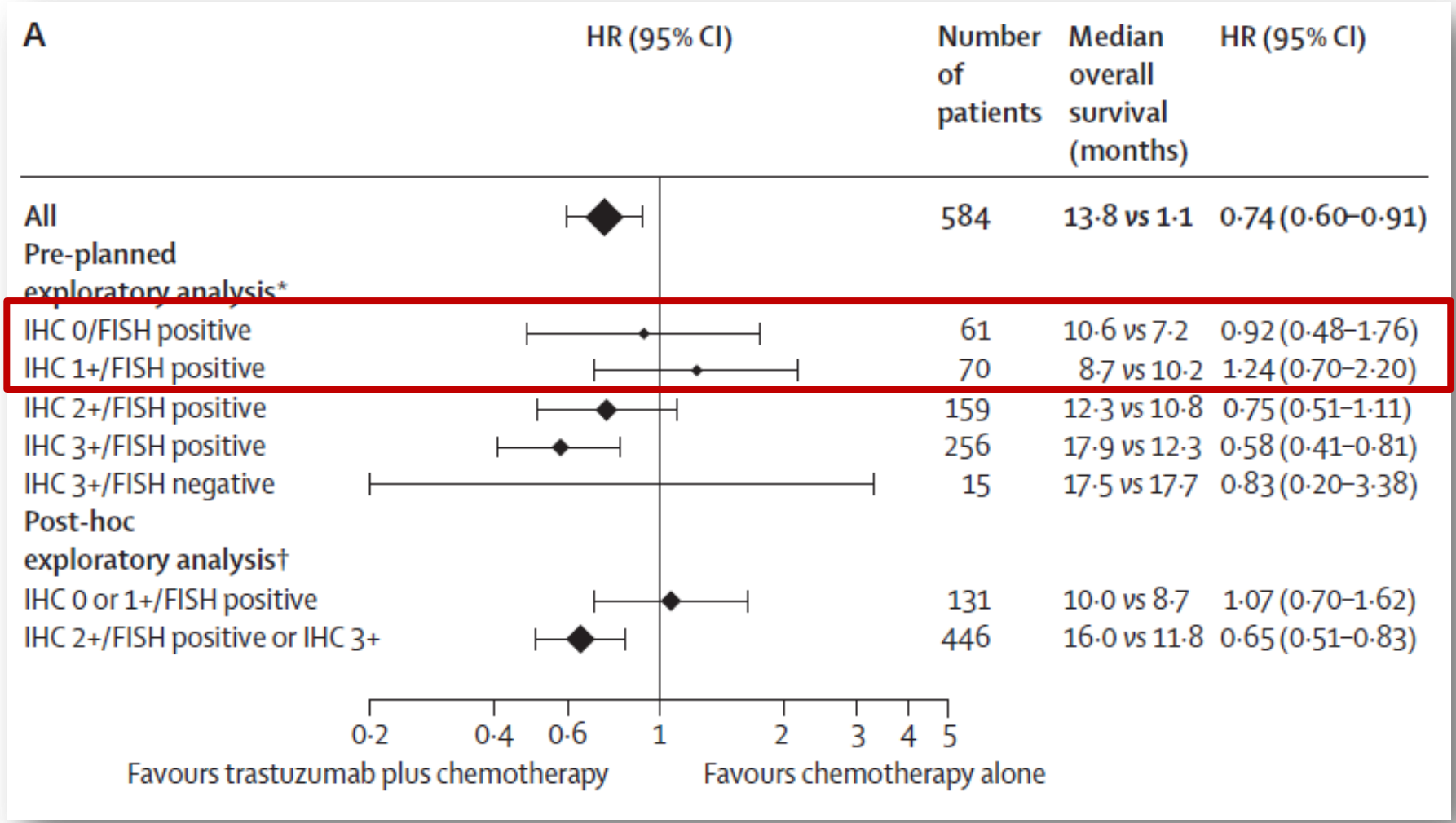
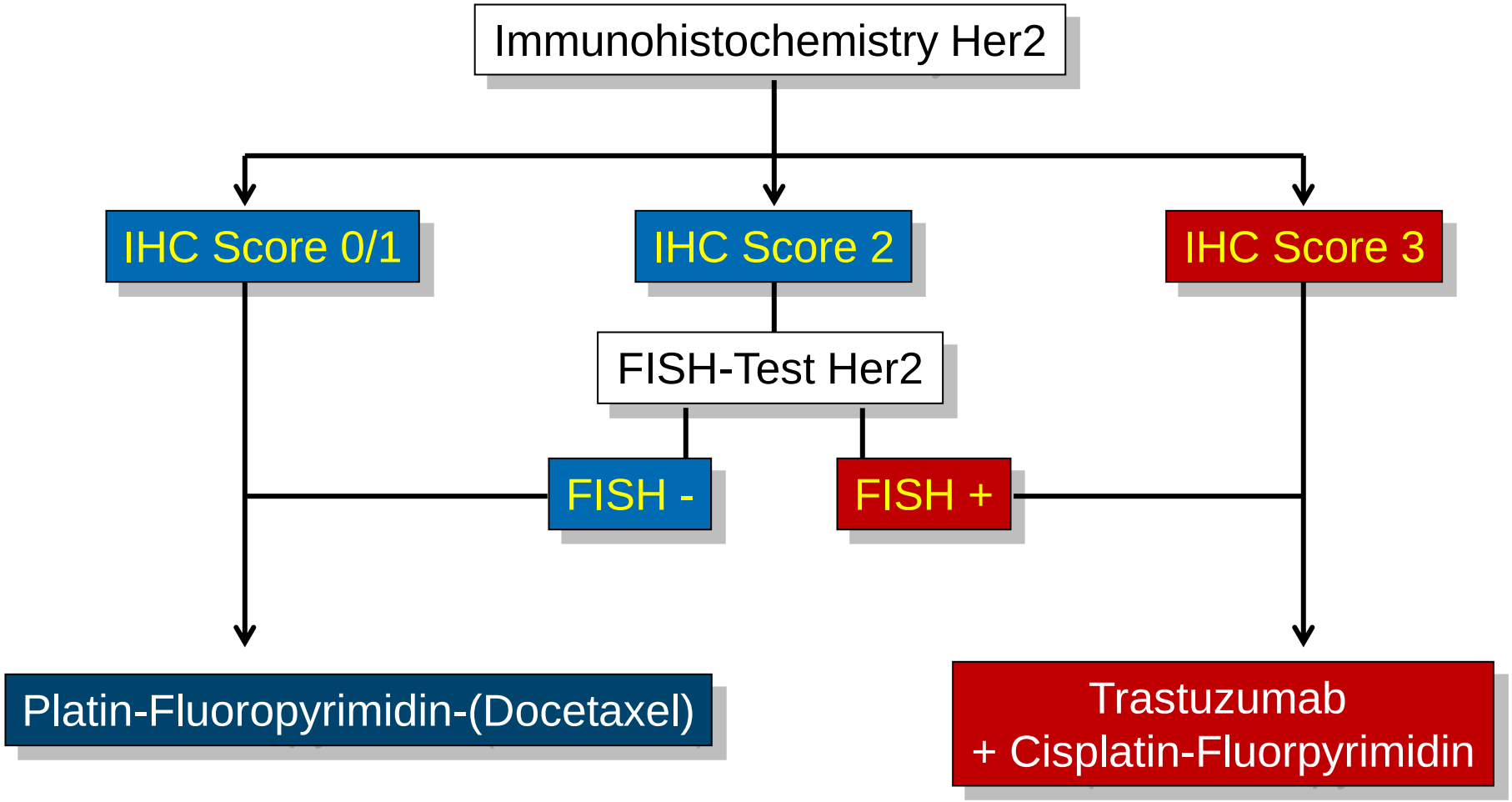


Bang Y et al. *Lancet 2010*; 28: 487-497

1st Line Treatment Algorithm



Lordick F et al. *Future Oncology* 2011;7:187-99

Molecular Pathology

reviews

Annals of Oncology 24: 1958–1963, 2013
doi:10.1093/annonc/mdt153
Published online 23 April 2013

European Consensus Conference for external quality assessment in molecular pathology

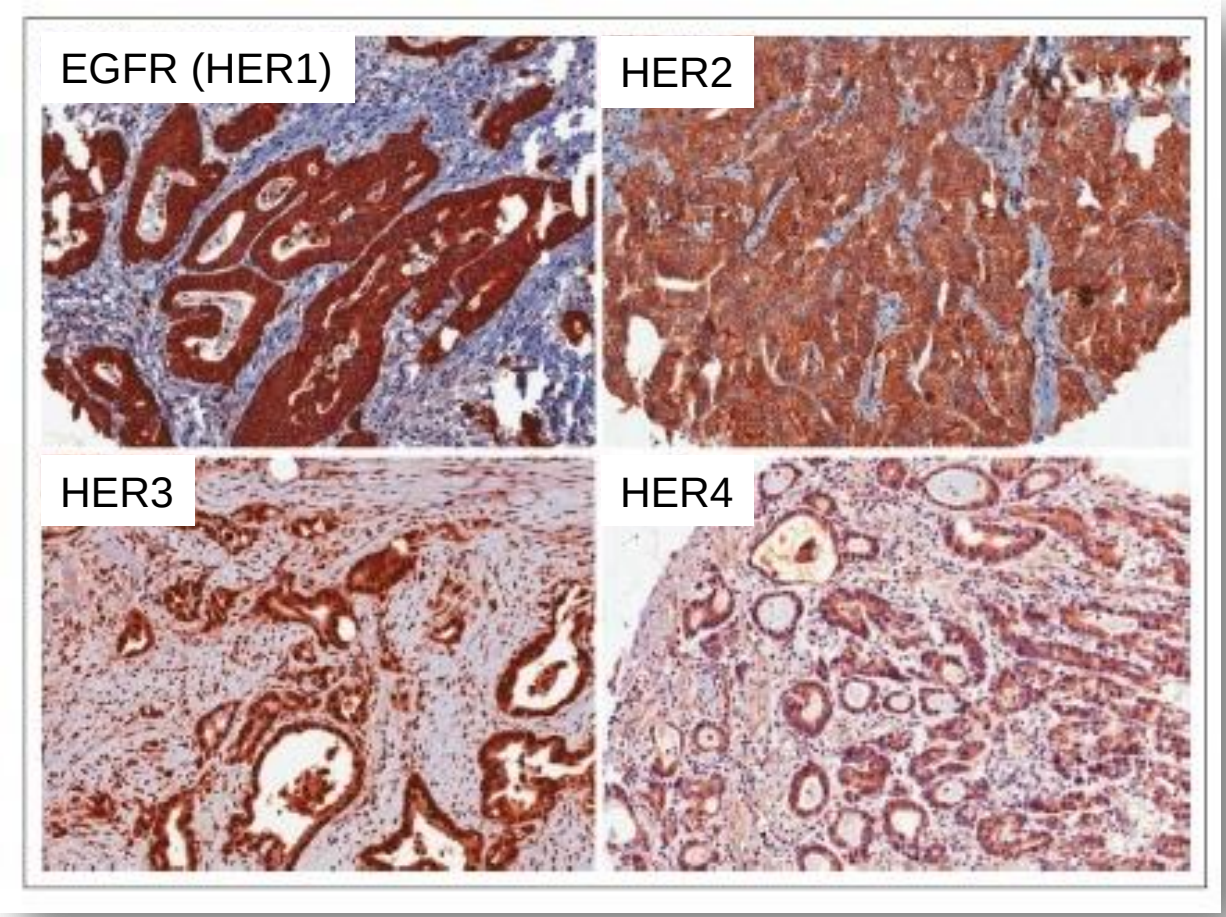
J. H. van Krieken[1], A. G. Siebers[1] & N. Normanno[2*] On behalf of the Quality Assurance for Molecular Pathology group[†]

[1]*Department of Pathology 824, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands;* [2]*Cell Biology and Biotherapy Unit, INT-Fondazione Pascale, Naples, Italy*

Received 7 December 2012; revised 14 March 2013; accepted 15 March 2013

Molecular testing of tumor samples to guide treatment decisions is of increasing importance. Several drugs have been approved for treatment of molecularly defined subgroups of patients, and the number of agents requiring companion diagnostics for their prescription is expected to rapidly increase. The results of such testing directly influence the management of individual patients, with both false-negative and false-positive results being harmful for patients. In this

EGFR-Family-Dimers



Begnami et al. *J Clin Oncol* 2011; 29: 3030-3036

EGFR-Family-Dimers

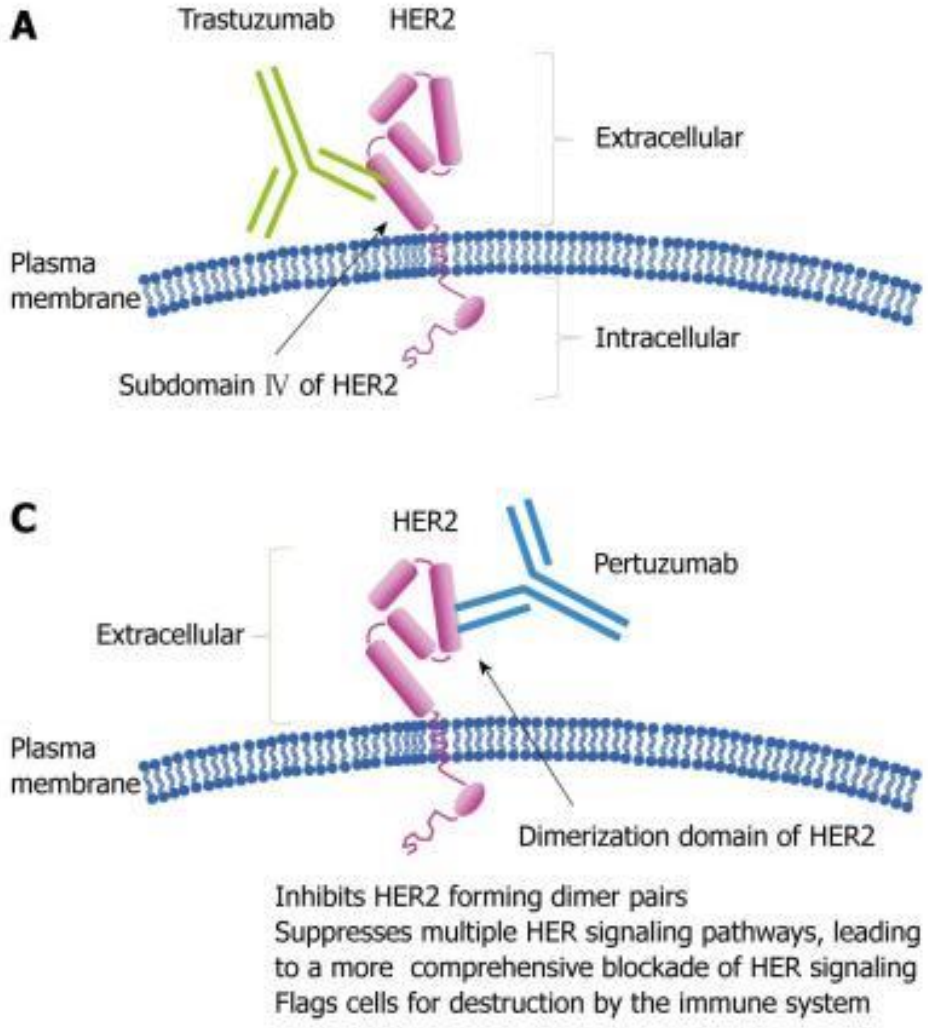
Table 3. HER Dimerization Observed in Gastric Carcinomas

Pair	Patient Cases	
	No.	%
HER1/HER3	4	2
HER1/HER4	1	1
HER2/HER3	28	15
HER2/HER4	10	5.5
HER3/HER4	51	28

Abbreviation: HER, human epidermal growth factor receptor.

