위암의 진단, 치료 및 임상시험

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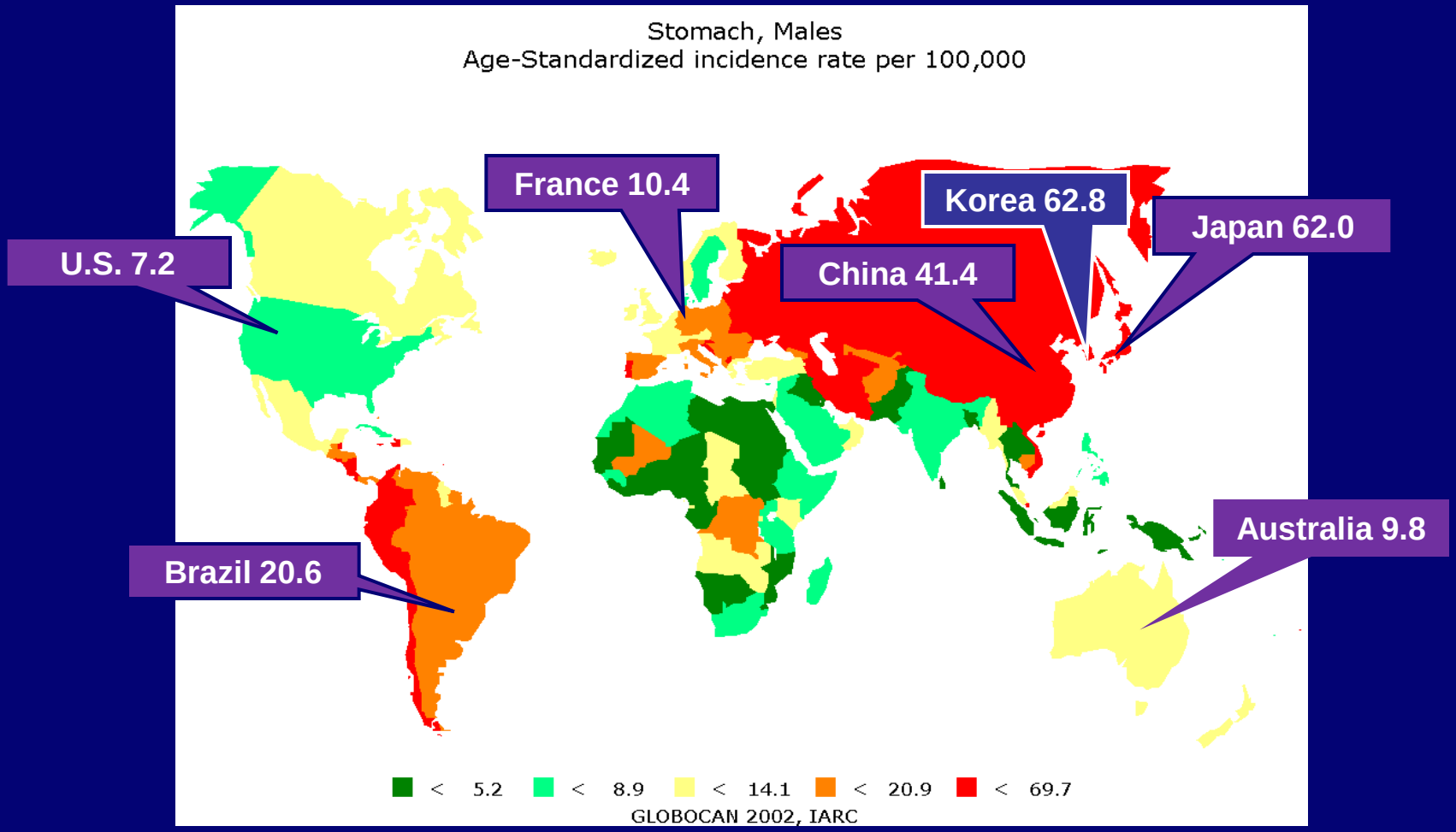
Gastric cancer: Epidemiology



- **Worldwide incidence: 940,000 per annum**
- **Worldwide mortality: 700,300 per annum**

Source: GLOBOCAN 2002

Factors associated with increased risk of stomach cancer

- Acquired
  - Nutritional
  - Cigarette smoking
  - *Helicobacter pylori* infection
  - Epstein-Barr virus
  - Radiation exposure
  - Prior gastric surgery for benign gastric ulcer disease
- Genetic
  - Family history
  - Hereditary nonpolyposis colon cancer
  - Li-Fraumeni syndrome
- Precursor lesions
  - Adenomatous gastric polyps
  - Chronic atrophic gastritis
  - Dysplasia/Intestinal metaplasia

East *vs*. West

- Genetic background
- Etiology – *H.pylori,* diet
- Incidence
- Pathogenesis
  - location, histologic subtypes
- Diagnosis
- Surgery
- Chemotherapy

Symptoms of gastric cancer

- Epigastric discomfort, pain or palpable mass
- Obstructive symptoms
  - Dysphagia (swallowing difficulty)
  - Early satiety
  - Persistent vomiting
- UGI bleeding
- Constitutional Symptoms
  - Anorexia
  - Fatigue
- Weight loss

Diagnosis

- Endoscopy with biopsy
- UGI (upper GI series)
- EUS (endoscopic ultrasound)
- CT scan
- PET scan
- Tumor marker; CEA, CA19-9
- Laparoscopy

Treatment

- Surgery
- Chemotherapy
- Radiotherapy

Surgical treatment

- Laparotomy
- Laparoscopy
- Robotic surgery
- Endoscopic resection

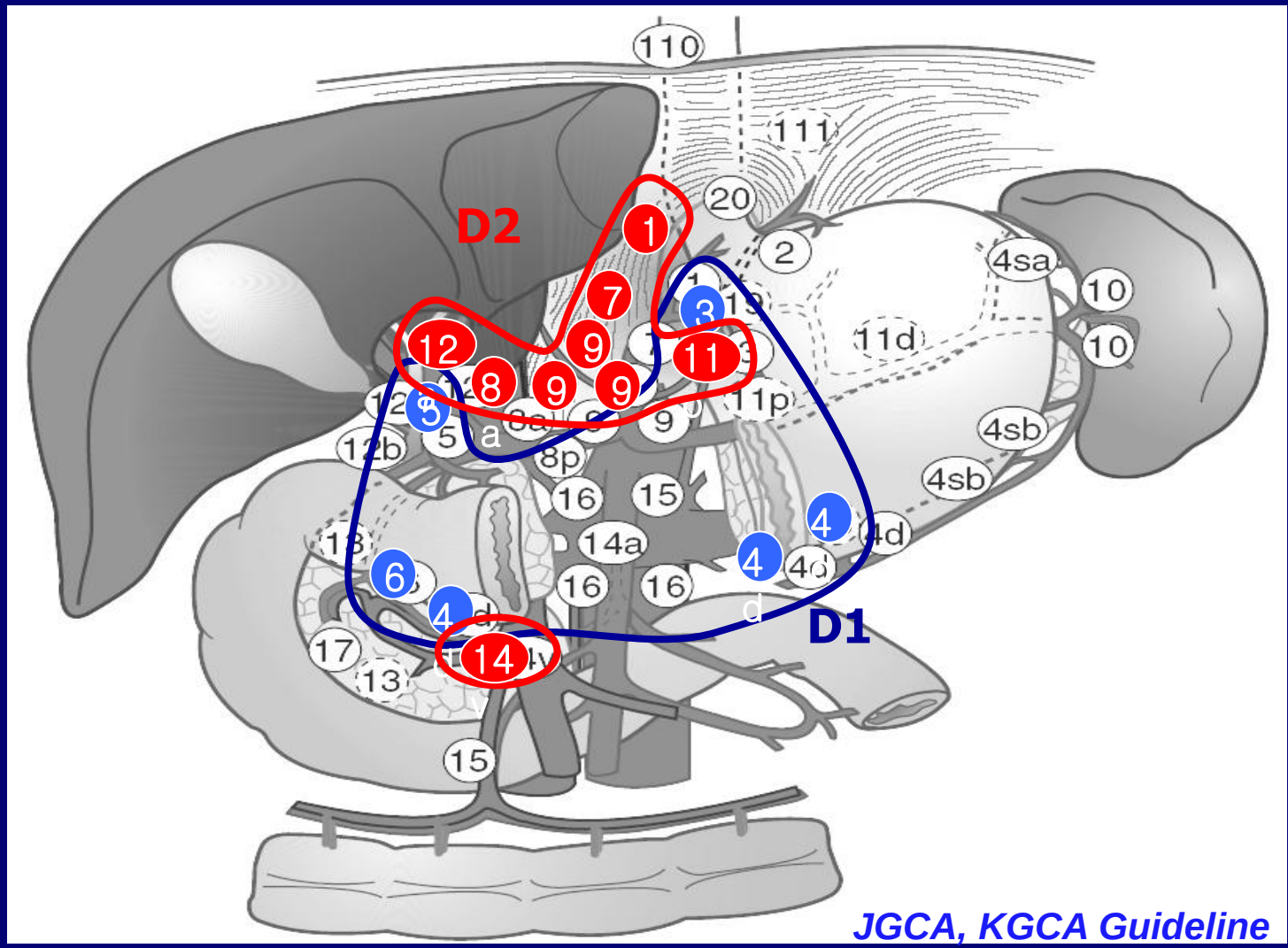
5 Year actual survival after gastrectomy

	SNUH[1]	NCC[2]	MSKCC[3]	DGCC[4]
No of Pts	6,314	6,730	752	331
Ia	92.6	91.5	95	81
Ib	84.0	84.6	85	61
II	67.4	69.3	54	42
IIIa	50.0	50.4	37	28
IIIb	30.6	30.6	11	13
IV	13.1	5.4	7	28

1. Yang HK et al. BJC 2001;88:1408-12 2. Sasako M et al. Gastric Cancer 1997;223-48 3. Karpeh MS et al. Ann Surg 2000;232:362-71 4. Bonenkamp JJ et al. NEJM 340;908-14

Lymph node dissection; D2 vs. D1

LD/L



Adjuvant treatment for resectable gastric cancer

- Postoperative radiotherapy/chemoradiotherapy
- Perioperative chemotherapy
- Postoperative adjuvant chemotherapy

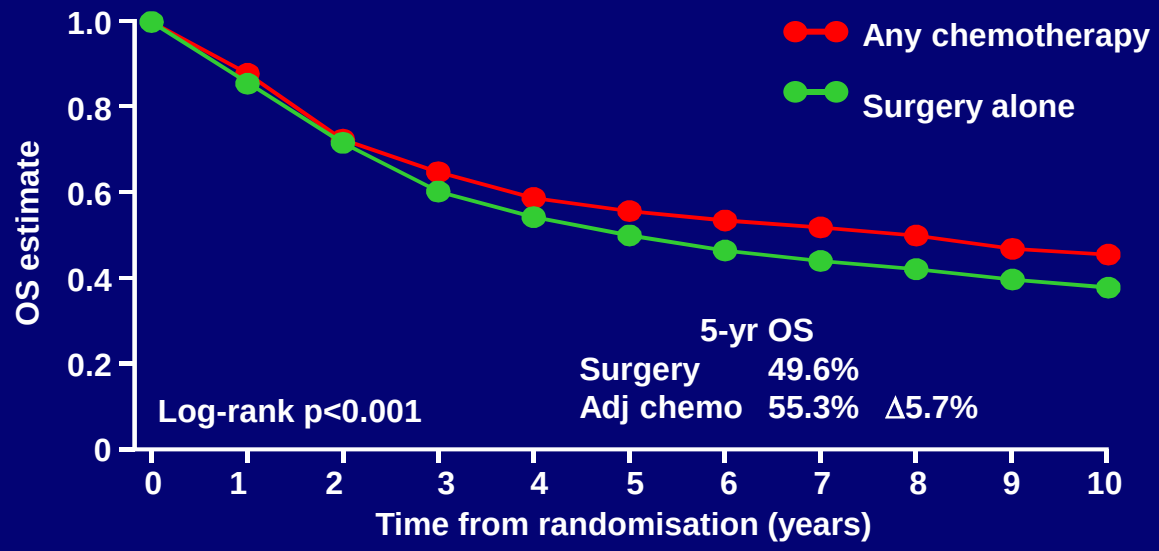
Adjuvant chemotherapy: Meta-analysis

Study	No of trials	No of patients	Odds ratio [95% CI]
Hermans (1993)	11	2,096	0.88 [0.72-1.08]
Hermans (1994)	13	2,414	0.82 [0.68-0.98]
Earle (1999)	13	1,990	0.80 [0.66-0.97]
Janunger (2001)	21	3,962	0.84 [0.74-0.96]
Panzini (2002)	17	3,118	0.72 [0.62-0.84]

Janunger KG, et al. Acta Oncologica 2001;40:309-26

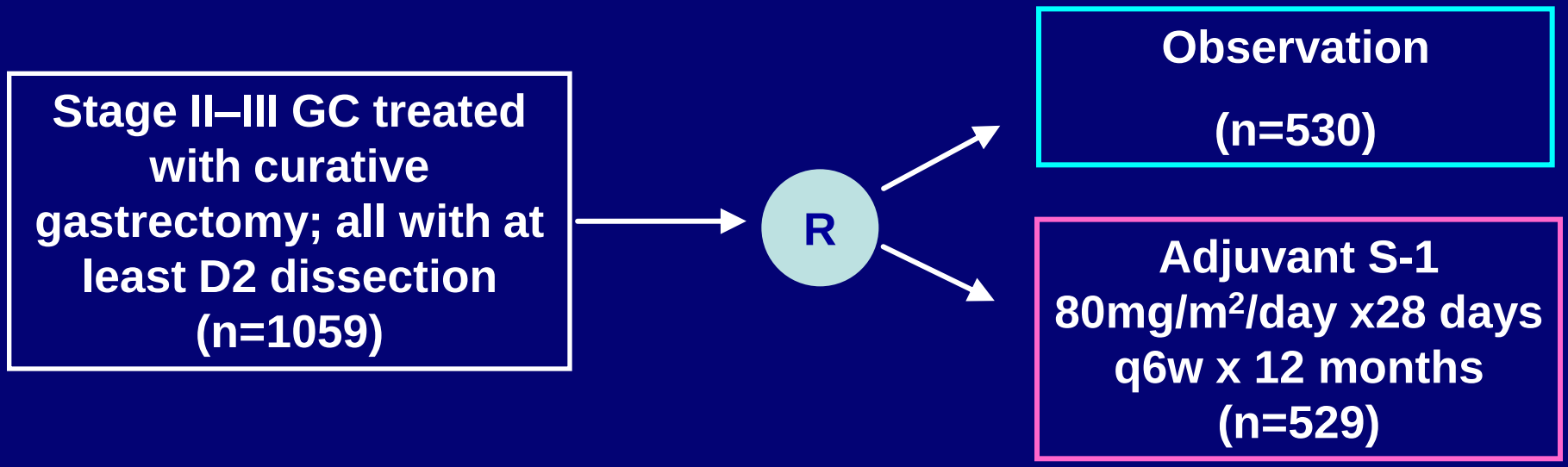
Adjuvant chemotherapy: GASTRIC meta-analysis

- Rates of recurrence are high following surgical resection of GC (40%–80%)[1,2]
- Adjuvant therapy is recommended to reduce recurrence and improve survival[3]



1. Gallo, et al. World J Gastroenterol 2006; 2. Gunderson. Semin Radiat Oncol 2002
3. The GASTRIC Group, JAMA 2010

Adjuvant chemotherapy: ACTS-GC



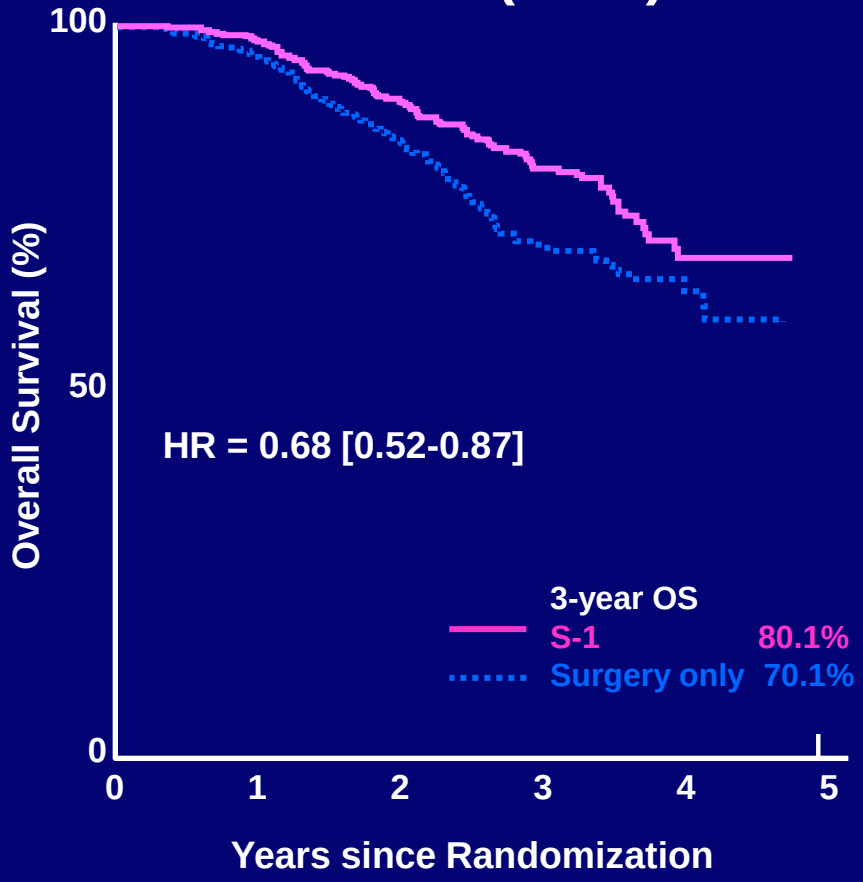
- Stratified by stage & institution
- Primary endpoint: 5 year overall survival

Sakuramoto et al. N Engl J Med 2007; 357:1810-20

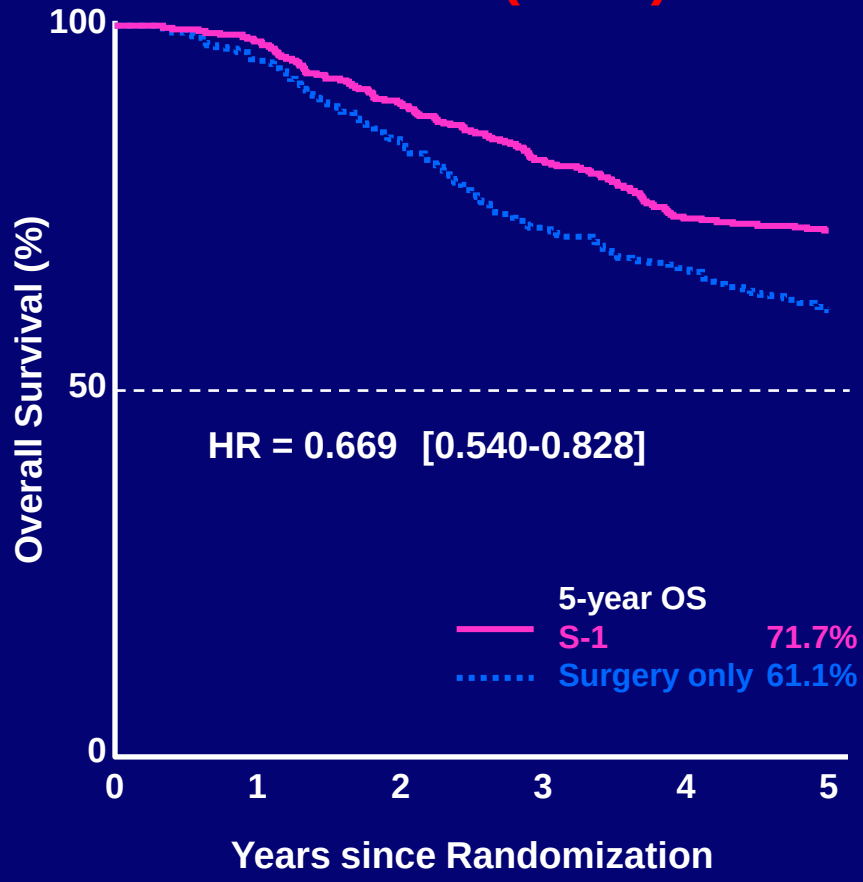
Overall survival

all randomized

NEJM (2007)