Begnami et al. *J Clin Oncol* 2011; 29: 3030-3036

Anti-HER2/HER3-directed Therapy



from: **Park et al**. *World J Clin Onc* 2011; 2: 125-34

Trastuzumab-Pertuzumab-Combination (Breast Cancer)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 12, 2012 VOL. 366 NO. 2

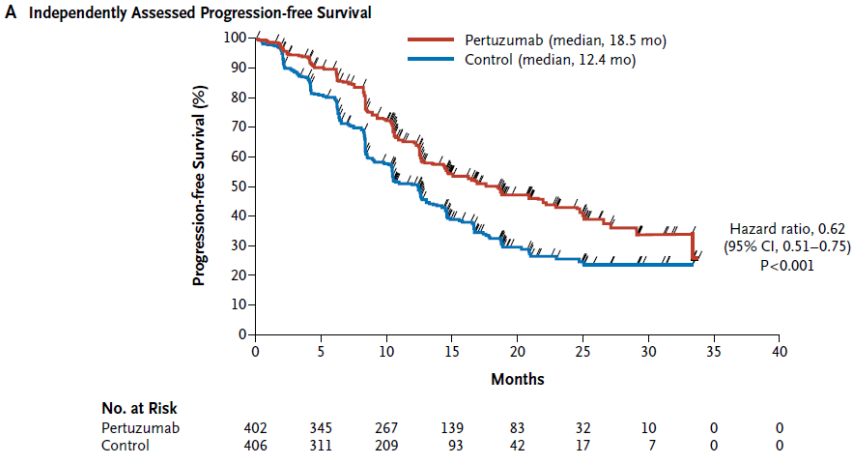
Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

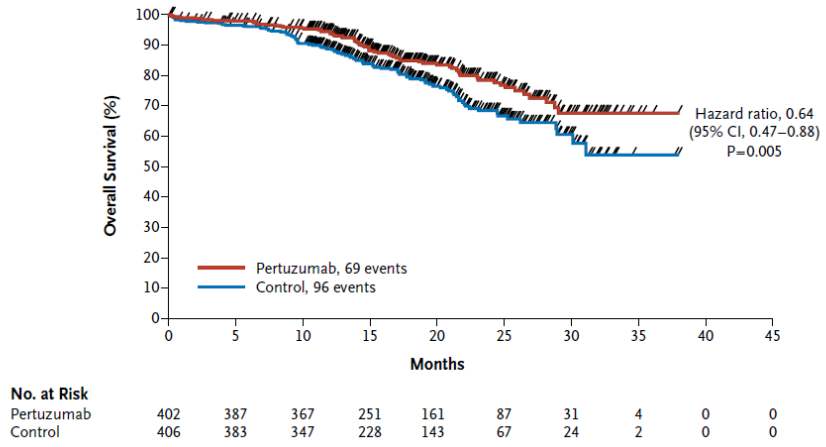
José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

n=808 pts

HER-2 pos., metastatic BC

- **docetaxel + trastuzumab +/- pertuzumab**





Trastuzumab-Pertuzumab-Combination (Stomach Cancer)

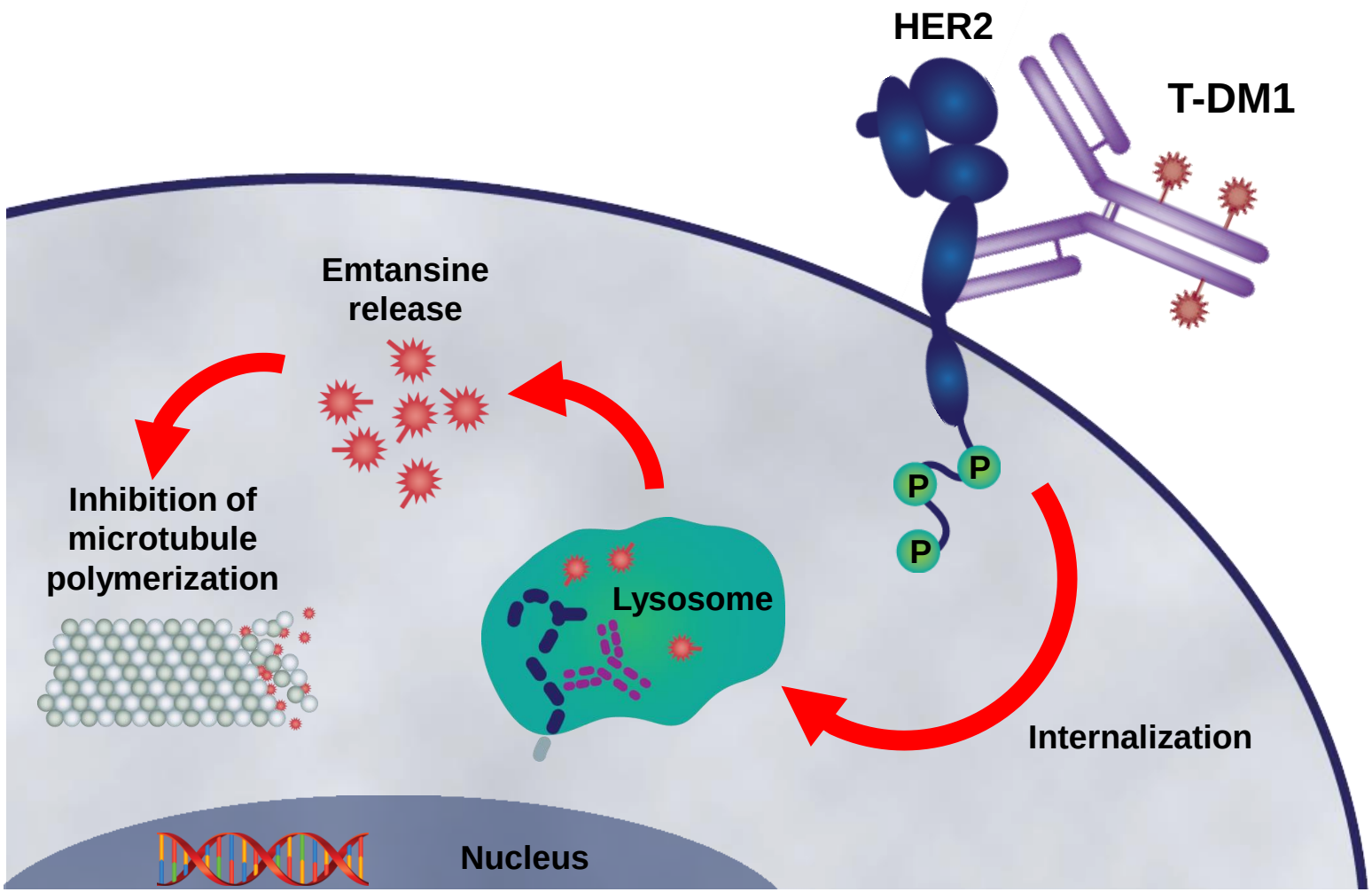
Ongoing: JACOB Study
(RCT Stage IV)

JACOB
BO25114

Ongoing: INNOVATION Study
(RCT Stage IV)

EORTC
European Organisation for Research and Treatment of Cancer

Trastuzumab-DM1



From **Spector NL, Blackwell KL**. *J Clin Oncol* 2009

Trastuzumab-DM1 (Breast Cancer)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D., José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D., Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D., and Kim Blackwell, M.D., for the EMILIA Study Group

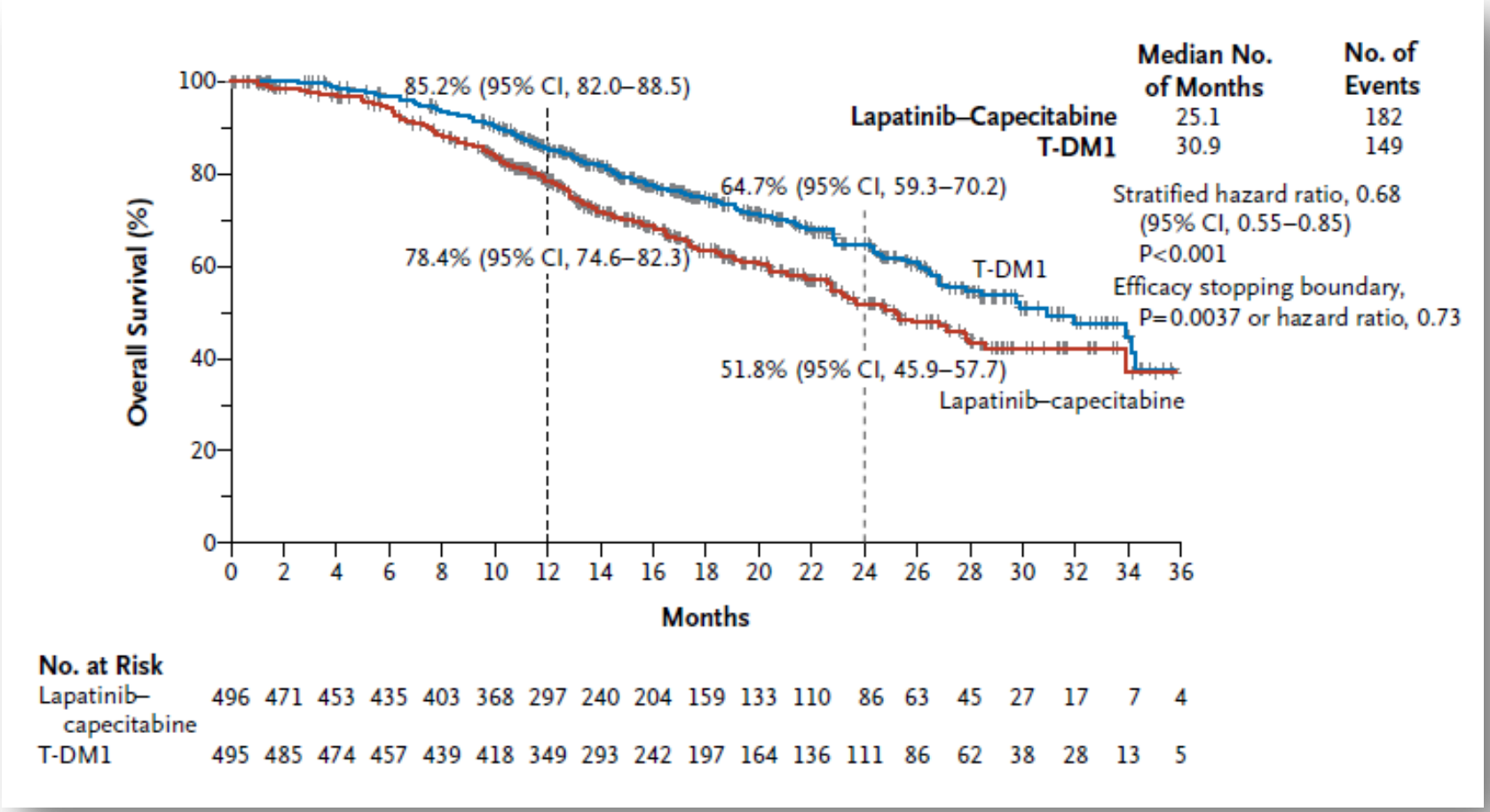
ABSTRACT

BACKGROUND

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate incorporating the human epidermal growth factor receptor 2 (HER2)–targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1. The

From Sunnybrook Odette Cancer Centre, Toronto (S.V.); Mount Vernon Cancer Centre, Northwood, United Kingdom (D.M.);

Trastuzumab-DM1 (Breast Cancer)



2nd Interims Survival Analysis

Trastuzumab-DM1 (Breast Cancer)

Table 3. Adverse Events in the Safety Population.*

Adverse Event	Lapatinib plus Capecitabine (N=488)		T-DM1 (N=490)	
	Events of Any Grade	Grade 3 or 4 Events	Events of Any Grade	Grade 3 or 4 Events
	number of patients (percent)			
Any event	477 (97.7)	278 (57.0)	470 (95.9)	200 (40.8)
Specific events†				
Diarrhea	389 (79.7)	101 (20.7)	114 (23.3)	8 (1.6)
Palmar–plantar erythrodysesthesia	283 (58.0)	80 (16.4)	6 (1.2)	0
Vomiting	143 (29.3)	22 (4.5)	93 (19.0)	4 (0.8)
Neutropenia	42 (8.6)	21 (4.3)	29 (5.9)	10 (2.0)
Hypokalemia	42 (8.6)	20 (4.1)	42 (8.6)	11 (2.2)
Fatigue	136 (27.9)	17 (3.5)	172 (35.1)	12 (2.4)
Nausea	218 (44.7)	12 (2.5)	192 (39.2)	4 (0.8)
Mucosal inflammation	93 (19.1)	11 (2.3)	33 (6.7)	1 (0.2)
Anemia	39 (8.0)	8 (1.6)	51 (10.4)	13 (2.7)
Elevated ALT	43 (8.8)	7 (1.4)	83 (16.9)	14 (2.9)
Elevated AST	46 (9.4)	4 (0.8)	110 (22.4)	21 (4.3)
Thrombocytopenia	12 (2.5)	1 (0.2)	137 (28.0)	63 (12.9)

Trastuzumab-DM1 (Stomach Cancer)

Ongoing: GATSBY Study
(RCT Stage IV 2nd line)

Arm A: trastuzumab emtansine 3.6 mg/kg Q3W *IV*

Arm B: trastuzumab emtansine 2.4 mg/kg QW *IV*

Arm C (control arm): Docetaxel 75 mg/m^2 Q3W *IV* or paclitaxel 80 mg/m^2 QW *IV* according to investigator choice. The choice of taxane *will be selected on an individual patient basis and* must be made prior to randomization and remain consistent throughout the study-, *unless the patient is intolerant due to a hypersensitivity reaction or toxicity (see below for further details).*

Lapatinib

Lapatinib in combination with capecitabine plus oxaliplatin in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: The TRIO-013/LOGiC Trial

JR Hecht, Y Bang, S Qin, H Chung, J Xu, J Park, K Jeziorski, Y Shparyk, PM Hoff, AF Sobrero, P Salman, J Li, S Protsenko, ME Buyse, K Afenjar, T Kaneko, A Kemner, S Santillana, MF Press, DJ Slamon

TRIO Translational Research In Oncology

ASCO Annual '13 Meeting

Lapatinib

R **1:1**

Arm A: CapeOX q3w plus daily Lapatinib

Arm B: CapeOX q3w plus Placebo

Study population	Overexpression or Amplification of HER2 (IHC 2+ plus FISH+ or IHC 3+ or FISH, CISH or SISH amplified)
Primary endpoint	Overall Survival (10.3 -> 14 months), n=545
Sec. Endpoint	Progression-free Survival, Response, toxicity
Stratification	Previous adj. therapy; region Asia, North America, ROW