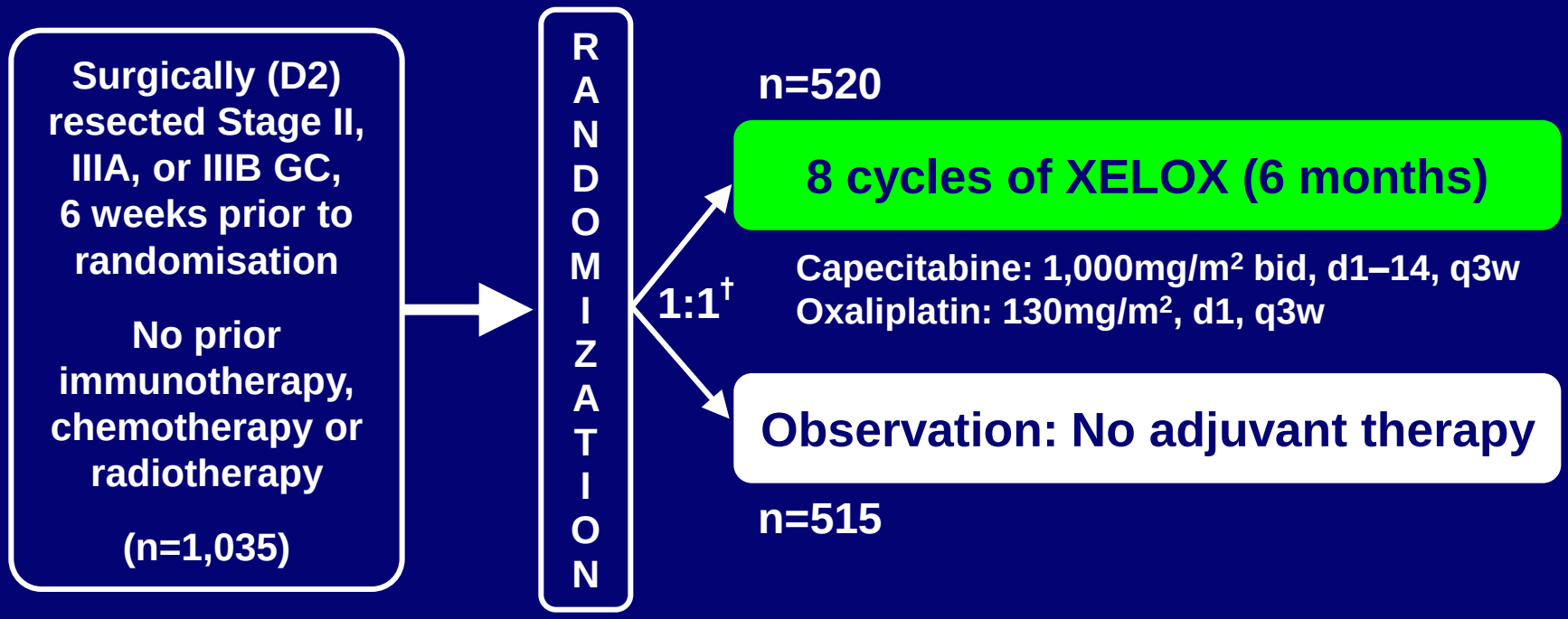


ESMO (2010)



Sakuramoto et al. N Engl J Med 2007; 357:1810-20, Sasako M et al. ESMO 2010,

CLASSIC study design

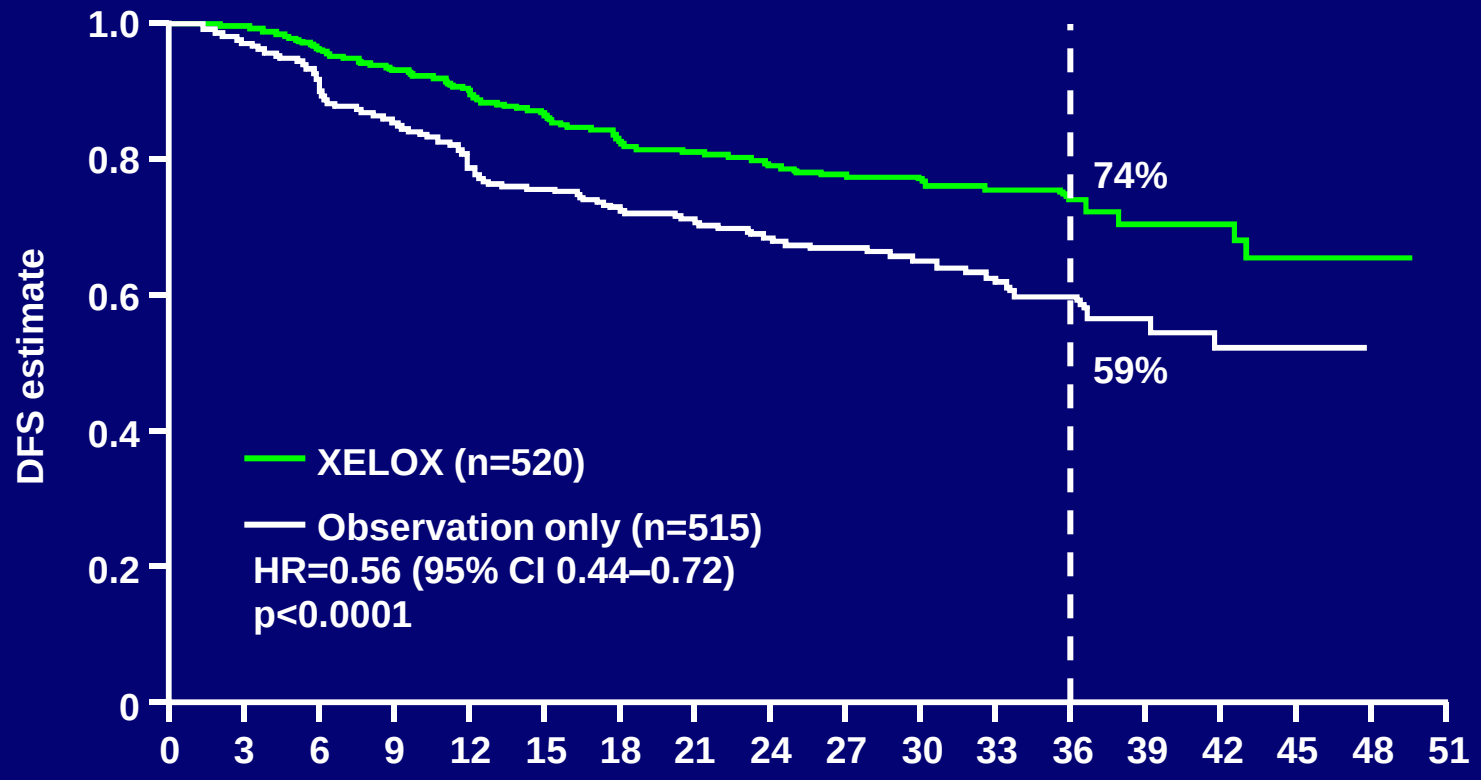


- **Primary endpoint: 3-year DFS‡**
- **Secondary endpoints: overall survival and safety profile**

†Stratified by stage and country with age, sex, and nodal status as covariates
‡GASTRIC project: 3-year DFS and 5-year overall survival are strongly associated, Burzykowski et al. ASCO 2009

Bang, YJ et al. Lancet 2012

Primary endpoint: 3-year DFS (ITT) at interim analysis



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Observation only	515	442	415	388	353	332	289	255	211	188	148	120	58	25	22	20	6	0
XELOX	520	462	442	425	409	379	332	295	246	218	166	147	73	31	30	25	10	0

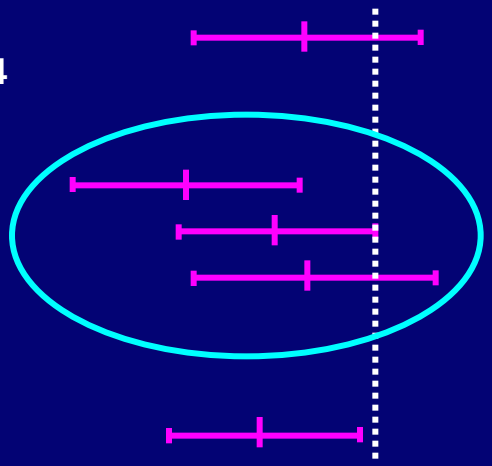
Median follow-up 34.3 months (range 16–51)

Bang, et al. ASCO 2011; manuscript in preparation

Subgroup analysis by stage

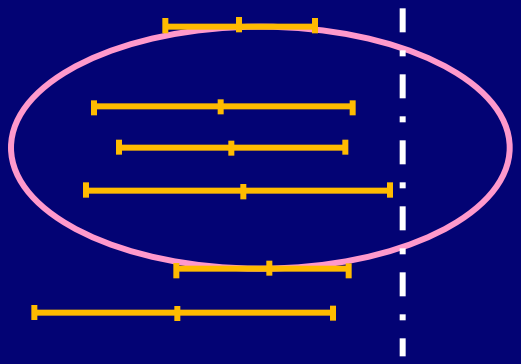
ACTS-GC

70-80	247	0.779(0.527-1.151)
Test for interaction P=0.4424		
Stage (Japanese Classification)		
II	465	0.509(0.338-0.765)
IIIA	397	0.708(0.510-0.983)
IIIB	172	0.791(0.520-1.205)
test for interaction p=0.2945		
Histological type		
Differentiated	423	0.670(0.478-0.938)