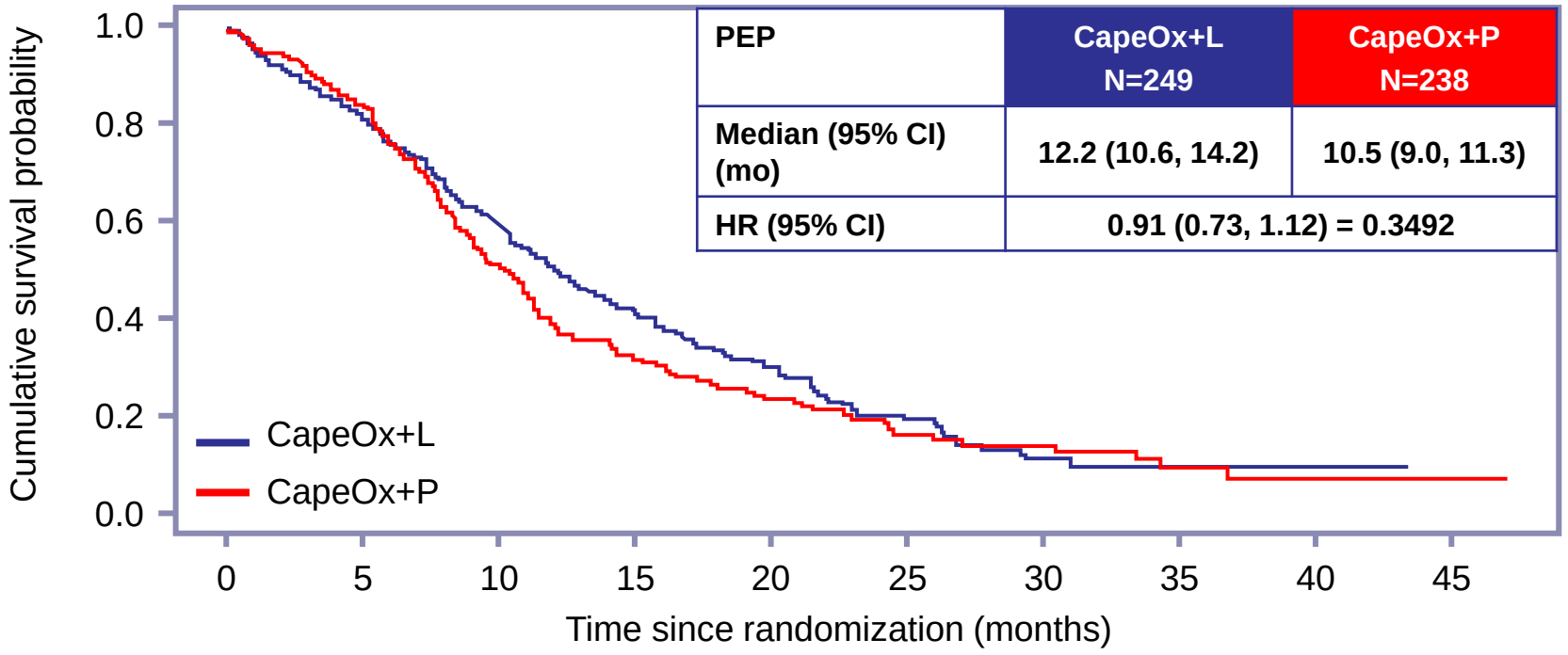
Lapatinib

- 545 patients recruited in 186 centers (2008-2012)
- 487 patients for the primary efficacy analysis (central: FISH+).
- 87% stomach cancers, 13% GEJ/esophageal cancers

Lapatinib

	CapeOx + Lapatinib N=249	CapeOx + Placebo N=238
Complete response	6 (2%)	5 (2%)
Partial response	126 (51%)	90 (38%)
Stable Disease	70 (28%)	94 (39%)
Disease Progression	20 (8%)	22 (9%)
Not evaluable/unknown	27 (11%)	27 (11%)
Overall RR	**53% (95%CI : 46.6−59.3)**	**40% (95% CI : 33.6−46.4)**
Median Duration of Response (month)	7.3 (95%CI : 6.4–8.4)	5.6 (95%CI : 4.8–6.0)
ORR by region		
North America	63 %	56 %
Asia	65 %	39 %
ROW	44 %	40 %

Lapatinib



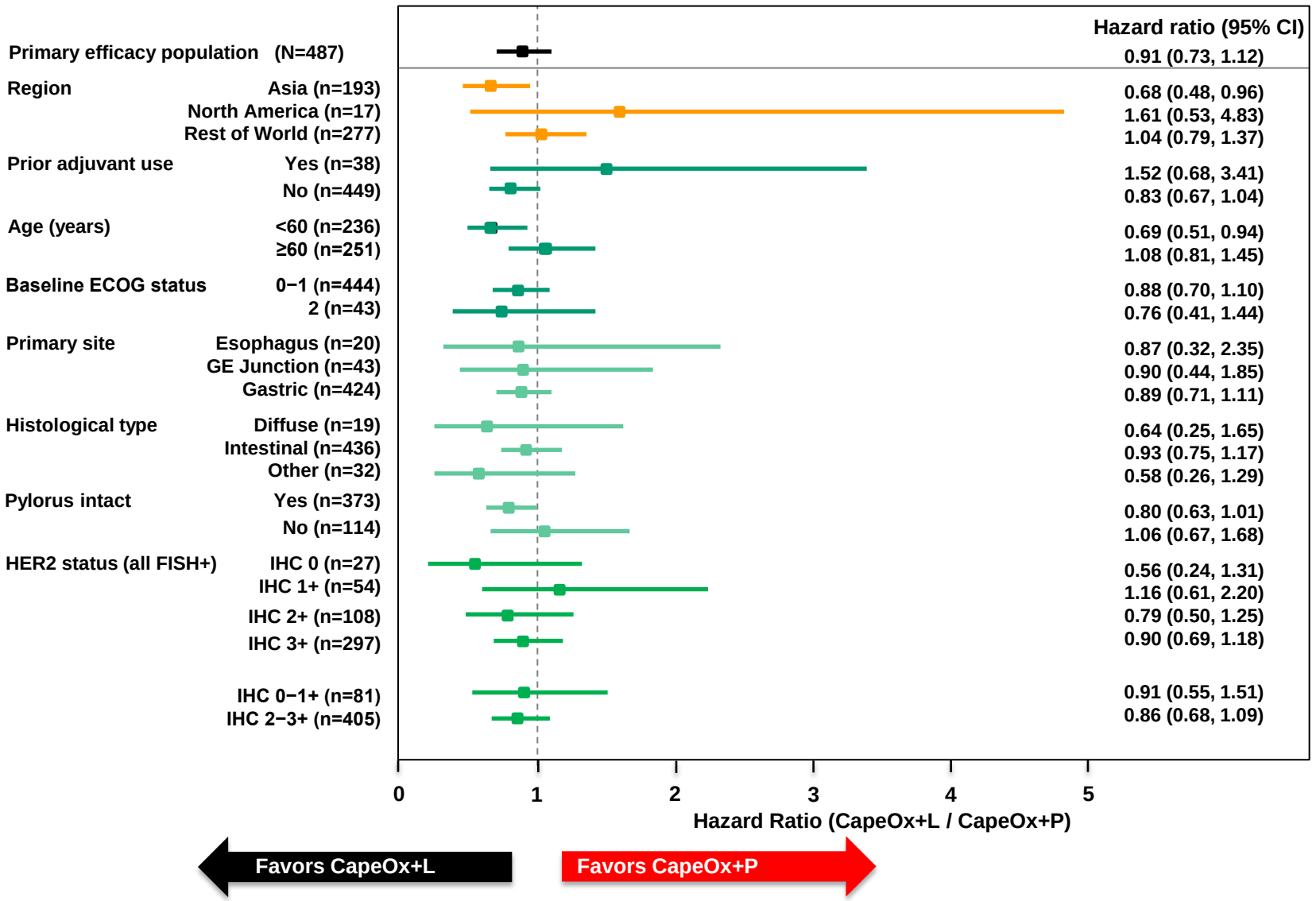
PEP	CapeOx+L N=249	CapeOx+P N=238
Median (95% CI) (mo)	12.2 (10.6, 14.2)	10.5 (9.0, 11.3)
HR (95% CI)	0.91 (0.73, 1.12) = 0.3492	

Subjects at risk										
CapeOx+L	249	199	133	83	47	24	9	3	3	
CapeOx+P	238	189	106	53	34	17	11	7	2	2

ITT analysis HR 0.91

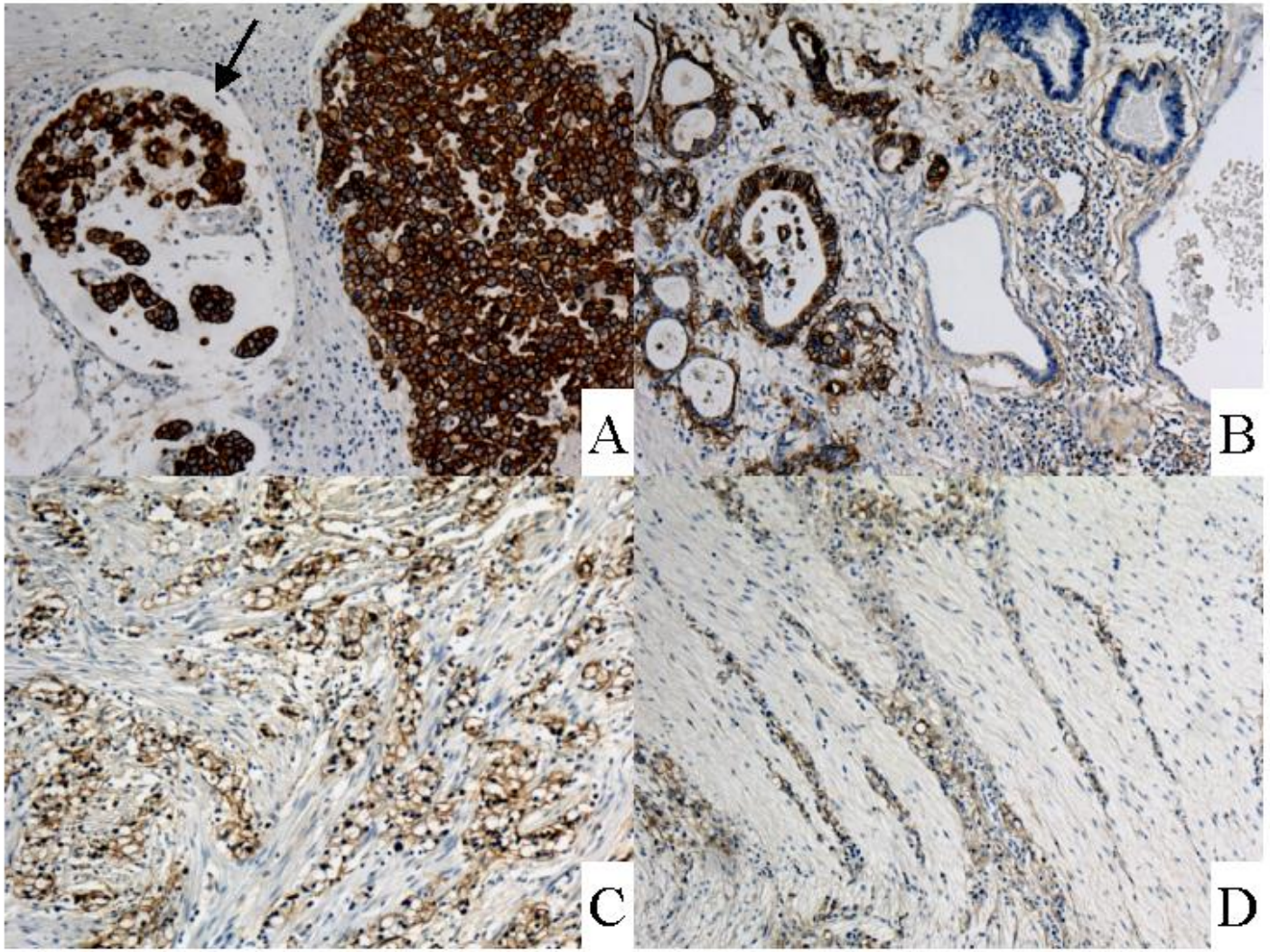
HR for OS 0.91 (p=0.35; median survival 12.2 versus 10.5 months)

Lapatinib


Hazard ratio (95% CI)
Primary efficacy population (N=487)
0.91 (0.73, 1.12)
Region
Asia (n=193)
0.68 (0.48, 0.96)
North America (n=17)
1.61 (0.53, 4.83)
Rest of World (n=277)
1.04 (0.79, 1.37)
Prior adjuvant use
Yes (n=38)
1.52 (0.68, 3.41)
No (n=449)
0.83 (0.67, 1.04)
Age (years)
<60 (n=236)
0.69 (0.51, 0.94)
≥60 (n=251)
1.08 (0.81, 1.45)
Baseline ECOG status
0−1 (n=444)
0.88 (0.70, 1.10)
2 (n=43)
0.76 (0.41, 1.44)
Primary site
Esophagus (n=20)
0.87 (0.32, 2.35)
GE Junction (n=43)
0.90 (0.44, 1.85)
Gastric (n=424)
0.89 (0.71, 1.11)
Histological type
Diffuse (n=19)
0.64 (0.25, 1.65)
Intestinal (n=436)
0.93 (0.75, 1.17)
Other (n=32)
0.58 (0.26, 1.29)
Pylorus intact
Yes (n=373)
0.80 (0.63, 1.01)
No (n=114)
1.06 (0.67, 1.68)
HER2 status (all FISH+)
IHC 0 (n=27)
0.56 (0.24, 1.31)
IHC 1+ (n=54)
1.16 (0.61, 2.20)
IHC 2+ (n=108)
0.79 (0.50, 1.25)
IHC 3+ (n=297)
0.90 (0.69, 1.18)
IHC 0−1+ (n=81)
0.91 (0.55, 1.51)
IHC 2−3+ (n=405)
0.86 (0.68, 1.09)
0
1
2
3
4
5
Hazard Ratio (CapeOx+L / CapeOx+P)
Favors CapeOx+L
Favors CapeOx+P

EGFR (HER1) in Gastric Cancer

mixed, 3+ intestinal, 0-3+



diffuse, 2+ diffuse, 1+

Gamboa et al. *Mod Pathol* 2004;17:579-87

EGFR (HER1) in Gastric Cancer

British Journal of Cancer (2010) 102, 500 – 505

www.bjcancer.com

Clinical Studies

Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO)

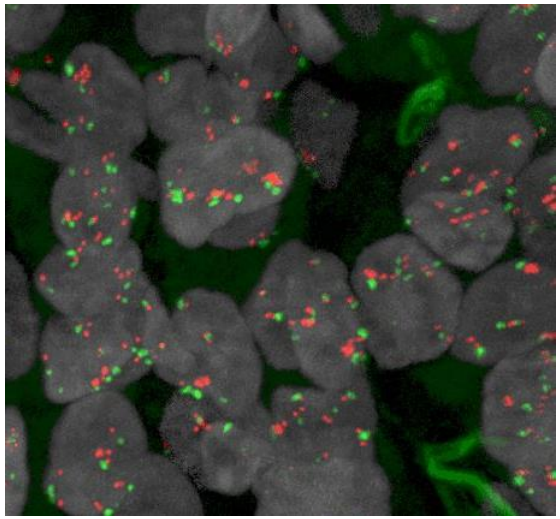
F Lordick*[,1], B Luber[2], S Lorenzen[1], S Hegewisch-Becker[3], G Folprecht[4], E Wöll[5], T Decker[6], E Endlicher[7], N Röthling[8], T Schuster[9], G Keller[2], F Fend[2,10] and C Peschel[1]