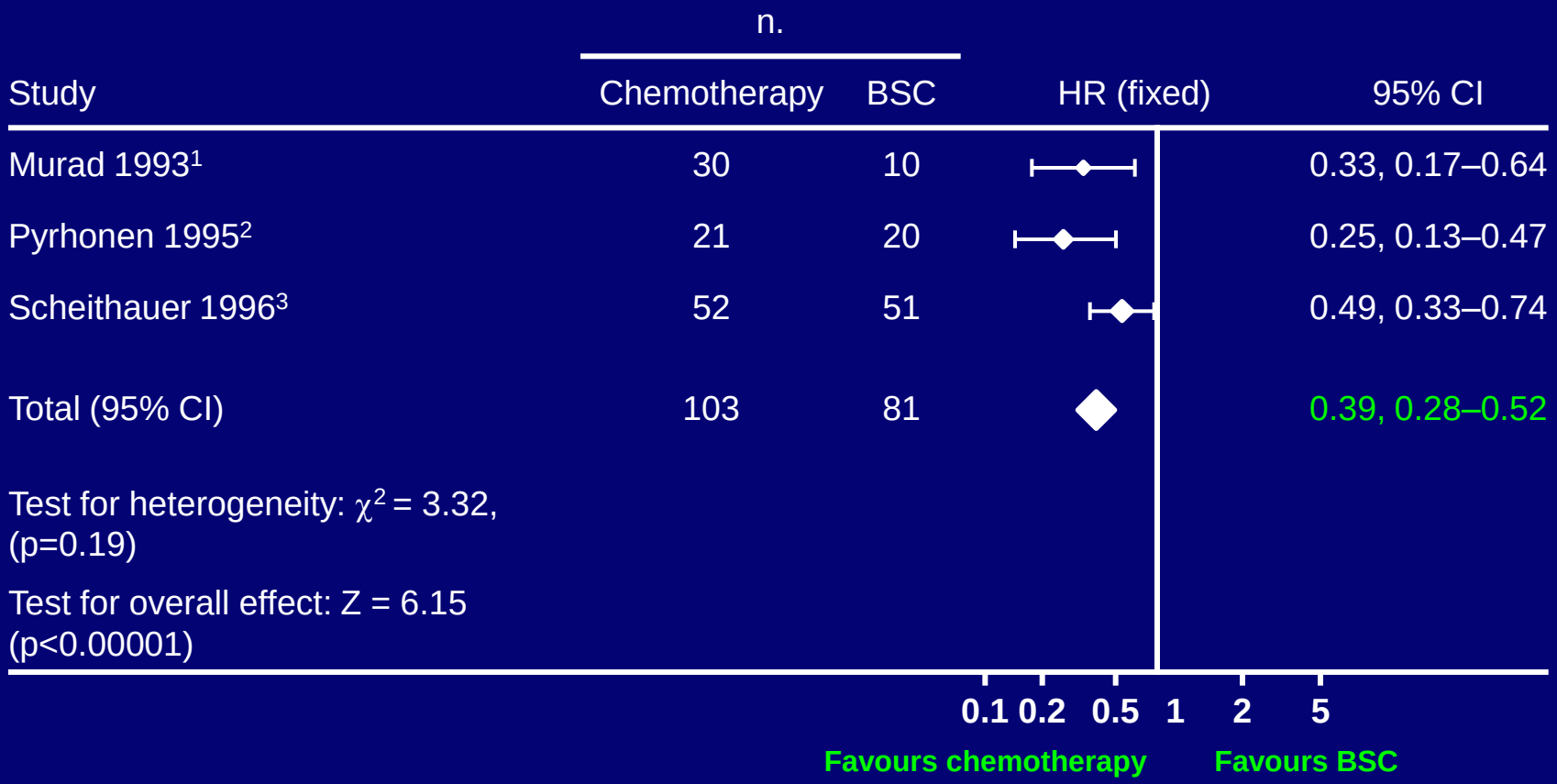


CLASSIC

All	All	1,035	0.58
Stage of Disease	Stage II	515	0.55
	Stage IIIA	377	0.57
	Stage IIIB	145	0.57
Age(years)	<65	766	0.62
	>65	269	0.48



Meta-analysis shows improved survival with chemotherapy *vs.* BSC in AGC



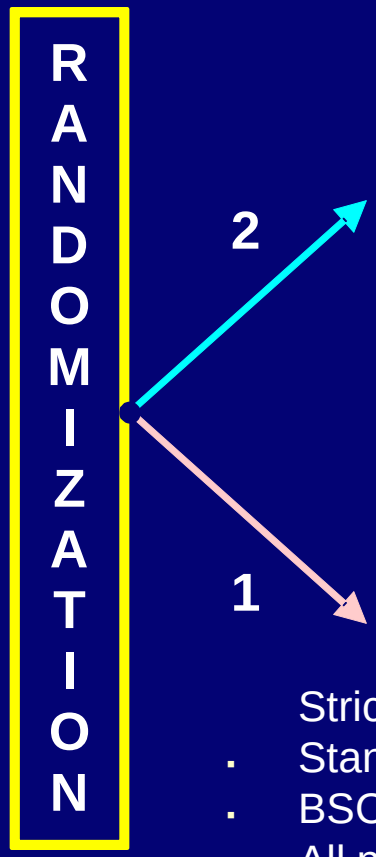
AGC = advanced gastric cancer

Wagner AD et al. J Clin Oncol 2006;24:2903-09

Second-line chemotherapy *vs*. BSC: Study design

- Stratified for PS & # prior therapy
- SLC regimen determined by investigators
- SLC continued until progression, toxicities, or withdrawal

(n = 193)



2

Docetaxel 60 mg/m² q3wks
or
Irinotecan 150 mg/m² q2wks

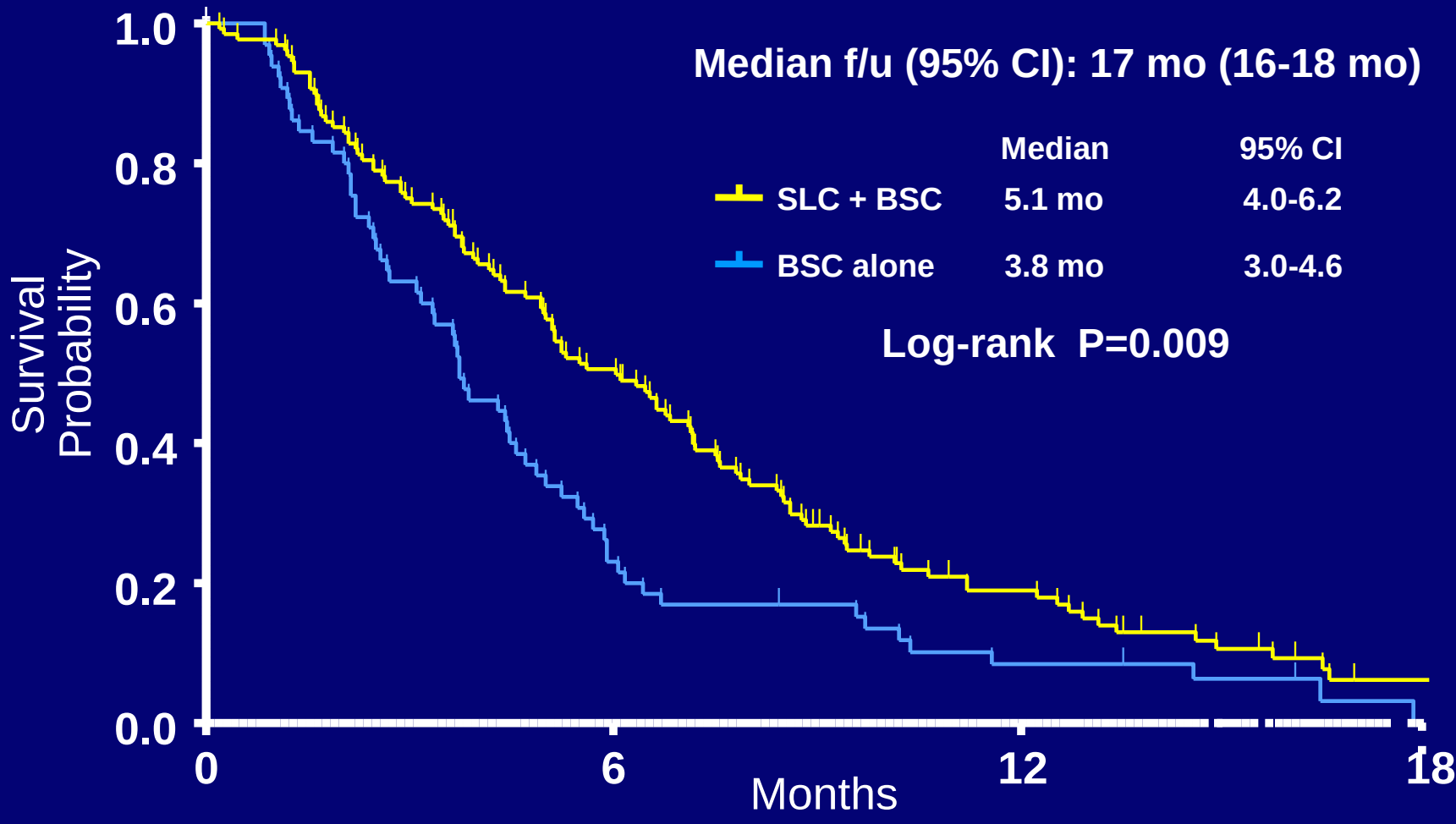
1

BSC alone

- Strict QC measures for BSC
- Standard BSC regimen *a priori* defined
- BSC patients could exit BSC at any time
- All patients treated & followed up in same way

Kang JH et al. J Clin Oncol 2012

Second-line chemotherapy *vs.* BSC: Overall survival



Kang JH et al. J Clin Oncol 2012

Randomized trials in 1990s

Study	n	Regimen	Response (%)	PFS/TTP	OS
SNUH[1]	324	FP / FAM / 5FU	51 / 25 / 26 p<0.01	22 / 12 / 9 wk p<0.01	37 / 30 / 31 wk NS
JCOG[2]	280	FP / 5FU / UFTM	34 / 11 / 9 p<0.01	3.9 / 1.9 / 2.4 mo p<0.01	7.1 / 7.3 / 6.0 mo NS
UK[3]	274	ECF / FAMTX	46 / 21 p<0.01	7.4 / 3.3 mo p<0.01	8.7 / 6.1 mo p<0.01

1. Kim, et al. Cancer 1993 2. Ohtsu, et al. J Clin Oncol 2003 3. Webb, et al. JCO 1997, Waters, et al. BJC 1999

Non-inferiority trials in 2000s

Study	n	1º endpoint	Regimen	Result
REAL-2[1]	964	OS	X v 5-FUi	+
			OXL v DDP	+
ML17032[2]	316	PFS	XP v CF	+
JCOG1912[3]	704	OS	S-1 v 5-FUci	+

C = cyclophosphamide
DDP = cisplatin; F = 5-fluorouracil
L = lapatinib; O = oxaliplatin
P = paclitaxel; X = capecitabine
5-FUi = 5-FU infusion
5-FUci = 5-FU continuous infusion