[1]Klinikum rechts der Isar, 3rd Medical Department, Technische Universität München, Ismaninger Straße 22, 81675 Munich, Germany; [2]Institute of Pathology, Technische Universität München, Ismaninger Straß22, 81675 Munich, Germany; [3]Onkologische Schwerpunktpraxis Eppendorf, Eppendorfer Landstr. 42, 20249 Hamburg, Germany; [4]1st Medical Department, Universitätsklinik Carl Gustav Carus, Fetscherstr.74, 01307 Dresden, Germany; [5]Medical Department, Klinik St. Vinzenz, Sanatoriumstrasse, 6511 Zams, Austria; [6]Onkologische Schwerpunktpraxis, Wilhelm-Hauff-Str. 41, 88214 Ravensburg, Germany; [7]1st Medical Department, Klinikum der Universität, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany; [8]Munich Centre

	n	Response (%)	mTTP (Mon)
FUFOX + Cetuximab ***Lordick F**, et al. BJC **2010***	**46**	**65%** 95% CI, 50–79%	**7,6** 95% CI, 5.0–10.1

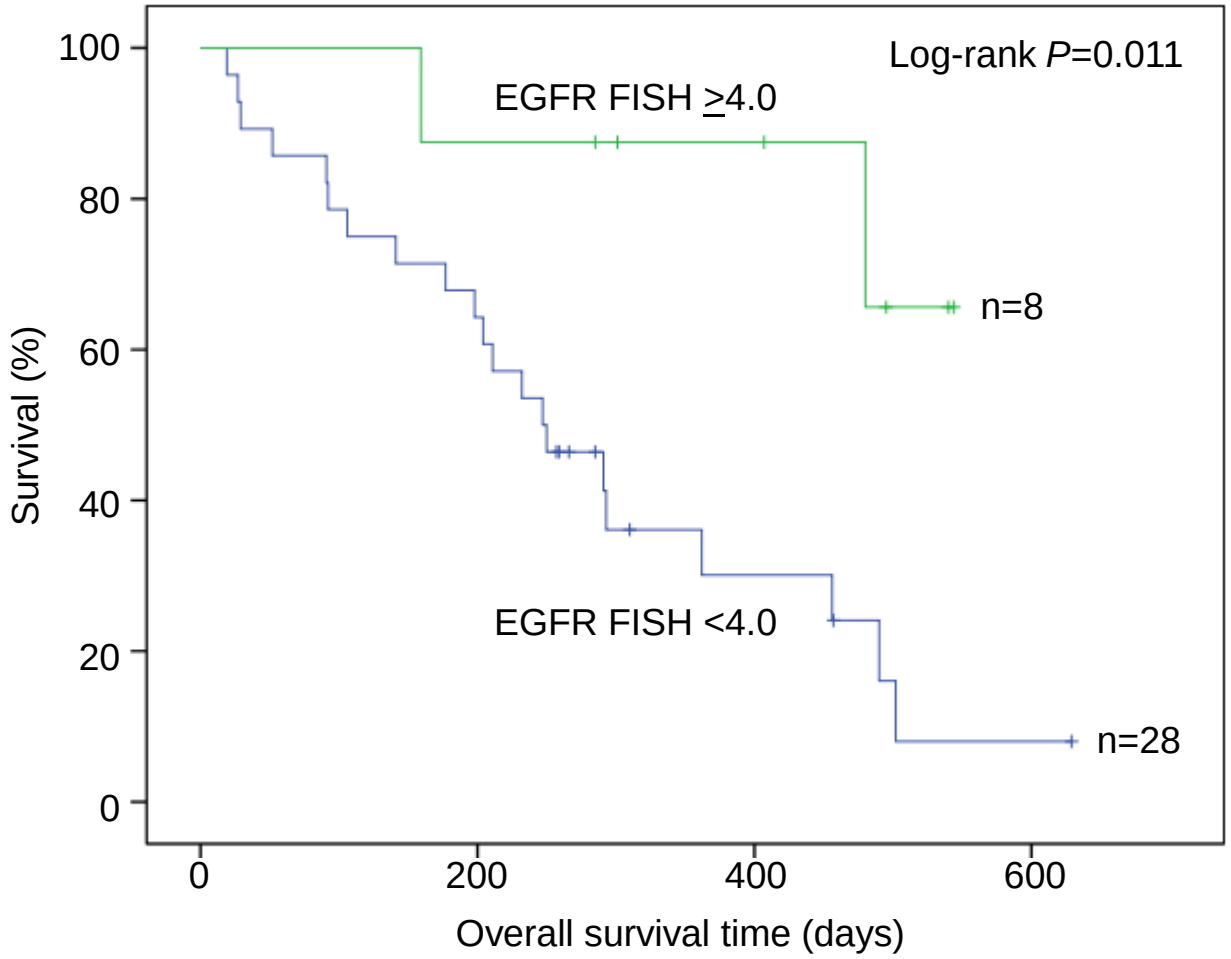
Lordick F, et al. *Br J Canc* 2010; 102: 500-505

EGFR (HER1) in Gastric Cancer



EGFR gene amplification:
EGFR: 8.20 signals per nucleus
EGFR/CEP7 ratio: 1.36

EGFR (red), chromosome 7 (green)



Luber B,… Lordick F. *BMC Cancer* 2011;11:509

EGFR (HER1) in Gastric Cancer

R A N D O M

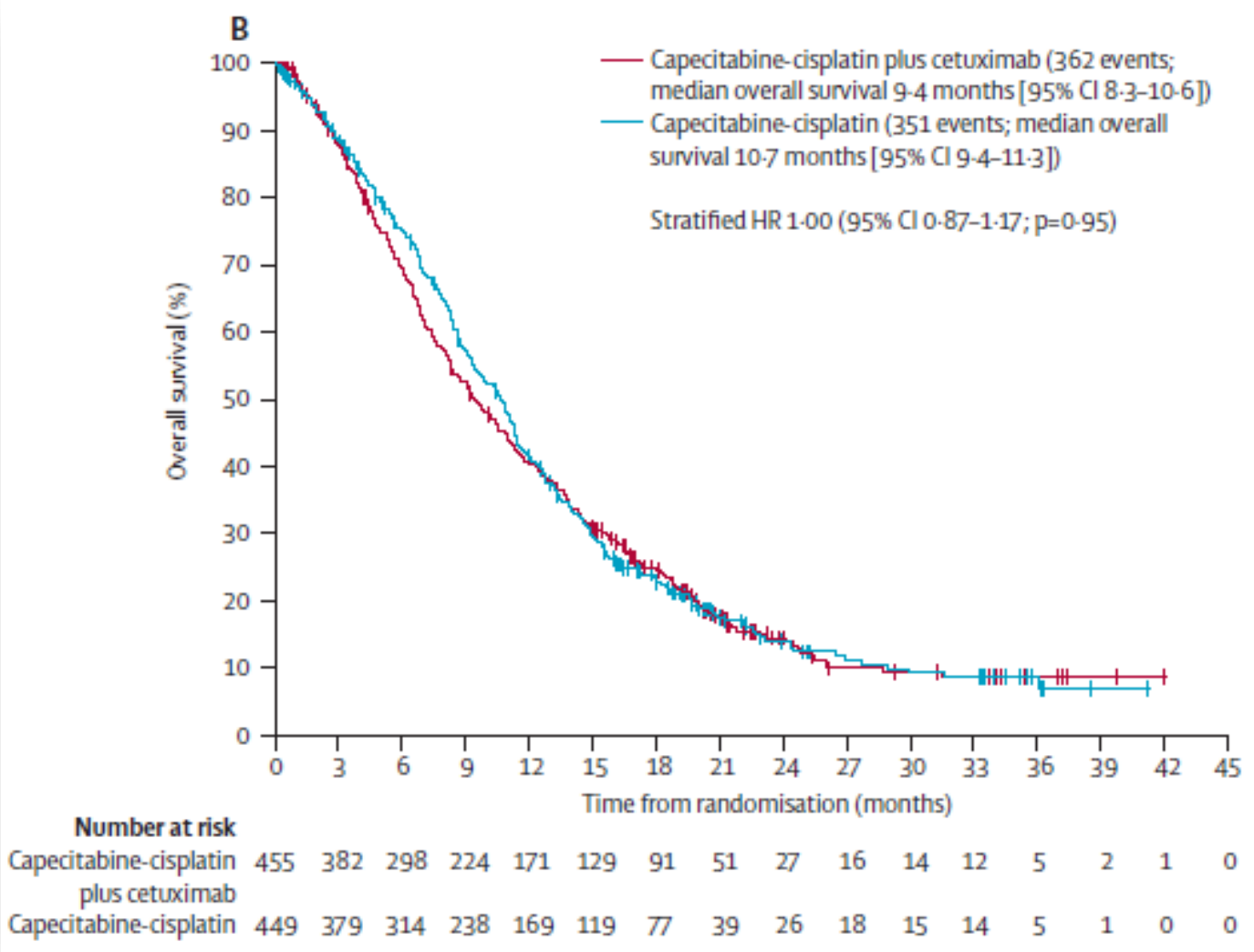
Cisplatin	**80mg/m² d1**
Capecitabine q3w	**1000mg/m² twice daily; d1-14**

- Until radiographically documented PD or unacceptable toxicity
- Primary endpoint: Progression Free Survival (PFS) time

Cisplatin	**80mg/m² d1**
Capecitabine q3w	**1000mg/m² twice daily; d1-14**
Cetuximab	**400mg/m² loading dose, then 250mg/m² per week**

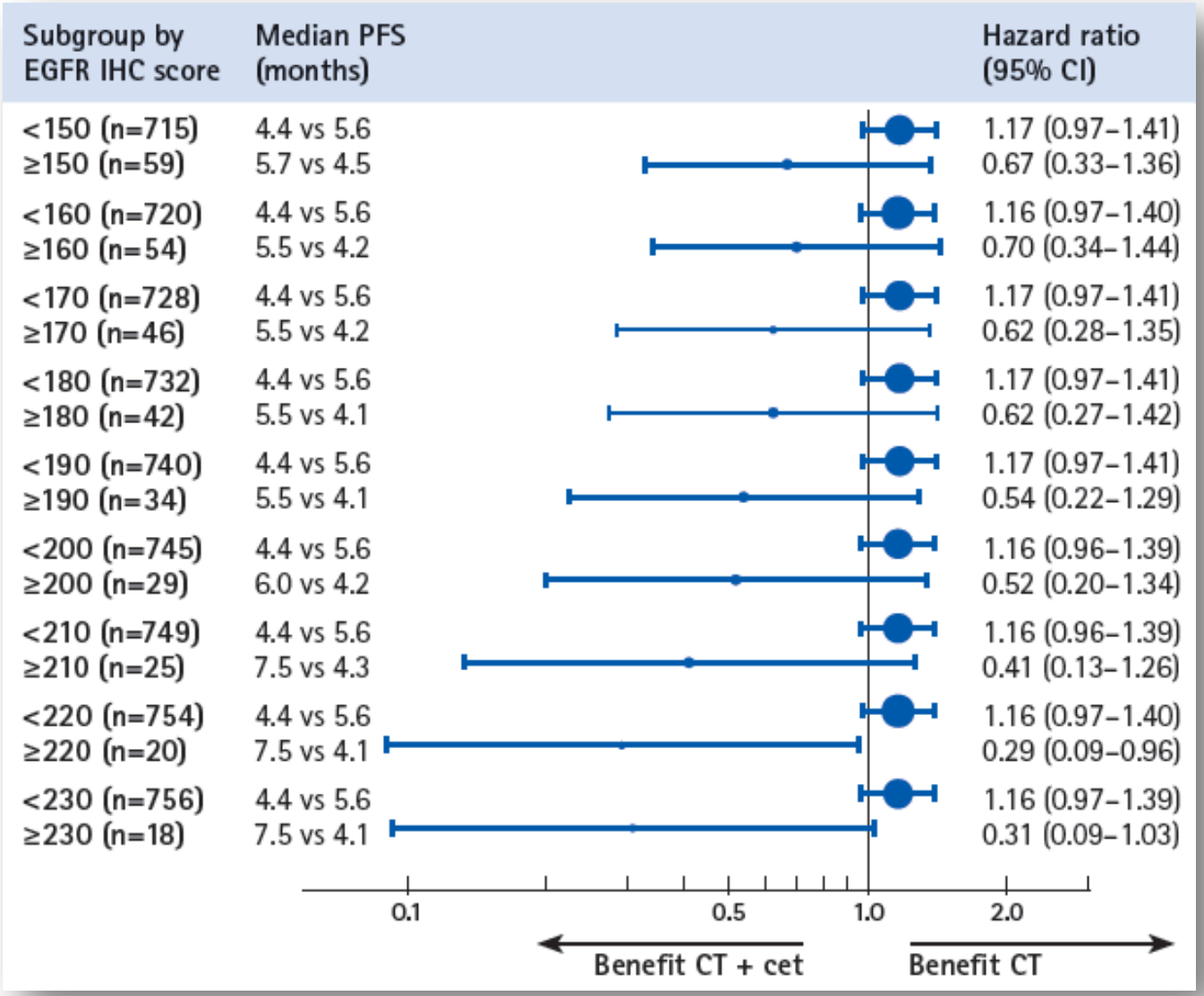
Lordick et al. *Lancet Oncol* 2013; 14: 490-499

EGFR (HER1) in Gastric Cancer



Lordick et al. *Lancet Oncol* 2013; 14: 490-499

EGFR (HER1) in Gastric Cancer



Lordick et al. *Lancet Oncol* 2013; 14: 490-499

EGFR (HER1) in Gastric Cancer

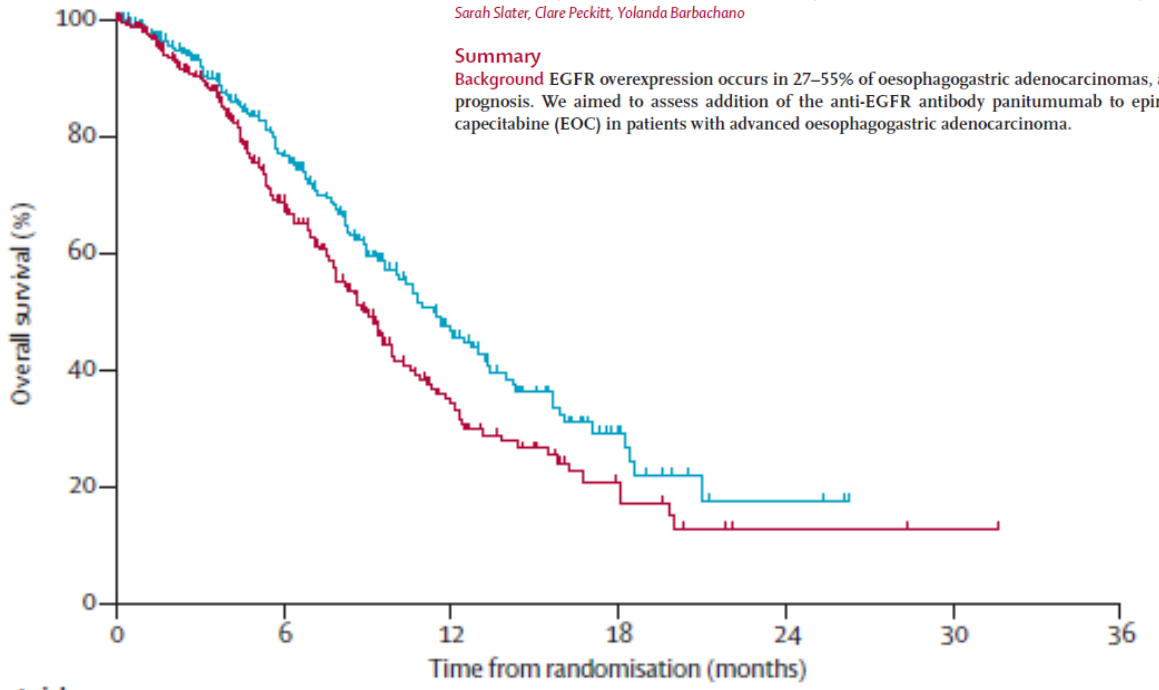
Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial

Tom Waddell, Ian Chau, David Cunningham, David Gonzalez, Alicia Frances, Clare Okines, Andrew Wotherspoon, Claire Saffery, Gary Middleton, Jonathan Wadsley, David Ferry, Wasat Mansoor, Tom Crosby, Fareeda Coxon, David Smith, Justin Waters, Timothy Iveson, Stephen Falk, Sarah Slater, Clare Peckitt, Yolanda Barbachano

Summary

Background EGFR overexpression occurs in 27–55% of oesophagogastric adenocarcinomas, and correlates with poor prognosis. We aimed to assess addition of the anti-EGFR antibody panitumumab to epirubicin, oxaliplatin, and capecitabine (EOC) in patients with advanced oesophagogastric adenocarcinoma.