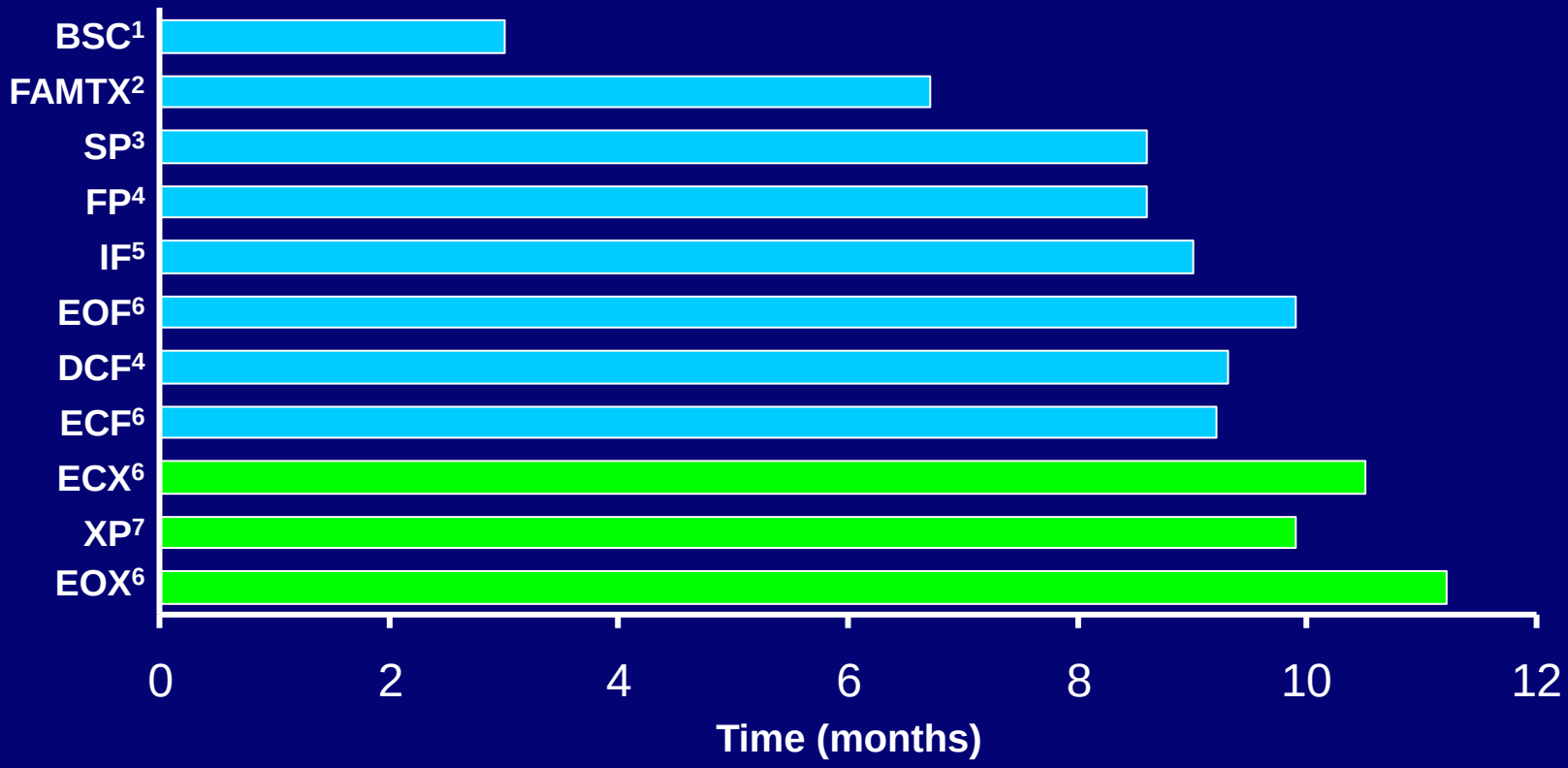
1. Cunningham, et al. N Engl J Med 2008 2. Kang, et al. Ann Oncol 2009 3. Boku N, et al. Proc Am Soc Clin Oncol 2007

Superiority trials in 2000s

Study	n	1º endpoint	Regimen	Result
V325[1]	457	TTP	DCF vs CF	+
V306[2]	333	TTP	IF vs CF	–
JCOG1912[3]	704	OS	IP vs 5-FUci	–
SPIRITS[4]	305	OS	S-1P vs S-1	+
TOP-002[5]	326	OS	IRIS vs S-1	–
FLAGS[6]	1053	OS	S-1P vs CF	–

1. Van Cutsem, et al JCO 2006, 2. Dank, et al. ASCO 2005 , 3. Boku, et al. ASCO 2007, 4. Koizumi, et al. Lancet Oncol 2008 , 5. Imamura, et al. ASCO-GI 2008, 6. Ajani, et al. ASCO GI 2009

Median OS observed in trials of current therapies in advanced GC



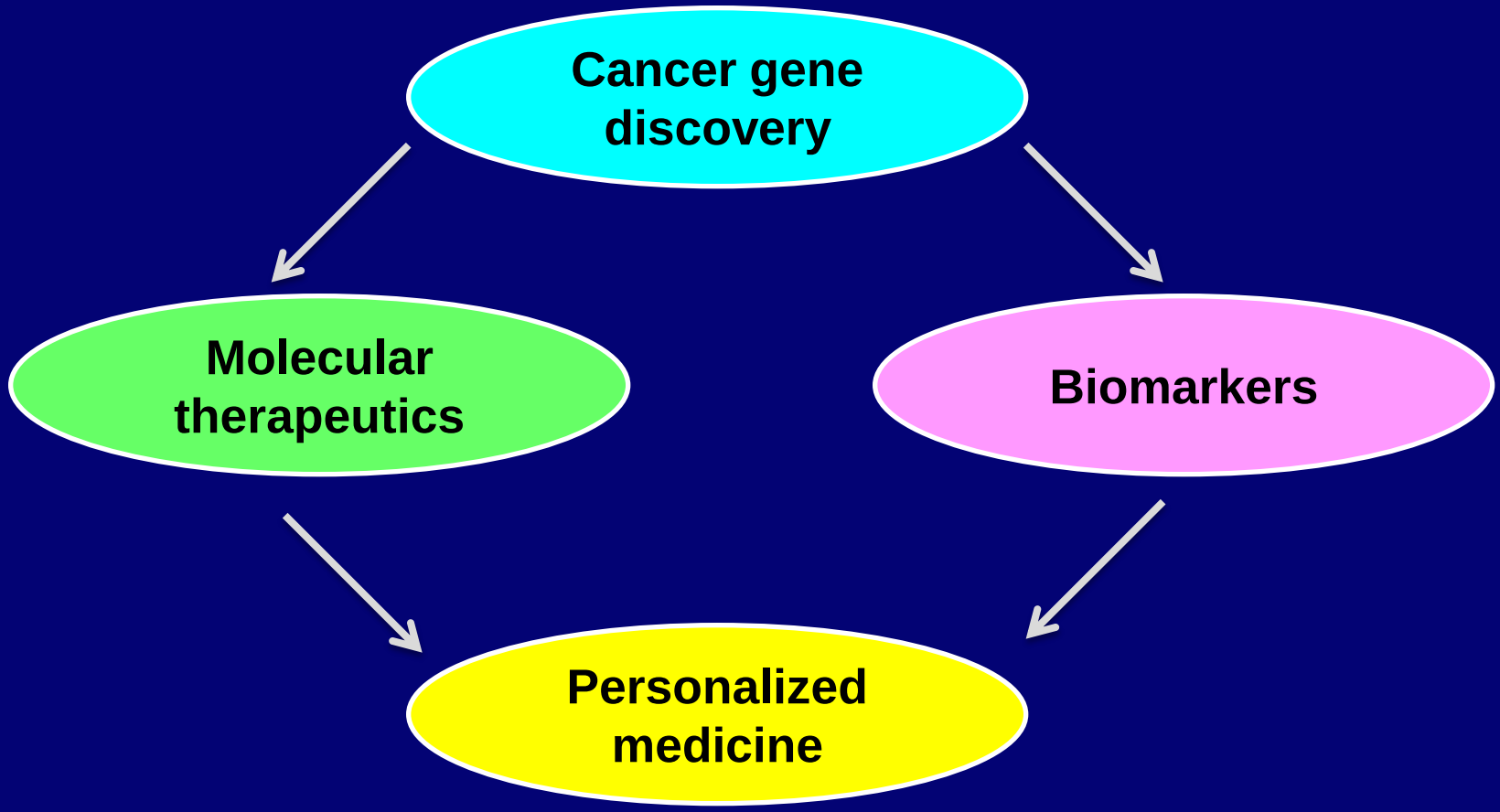
BSC = best supportive care; F = 5-FU; A = doxorubicin
MTX = methotrexate; S = S-1; C/P = cisplatin; I = irinotecan
E = epirubicin; O = oxaliplatin; D = docetaxel

1. Murad, et al. Cancer 1993; 2. Vanhoefer, et al. JCO 2000
3. Ajani, et al. ASCO 2009; 4. Van Cutsem, et al. JCO 2006
5. Dank, et al. Ann Oncol 2008; 6. Cunningham, et al. NEJM 2008
7. Kang, et al. Ann Oncol 2009

What's Next ?

- Targeted therapy
- Personalized medicine

Exploiting the cancer genome



Adapted from Workman P. Eur J Cancer 2002

What is ‘Targeted therapy’?