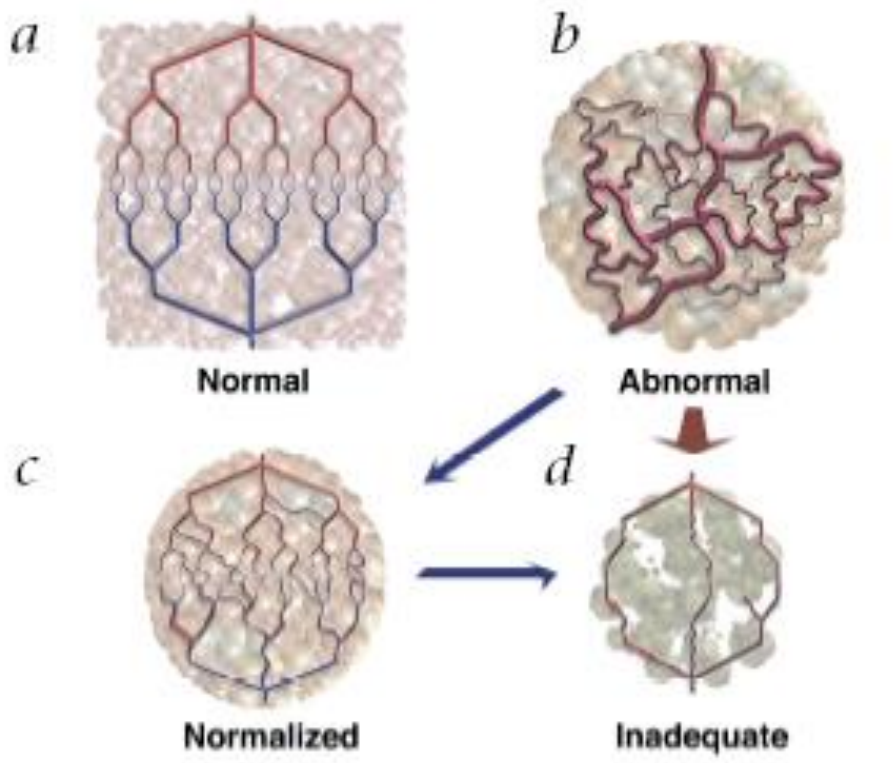
Lancet Oncol 2013; 14: 481–89
Published Online
April 15, 2013
http://dx.doi.org/10.1016/



Number at risk

EOC	275	135	49	12	3
mEOC+P	278	130	38	10	2

Anti-angiogenic Therapy



Jain, Science 2005: 307: 58-62

Gastric Cancer

- **Preclinical rationale**
- **Phase II – Studies**

AVAGAST

N=774

Stomach and EGJ

Stage IV

RANDOM

Bevacizumab + Cisplatin/Capecitabine q3w
Cis 6 cycles; Bevacizumab + Cape until progression

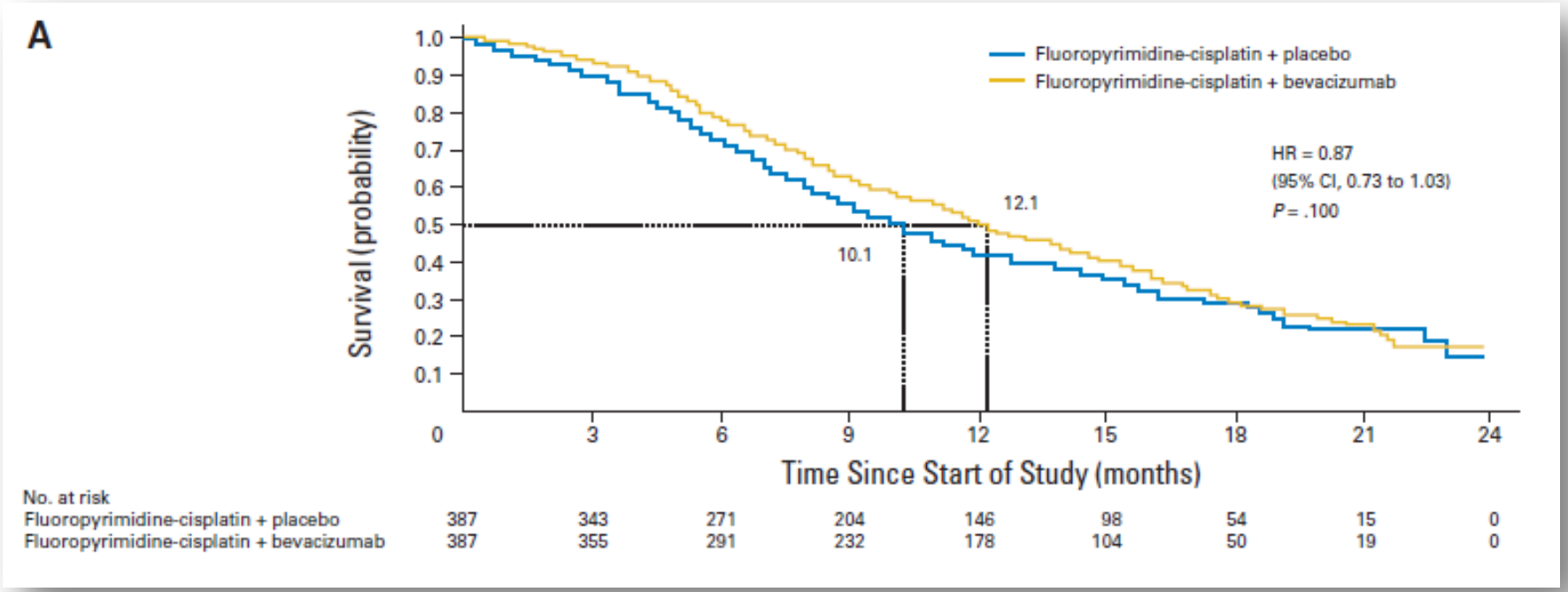
Primary endpoint: survival (superiority)

Cisplatin/Capecitabine q3w
Cis 6 cycles; Cape until progression

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

AVAGAST

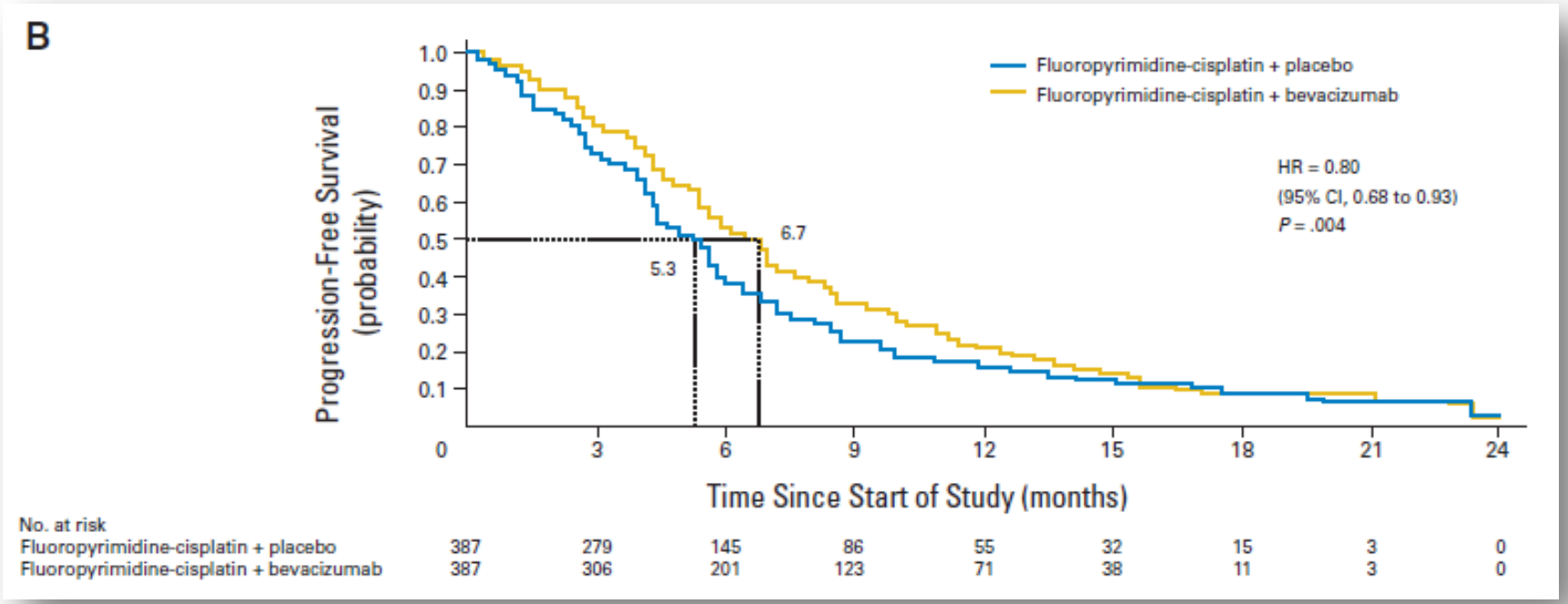
Survival: primary endpoint negative



Kang YK et al. *ASCO 2010*; LBA 4007

AVAGAST

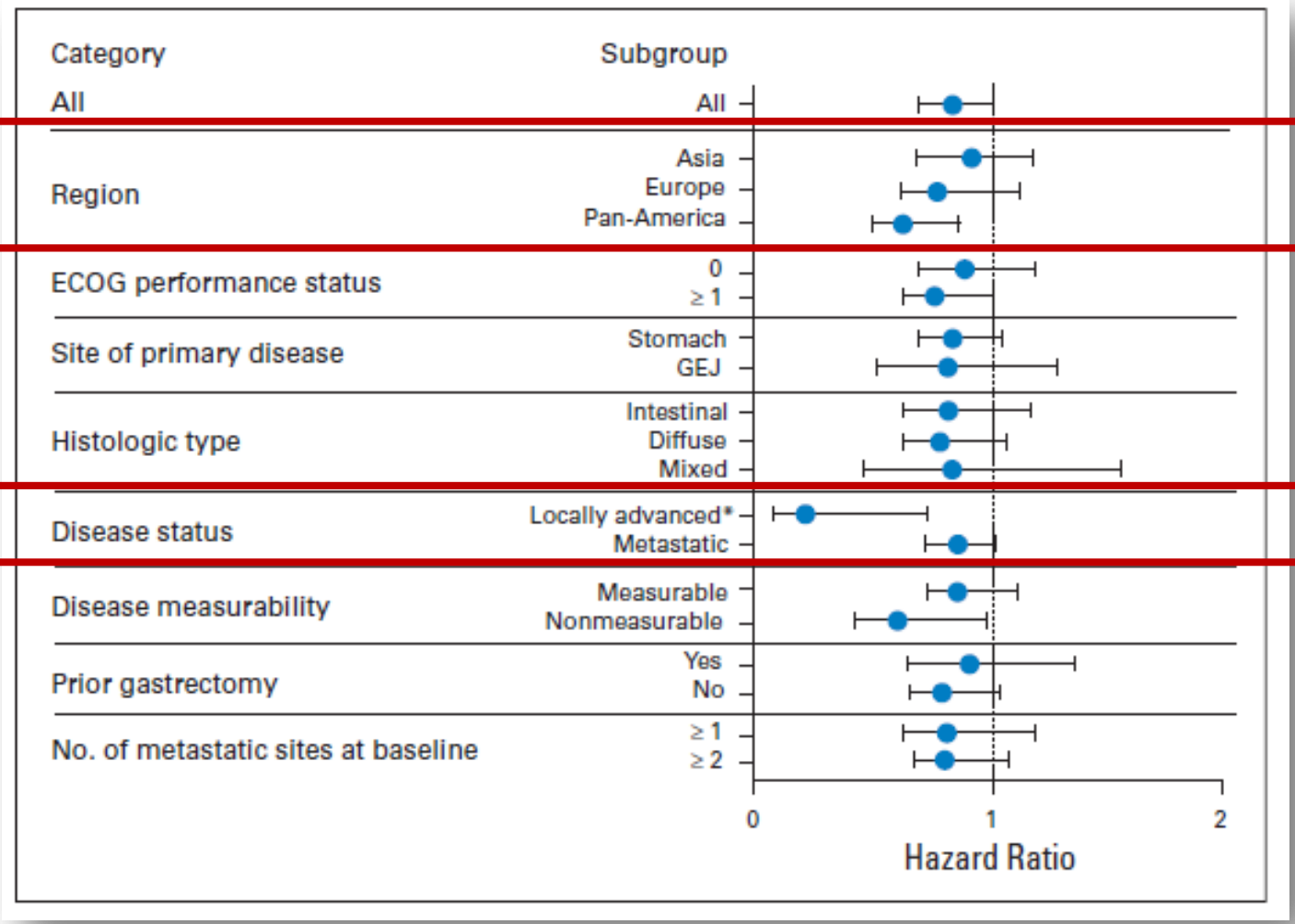
Disease-fee Survival: secondary endpoint positive