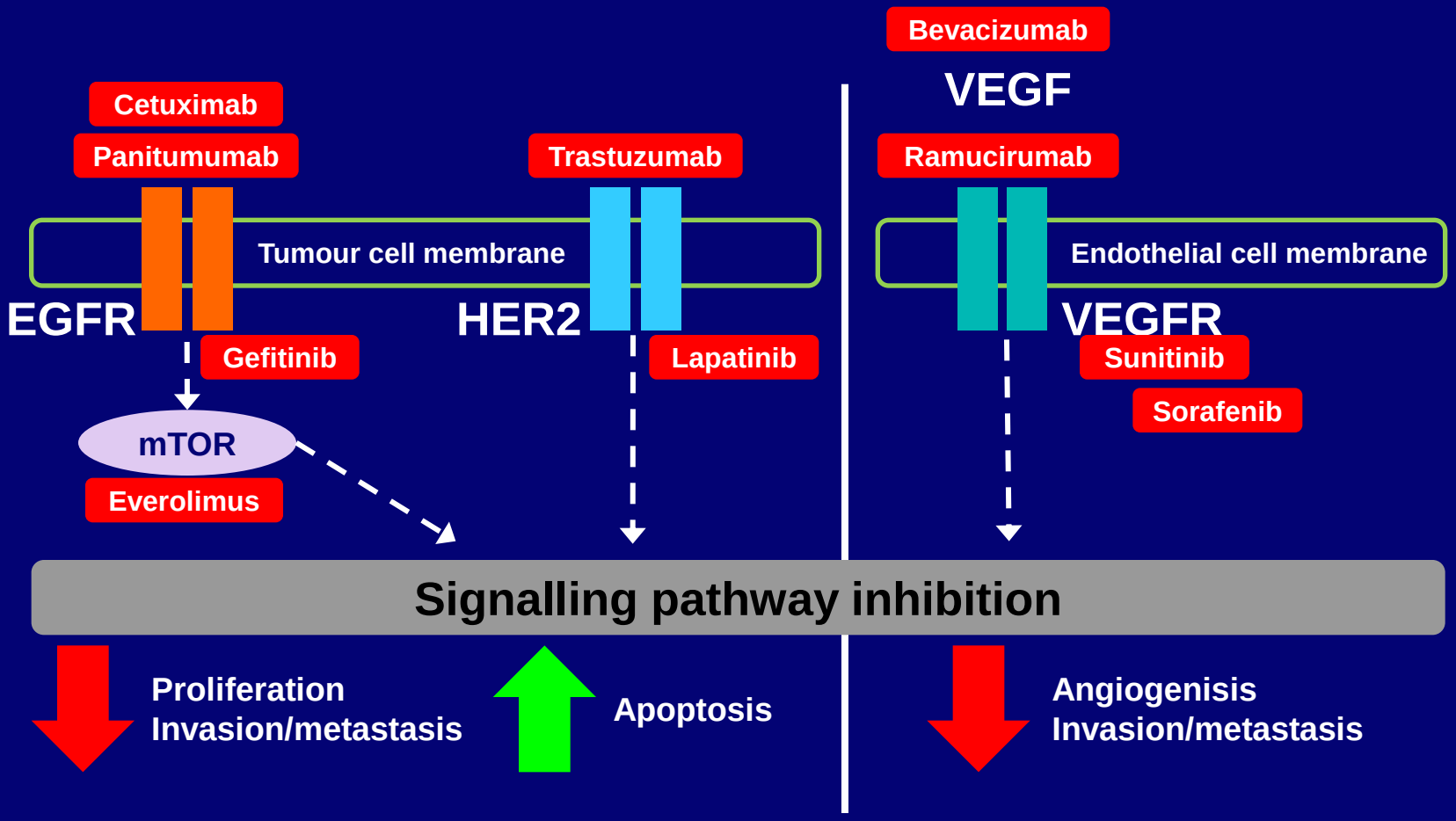
A therapy with a specific molecular target(s)

+

Predictability

Sledge GW Jr. JCO 2005

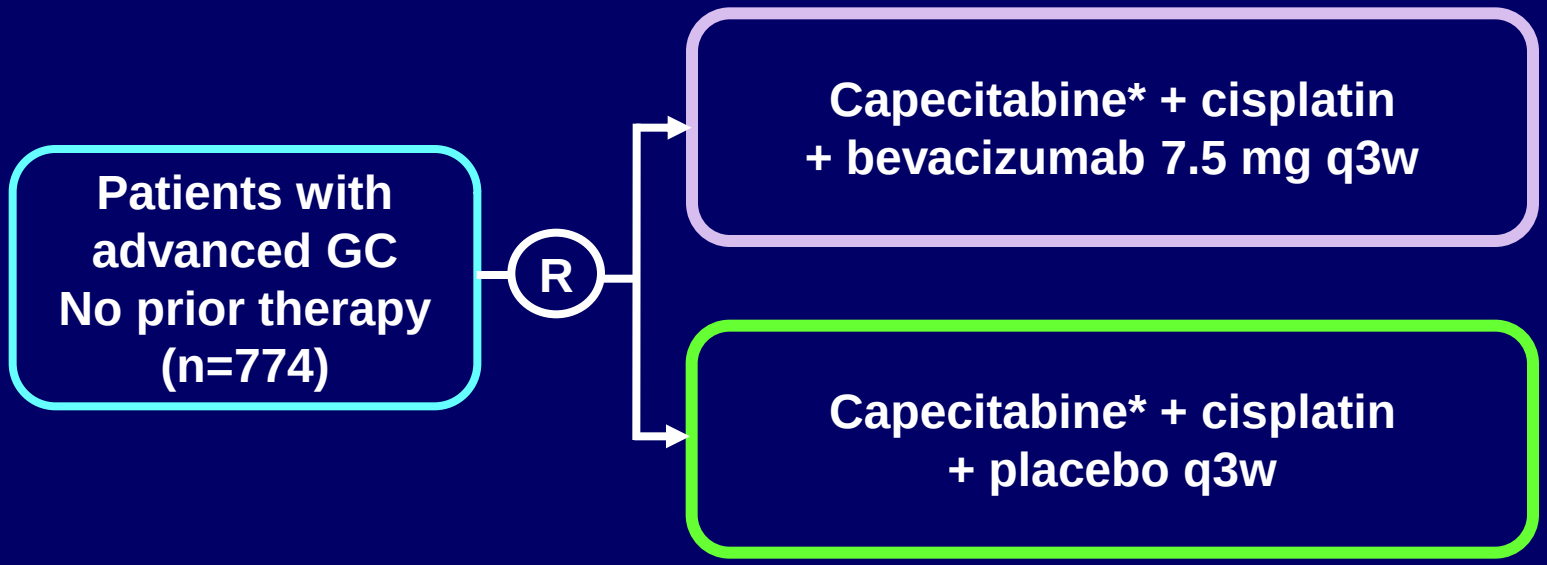
Targeted agents in advanced gastric cancer



mTOR = mammalian target of rapamycin

AVAGAST trial

• a Phase III, randomised, double-blind, international, multicentre study

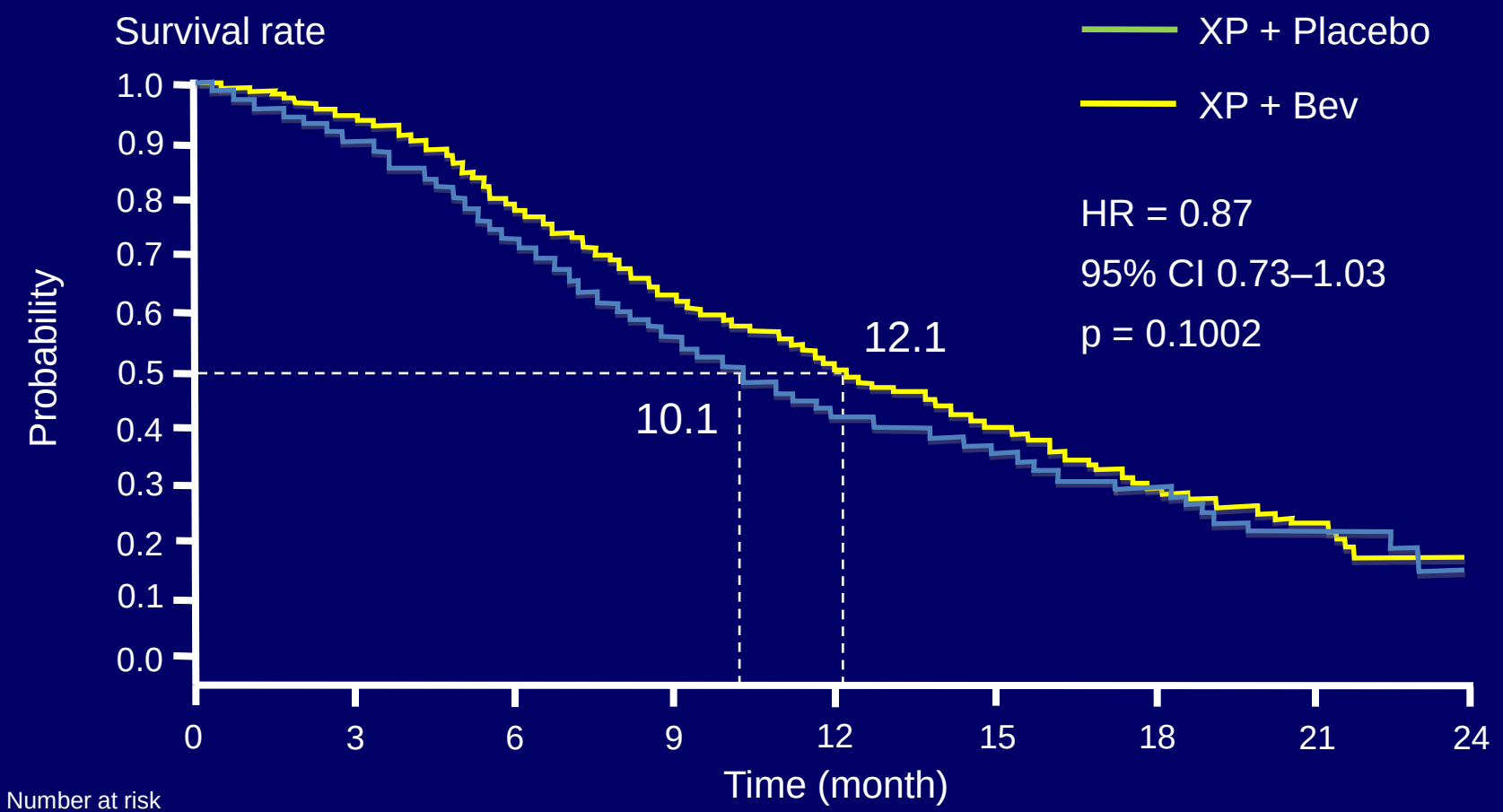


*5-FU also allowed if capecitabine contraindicated

- Primary end point: OS
- Secondary end points: PFS, PFS during first-line therapy, TTP, ORR, DoR, disease control rate

Ohtsu, et al. J Clin Oncol 2011

AVAGAST: Overall survival



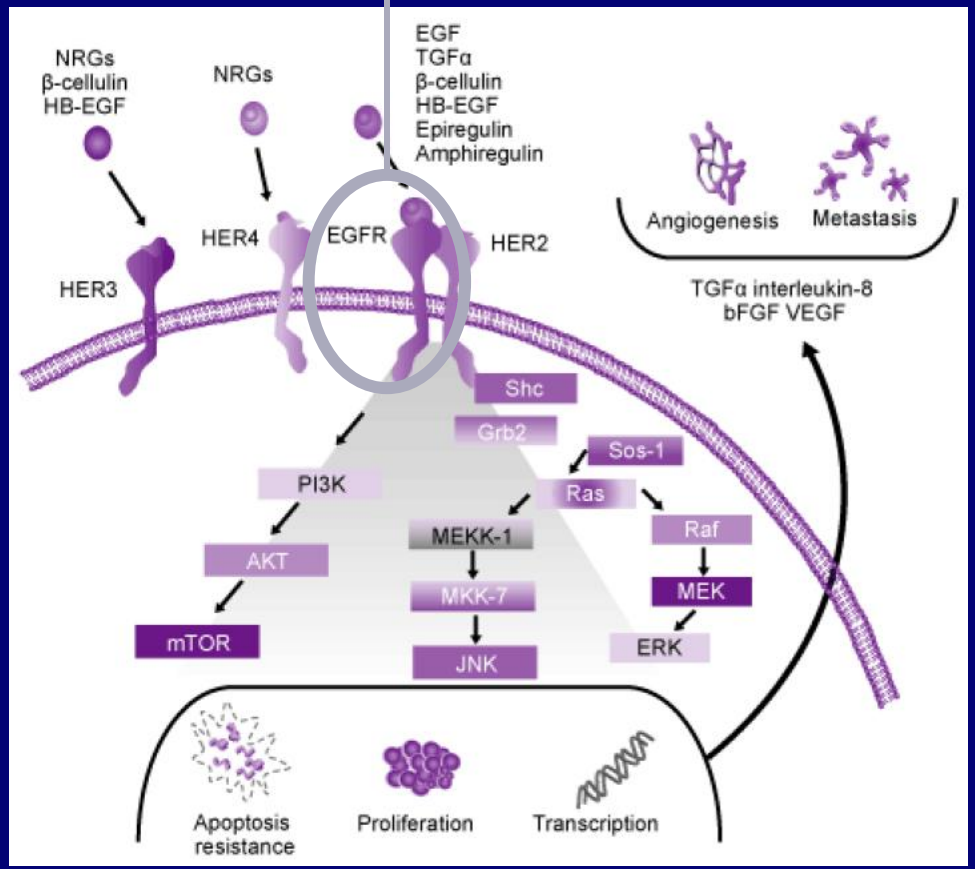
Number at risk

XP + Placebo	387	343	271	204	146	98	54	15	0
XP + Bev	387	355	291	232	178	104	50	19	0

Ohtsu, et al. J Clin Oncol 2011

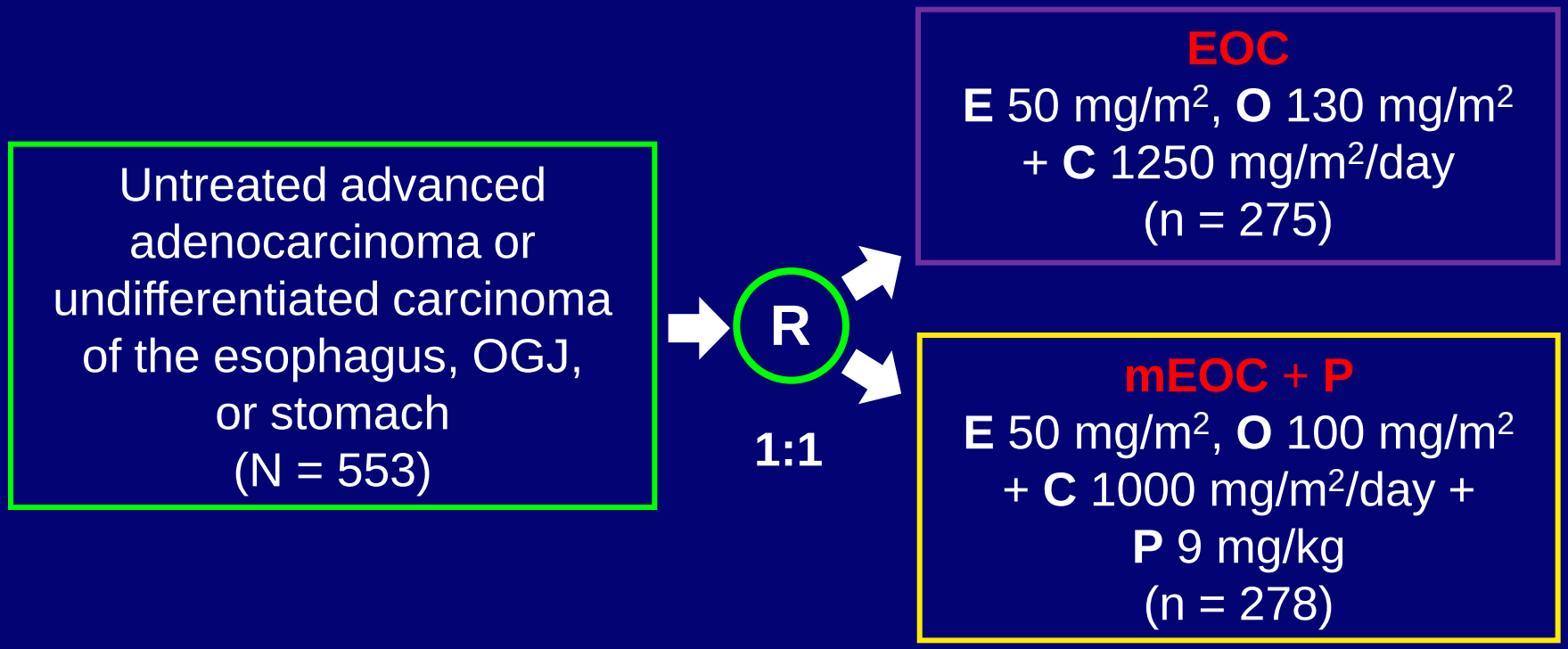
Targeting EGFR in Gastric Cancer

EGFR



Overexpression: > 50%
***KRAS/BRAF* mutations: rare**

REAL3 trial

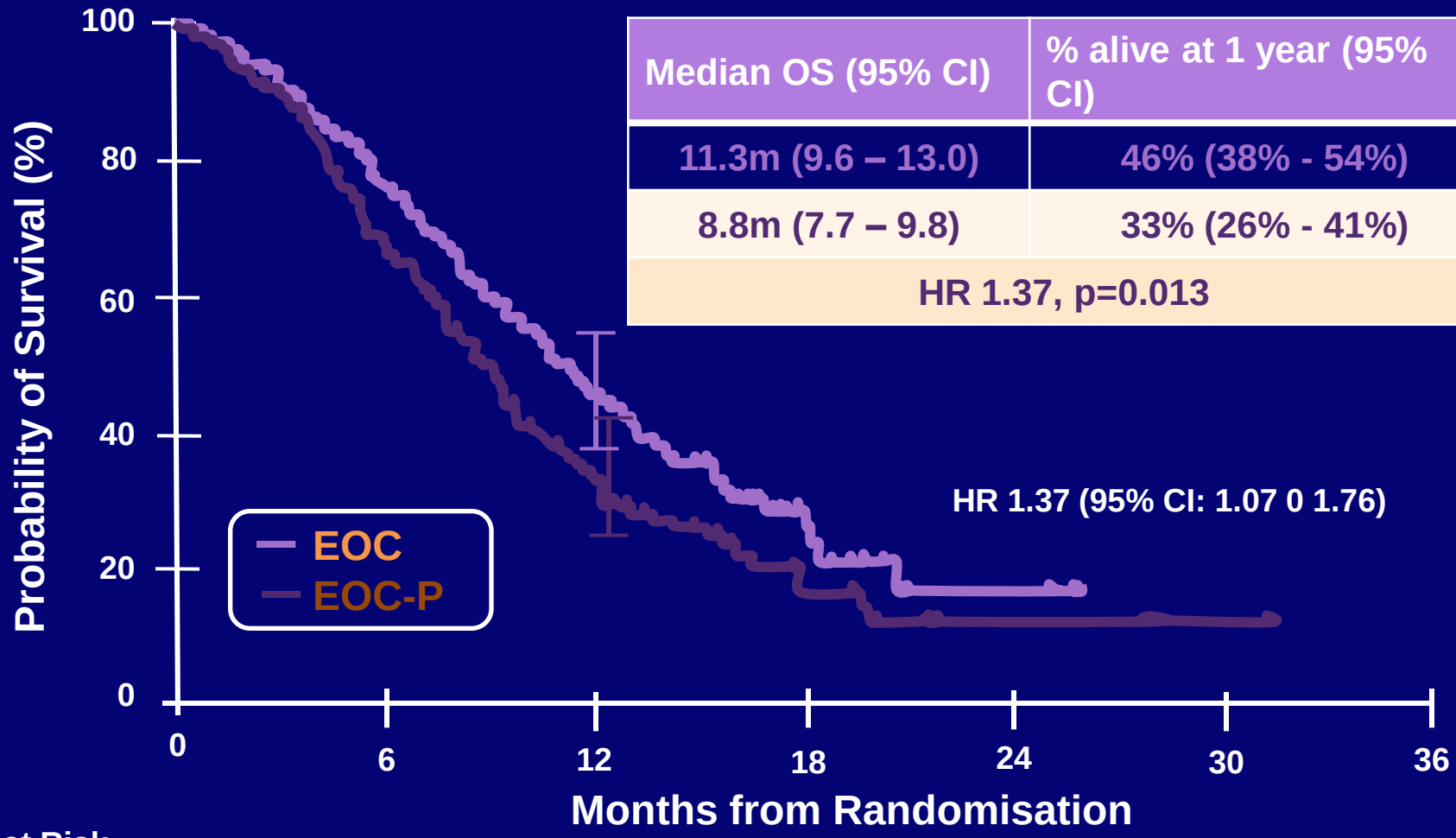


- Primary end point: OS
- Secondary end points: PFS,TTP, ORR, DoR, disease control rate

Waddell TS, et al. ASCO 2012. Abstract LBA4000

Primary Endpoint – OS

Median OS (95% CI)	% alive at 1 year (95% CI)
11.3m (9.6 – 13.0)	46% (38% - 54%)
8.8m (7.7 – 9.8)	33% (26% - 41%)
HR 1.37, p=0.013	