Kang YK et al. *ASCO 2010*; LBA 4007

AVAGAST

Subgroup Analysis



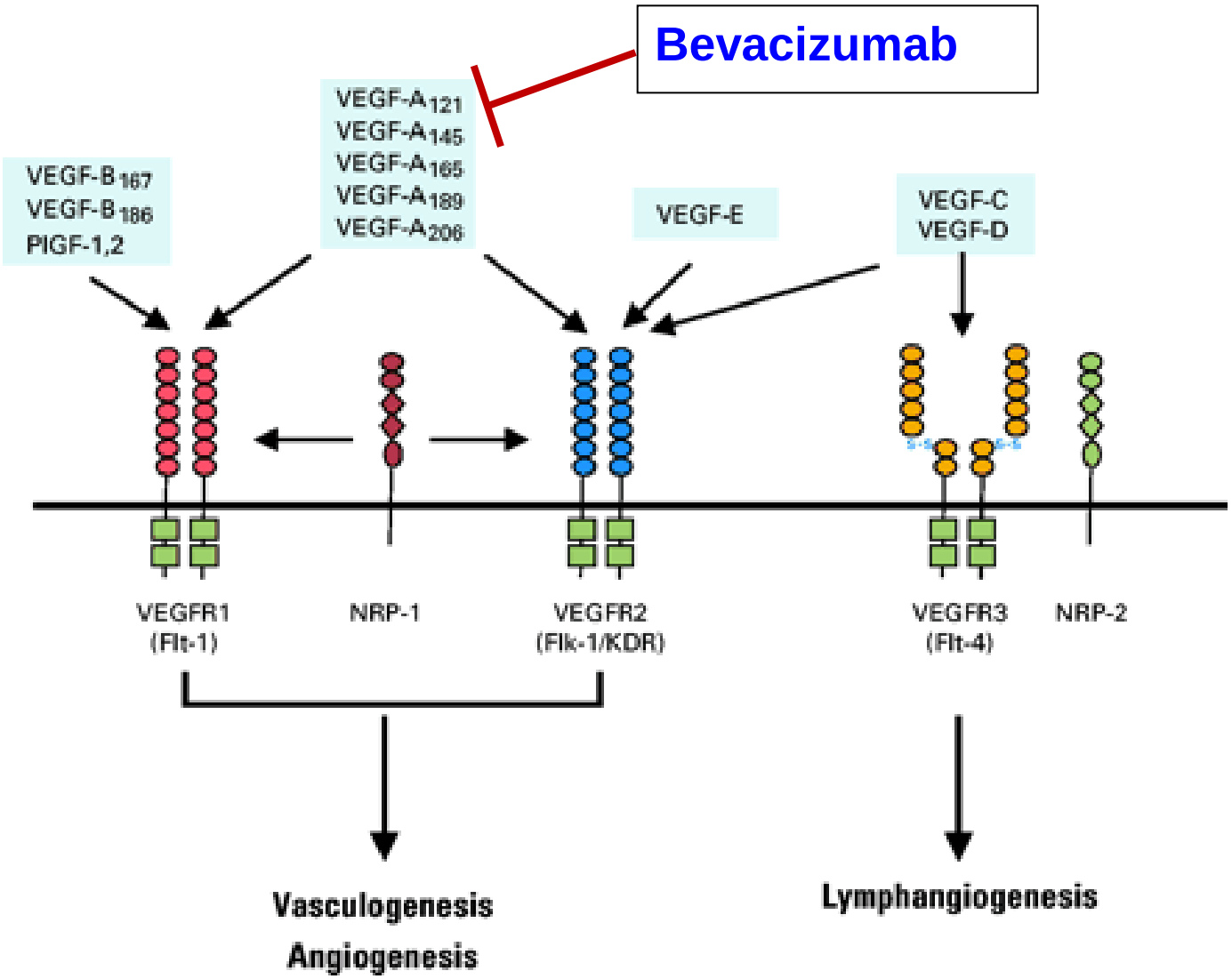
Ohtsu et al. *J Clin Oncol* 2011; 29:3968-3976

Anti-angiogenic Therapy in Gastric Cancer

Conclusions

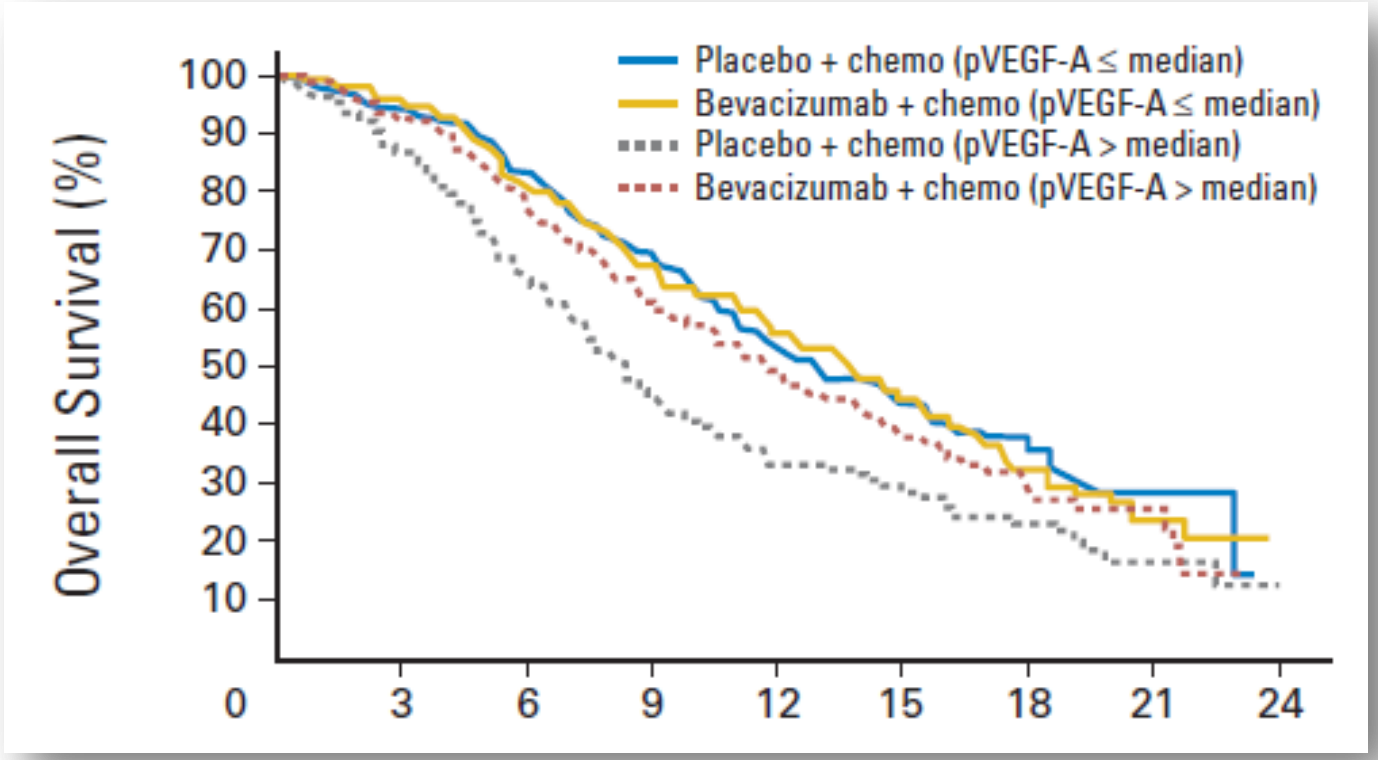
- The Avagast-Study is a negative trial
- Anti-angiogenic therapy has activity and more potential than AVAGAST shows
- Bevacizumab seems to be active in specific subgroups (tumor genetics, pharmacogenetics, ethnicity…?)
- Randomized controlled trial in the periopeartive setting is ongoing (MAGIC-B)

Anti-angiogenic Treatment with Bevacizumab



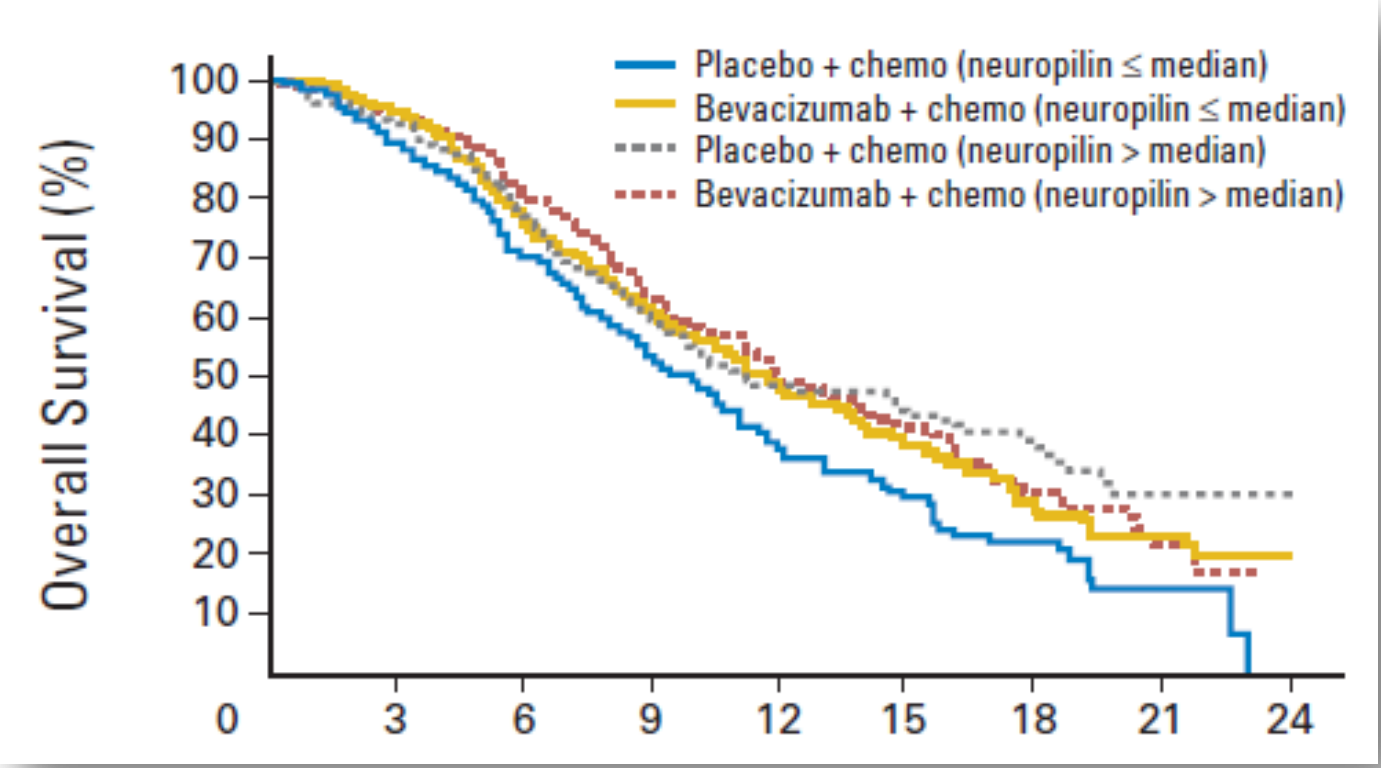
Hicklin DJ et al. *J Clin Oncol* 2005;23:1011-1027

Gastric Cancer – Biomarker VEGF-A Levels (Plasma) AVAGAST Study



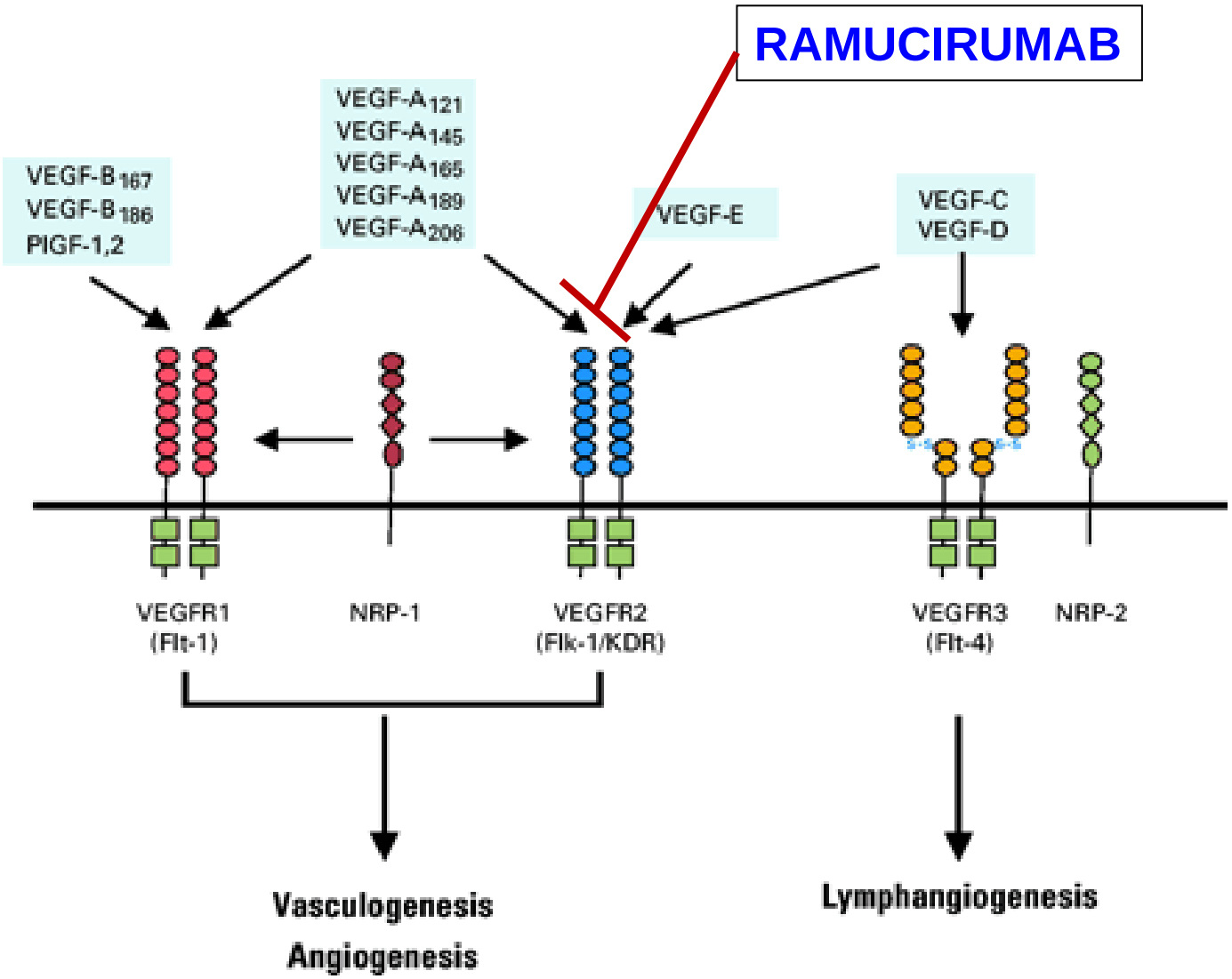
Van Cutsem E et al. *J Clin Oncol 2012*; 30: 2119-2127

Gastric Cancer – Biomarker Neuropilin Expression (Tumor) AVAGAST Study



Van Cutsem E et al. *J Clin Oncol 2012*; 30: 2119-2127

Anti-angiogenic Treatment with Ramucirumab



Hicklin DJ et al. *J Clin Oncol* 2005;23:1011-1027

Ramucirumab (Lilly)

VOLUME 28 · NUMBER 5 · FEBRUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase I Pharmacologic and Biologic Study of Ramucirumab (IMC-1121B), a Fully Human Immunoglobulin G_1 Monoclonal Antibody Targeting the Vascular Endothelial Growth Factor Receptor-2

Jennifer L. Spratlin, Roger B. Cohen, Matthew Eadens, Lia Gore, D. Ross Camidge, Sami Diab, Stephen Leong, Cindy O'Bryant, Laura Q.M. Chow, Natalie J. Serkova, Neal J. Meropol, Nancy L. Lewis, E. Gabriela Chiorean, Floyd Fox, Hagop Youssoufian, Eric K. Rowinsky, and S. Gail Eckhardt

From the University of Colorado at Denver, Aurora, CO; Fox Chase Cancer Center, Philadelphia, PA; Indiana University Simon Cancer Center, Indianapolis, IN; and ImClone Systems, New York, NY.

Submitted April 29, 2009; accepted October 6, 2009; published online ahead of print at www.jco.org on January 4, 2010.

Supported in part by ImClone Systems, a wholly owned subsidiary of Eli Lilly, and

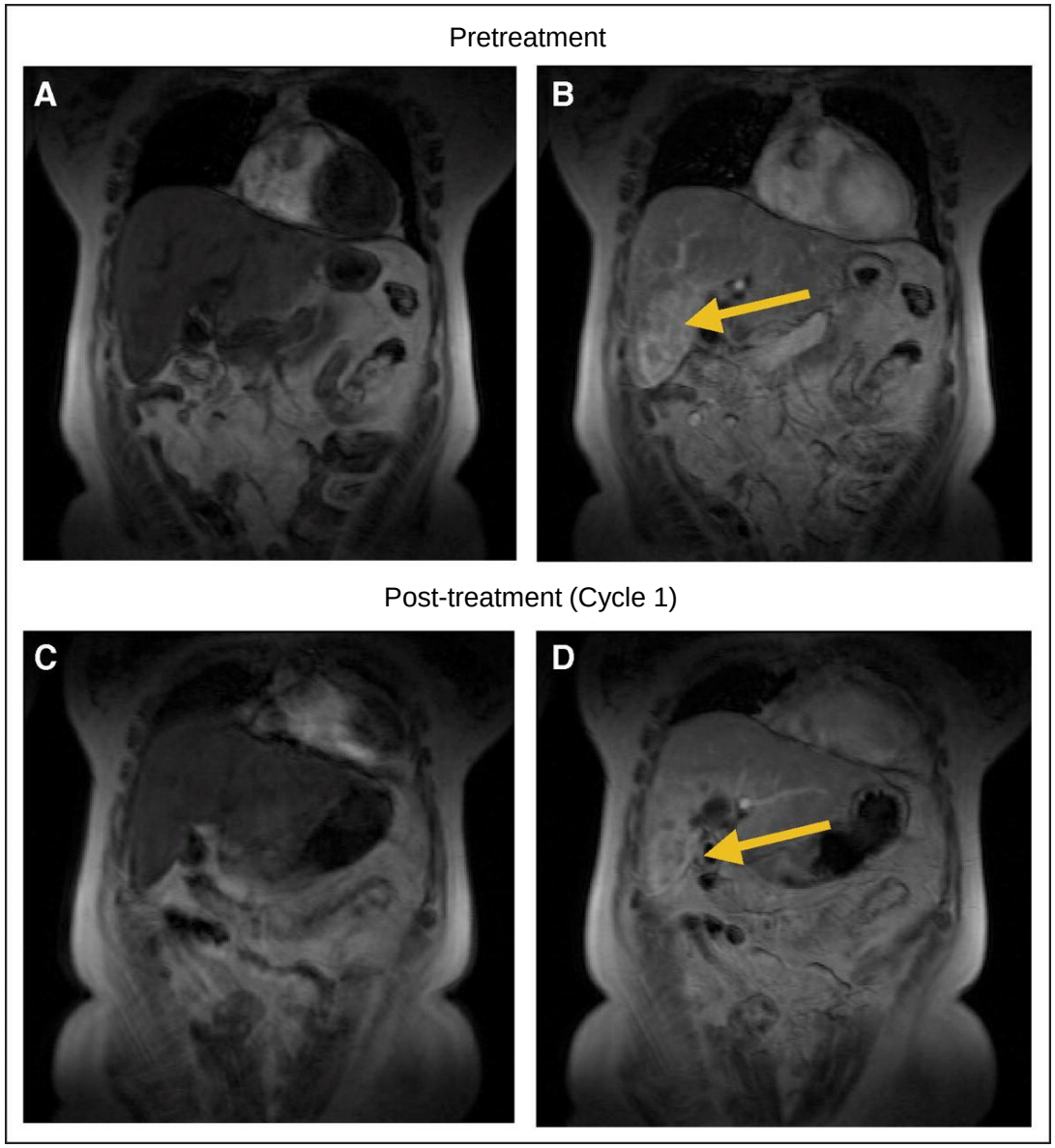
A B S T R A C T

Purpose

To evaluate the safety, maximum-tolerated dose (MTD), pharmacokinetics (PKs), pharmacodynamics, and preliminary anticancer activity of ramucirumab (IMC-1121B), a fully human immunoglobulin G_1 monoclonal antibody targeting the vascular endothelial growth factor receptor (VEGFR)-2.

Ramucirumab (Lilly)

DCE-MRI



Post
Gadolinium
Injection

Spratlin et al. *J Clin Oncol* 2010; 28: 780-787

Ramucirumab (REGARD Study)

Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial

*Charles S Fuchs, Jiri Tomasek, Cho Jae Yong, Filip Dumitru, Rodolfo Passalacqua, Chanchal Goswami, Howard Safran, Lucas Vieira dos Santos, Giuseppe Aprile, David R Ferry, Bohuslav Melichar, Mustapha Tehfe, Eldar Topuzov, John Raymond Zalcberg, Ian Chau, William Campbell, Choondal Sivanandan, Joanna Pikiel, Minori Koshiji, Yanzhi Hsu, Astra M Liepa, Ling Gao, Jonathan D Schwartz, Josep Tabernero, for the REGARD Trial Investigators**

Summary

Background Vascular endothelial growth factor (VEGF) and VEGF receptor-2 (VEGFR-2)-mediated signalling and angiogenesis can contribute to the pathogenesis and progression of gastric cancer. We aimed to assess whether ramucirumab, a monoclonal antibody VEGFR-2 antagonist, prolonged survival in patients with advanced gastric cancer.

Methods We did an international, randomised, double-blind, placebo-controlled, phase 3 trial between Oct 6, 2009,

Published Online
October 3, 2013
http://dx.doi.org/10.1016/
S0140-6736(13)61719-5

See Online/Comment
http://dx.doi.org/10.1016/

Fuchs et al. *Lancet Oncol* 2013; epub

Ramucirumab (REGARD Study)

N=335

Stomach and AEG

Stage IV

2nd-line

119 centers
29 countries

Ramucirumab 8mg/kg q2w
until progression

Randomization 2:1
Primary endpoint: overall survival (superiority)

Placebo q2w
until progression

Fuchs et al. *Lancet Oncol* 2013; epub

Ramucirumab (REGARD Study)

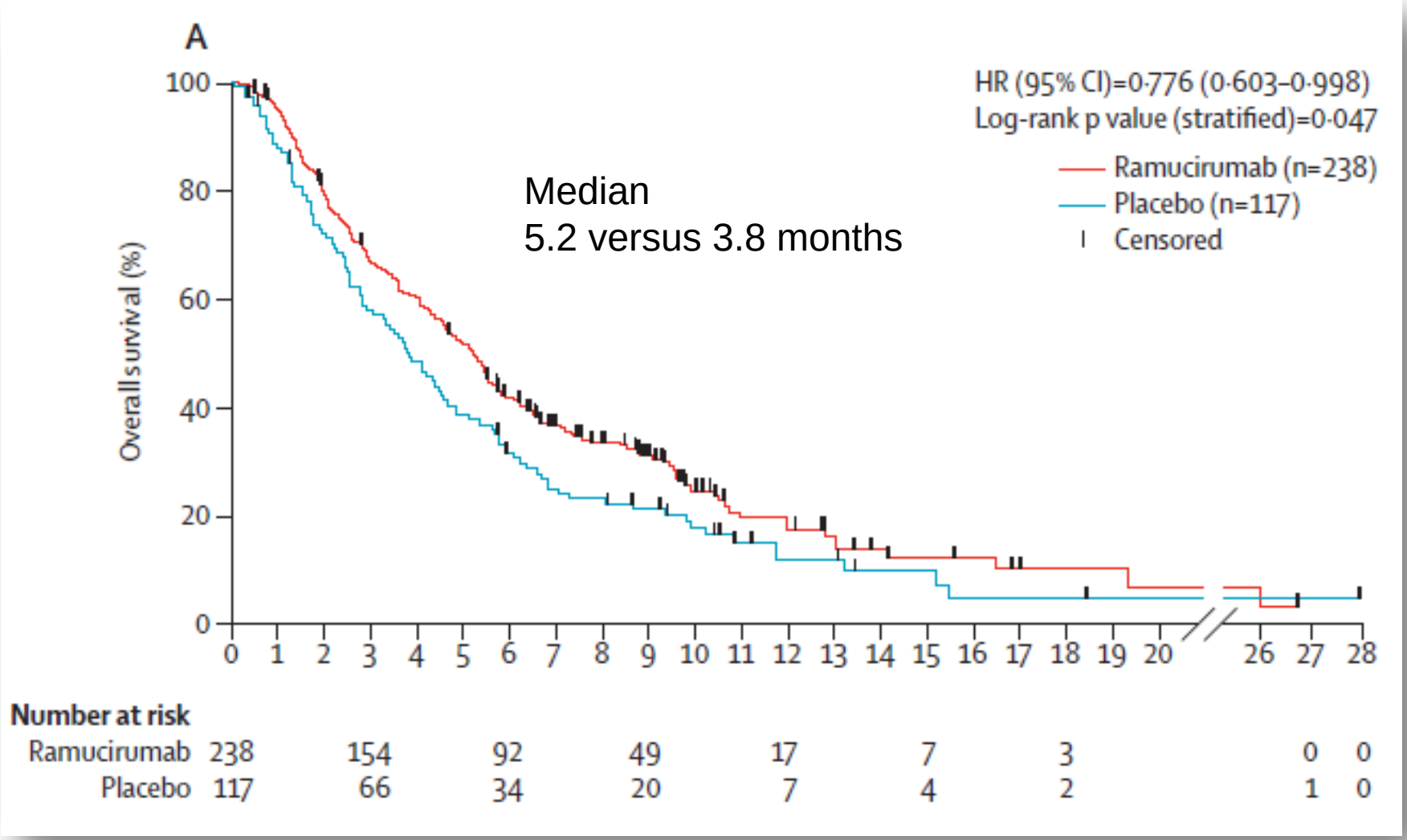
	Ramucirumab (n=238)	Placebo (n=117)	p value
Best overall response			
Complete response	1 (<1%)	0	..
Partial response	7 (3%)	3 (3%)	..
Stable disease	108 (45%)	24 (21%)	..
Progressive disease	78 (33%)	63 (54%)	..
Not evaluable	44 (18%)	27 (23%)	..
Objective response	8 (3%)	3 (3%)	0·76
Disease control rate*	116 (49%)	27 (23%)	<0·0001

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

Table 2: Objective tumour response

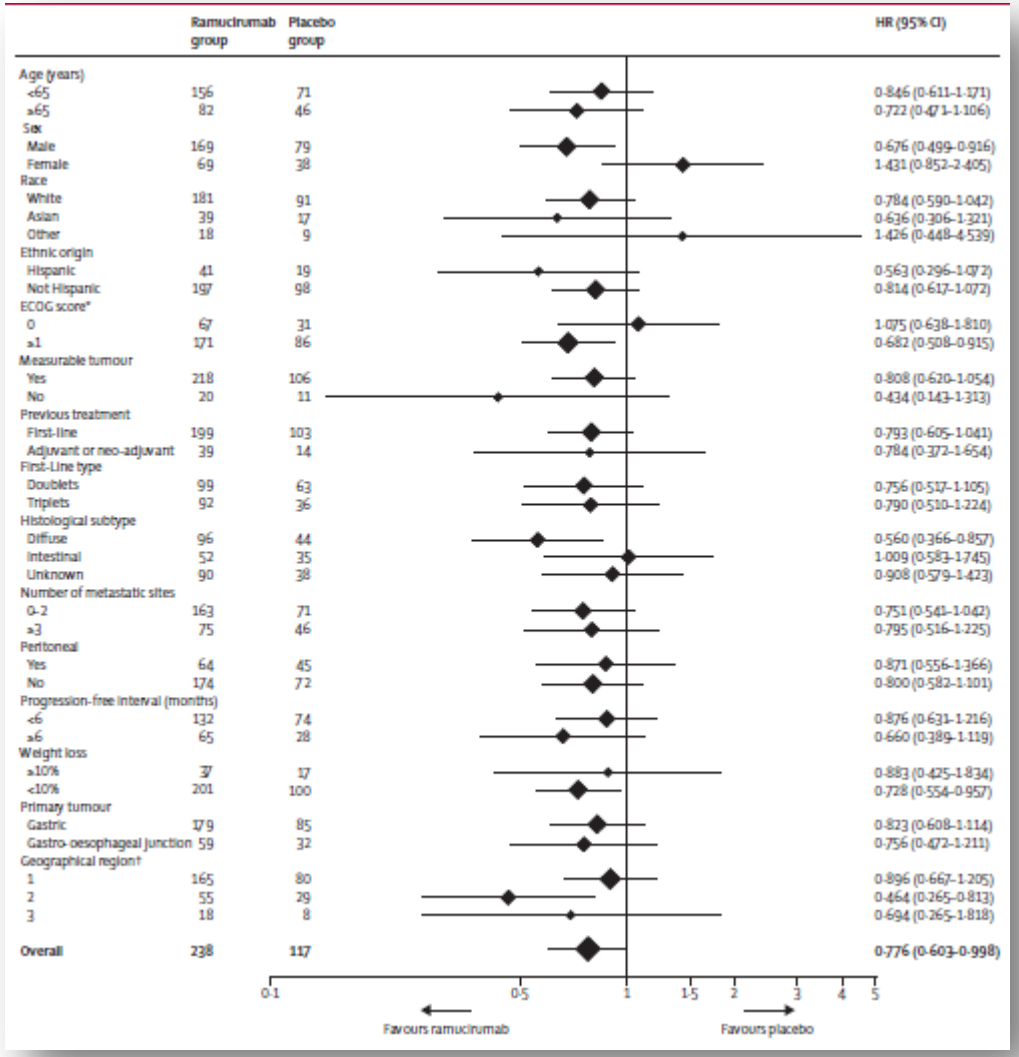
Fuchs et al. *Lancet Oncol* 2013; epub

Ramucirumab (REGARD Study)



Fuchs et al. *Lancet Oncol* 2013; epub

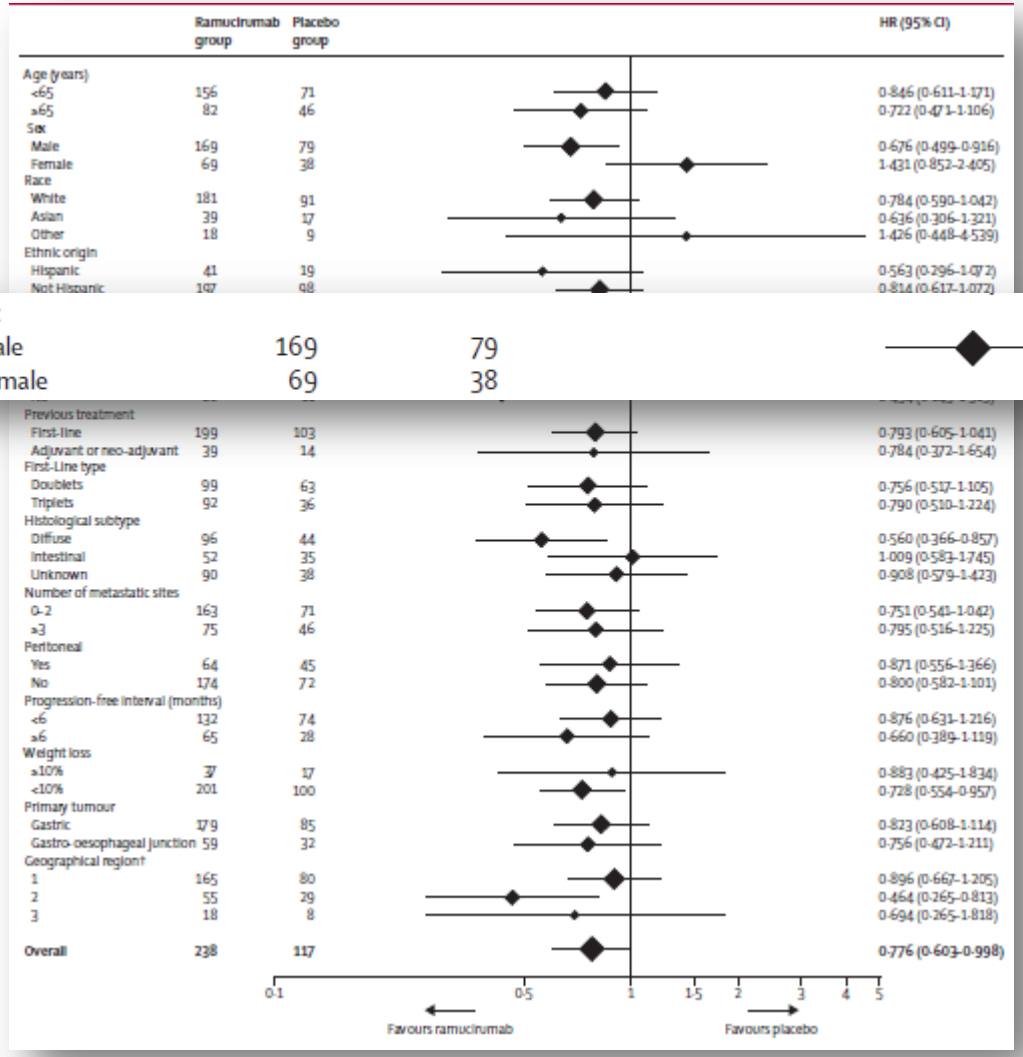
Ramucirumab (REGARD Study)



Subgroup analysis
Survival

Fuchs et al. *Lancet Oncol* 2013; epub

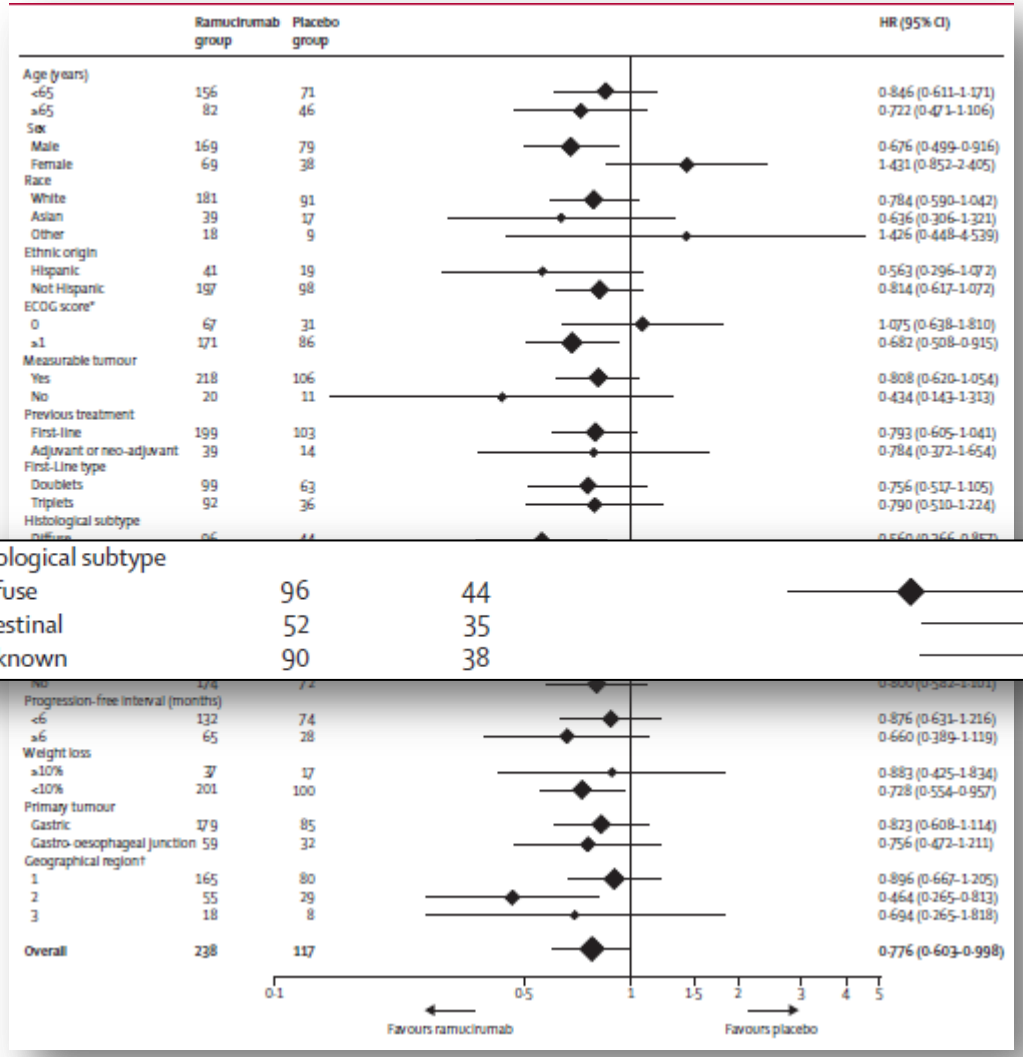
Ramucirumab (REGARD Study)



Sex
Male 169 79 0·676 (0·499–0·916)
Female 69 38 1·431 (0·852–2·405)

Fuchs et al. *Lancet Oncol* 2013; epub

Ramucirumab (REGARD Study)



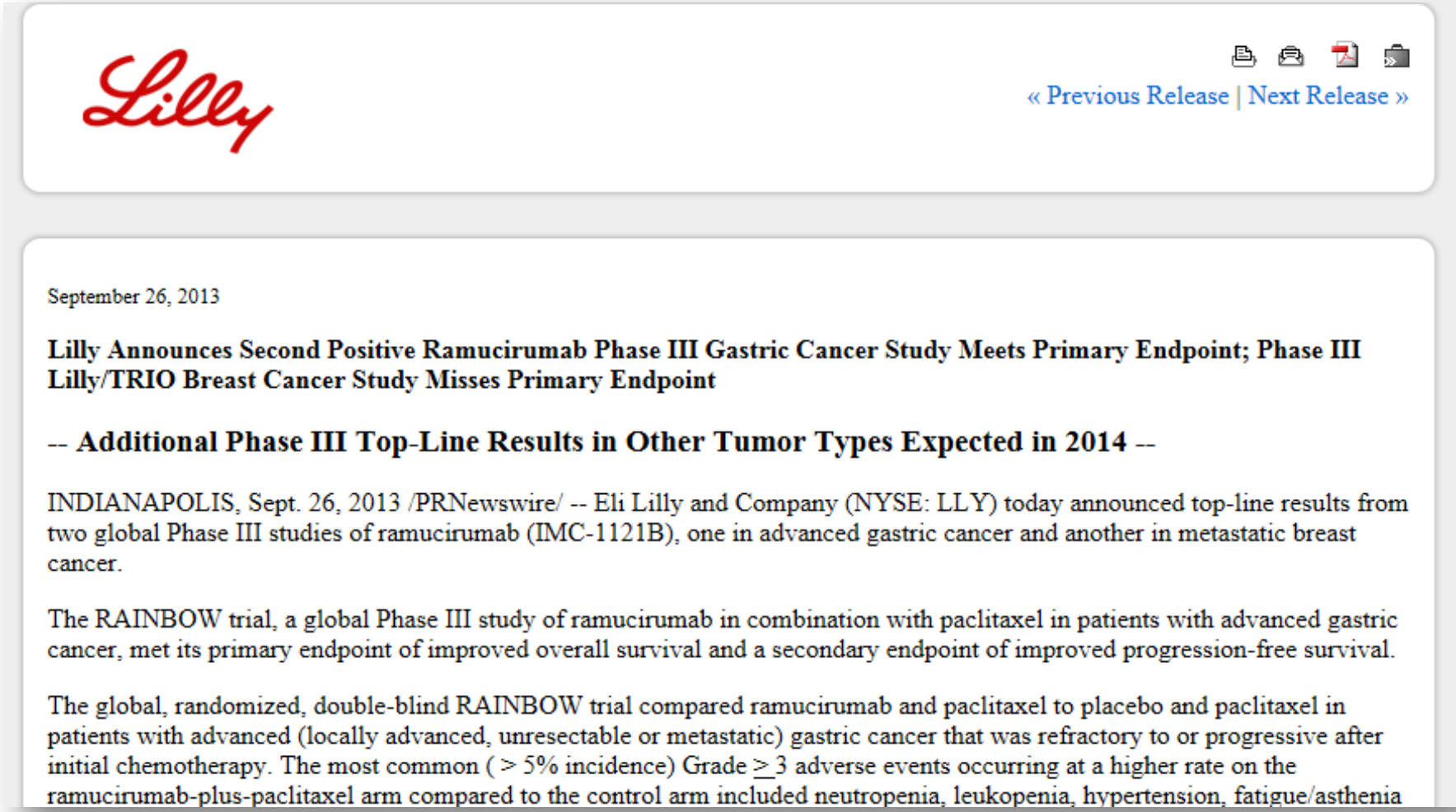
Fuchs et al. *Lancet Oncol* 2013; epub

Ramucirumab (REGARD Study)

	Ramucirumab (n=236)		Placebo (n=115)	
	Any event	Grade ≥3	Any event	Grade ≥3
Fatigue*	84 (36%)	15 (6%)	46 (40%)	11 (10%)
Abdominal pain†	68 (29%)	14 (6%)	32 (28%)	3 (3%)
Decreased appetite	57 (24%)	8 (3%)	26 (23%)	4 (3%)
Vomiting	47 (20%)	6 (3%)	29 (25%)	5 (4%)
Constipation	36 (15%)	1 (<1%)	26 (23%)	3 (3%)
Anaemia‡	35 (15%)	15 (6%)	17 (15%)	9 (8%)
Dysphagia	25 (11%)	5 (2%)	12 (10%)	5 (4%)
Dyspnoea	22 (9%)	4 (2%)	15 (13%)	7 (6%)
Adverse events of special interest				
Hypertension§	38 (16%)	18 (8%)	9 (8%)	3 (3%)
Bleeding or haemorrhage¶	30 (13%)	8 (3%)	13 (11%)	3 (3%)
Arterial thromboembolism‖	4 (2%)	3 (1%)	0	0
Venous thromboembolism**	9 (4%)	3 (1%)	8 (7%)	5 (4%)
Proteinuria	7 (3%)	1 (<1%)	3 (3%)	0
Gastrointestinal perforation	2 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
Fistula formation	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Infusion-related reaction	1 (<1%)	0	2 (2%)	0
Cardiac failure	1 (<1%)	0	0	0

Fuchs et al. *Lancet Oncol* 2013; epub

Ramucirumab RAINBOW Study



« Previous Release | Next Release »

September 26, 2013

Lilly Announces Second Positive Ramucirumab Phase III Gastric Cancer Study Meets Primary Endpoint; Phase III Lilly/TRIO Breast Cancer Study Misses Primary Endpoint

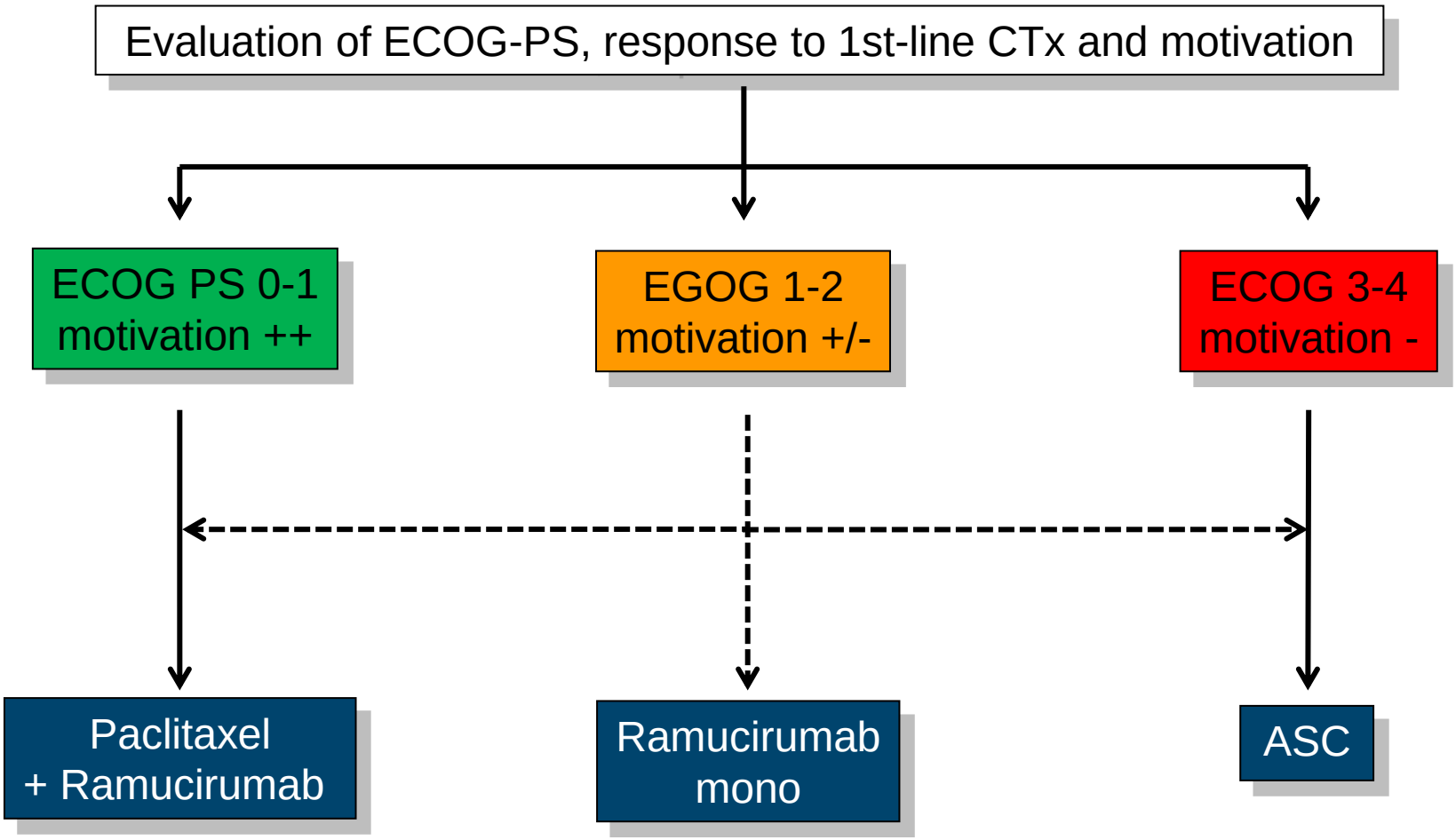
-- Additional Phase III Top-Line Results in Other Tumor Types Expected in 2014 --

INDIANAPOLIS, Sept. 26, 2013 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced top-line results from two global Phase III studies of ramucirumab (IMC-1121B), one in advanced gastric cancer and another in metastatic breast cancer.

The RAINBOW trial, a global Phase III study of ramucirumab in combination with paclitaxel in patients with advanced gastric cancer, met its primary endpoint of improved overall survival and a secondary endpoint of improved progression-free survival.

The global, randomized, double-blind RAINBOW trial compared ramucirumab and paclitaxel to placebo and paclitaxel in patients with advanced (locally advanced, unresectable or metastatic) gastric cancer that was refractory to or progressive after initial chemotherapy. The most common (> 5% incidence) Grade ≥ 3 adverse events occurring at a higher rate on the ramucirumab-plus-paclitaxel arm compared to the control arm included neutropenia, leukopenia, hypertension, fatigue/asthenia

Future Second-line Treatment



Thank you for your attention!

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