No. at Risk			
EOC	275	49	3
EOC-P	278	38	2

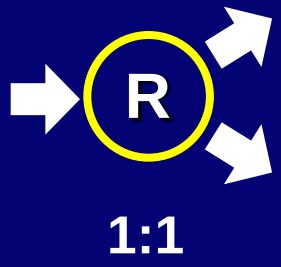
Based on 251 OS events

EXPAND trial

- **Previously Untreated Advanced Adenocarcinoma GEJ or Stomach**

- **Primary Outcome: PFS**
- **Secondary Outcome :OS, ORR, safety, quality of life**

- **74% male**
- **83% had stomach cancer;**
- **97% had metastatic disease**



1:1

CP

C 1000 mg/m^2 bid, days 1-14 **+ P** 80 mg/m^2, day 1, q21d

(n =449)

CP + Cetux

C 1000 mg/m^2 bid, days 1-14 **+ P** 80 mg/m2, day 1 **+ Cetux** 400 mg/m^2 initial dose then 250 mg/m^2 qw, q21d

(n =455)

Lordick F, et al. ESMO 2012

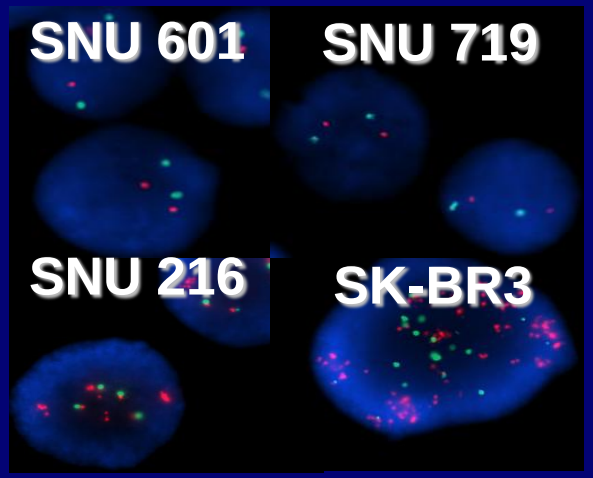
EXPAND: Outcomes

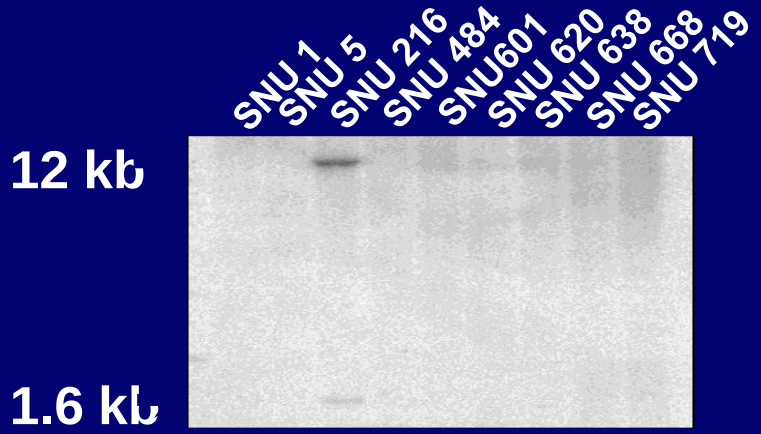
Measure	CP (n = 449)	CP + Cetux(n = 455)	HR
Median OS, mos	10.7	9.4	HR 1.004; 0.866–1.165, p=0.9547
Median PFS, mos	5.6	4.4	HR 1.091; 0.920–1.292, p=0.3158
ORR, %	30	29	

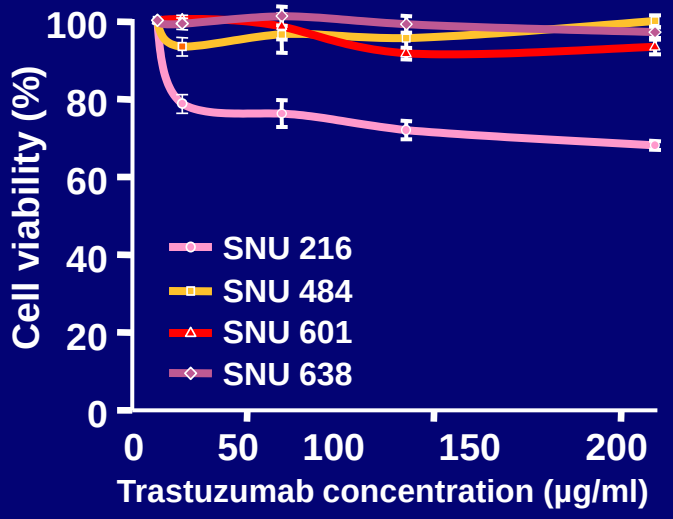
- Baseline characteristics were balanced between treatment arms
- Median duration of cetuximab treatment was 14.9 weeks with a relative dose intensity of ≥80% received by 82% of patients
- Safety profiles were consistent with those known for each agent but more grades 3/4 and serious adverse events were reported in the cetuximab arm.
- Negative results of this trial cannot be explained by toxicity.
- Tissue is available for biomarker analysis from 97% of included patients and the analysis is currently on-going

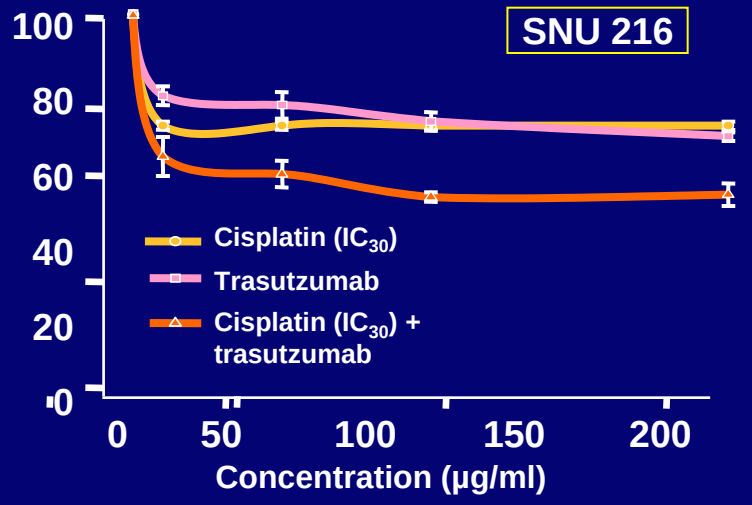
Lordick F, et al. ESMO 2012

In vitro efficacy of trastuzumab



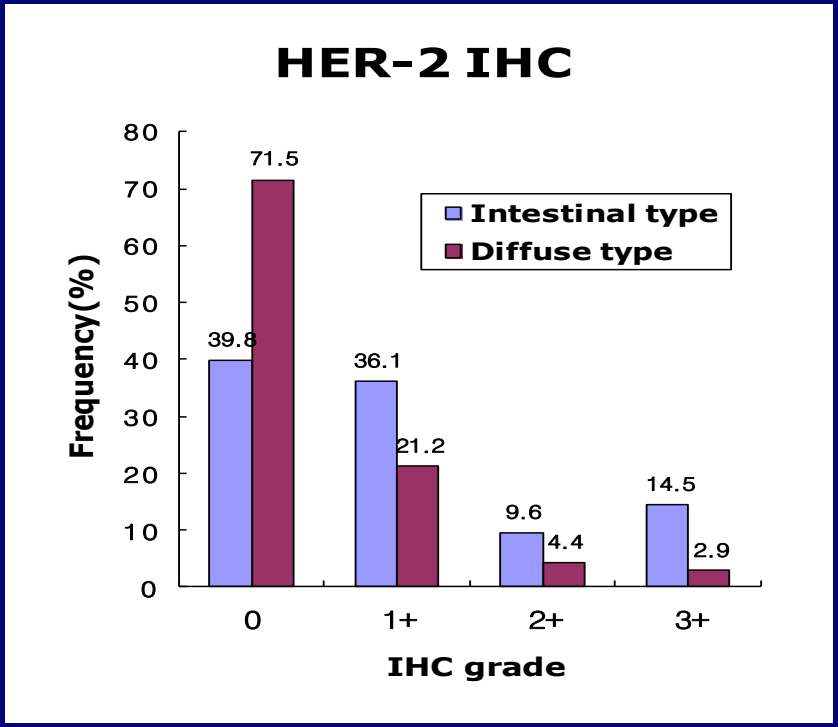


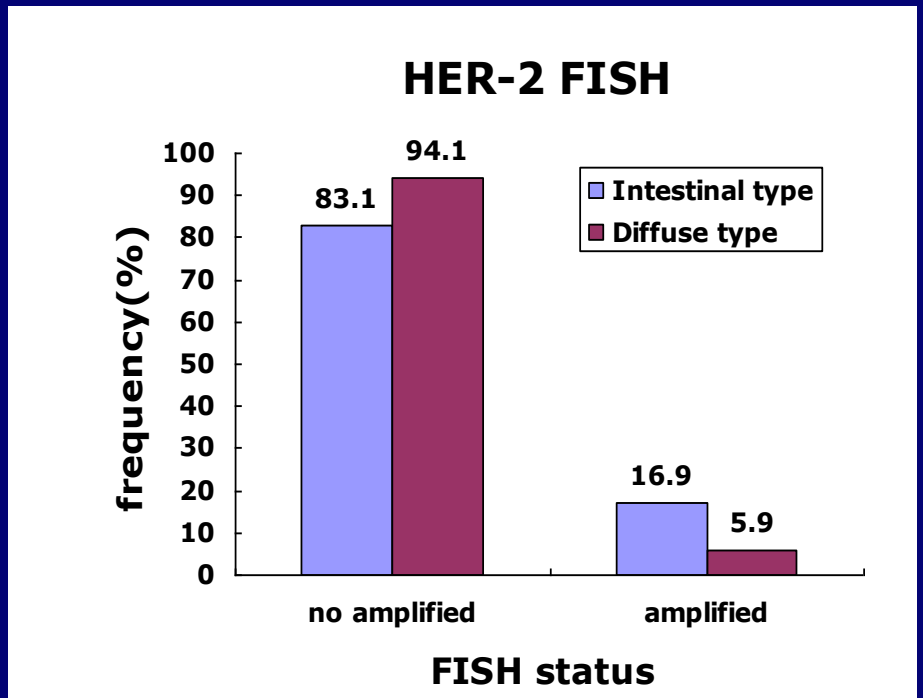




Kim SY, et al. Int J Oncol 2008;32:89-95

HER2 amplification in gastric cancer





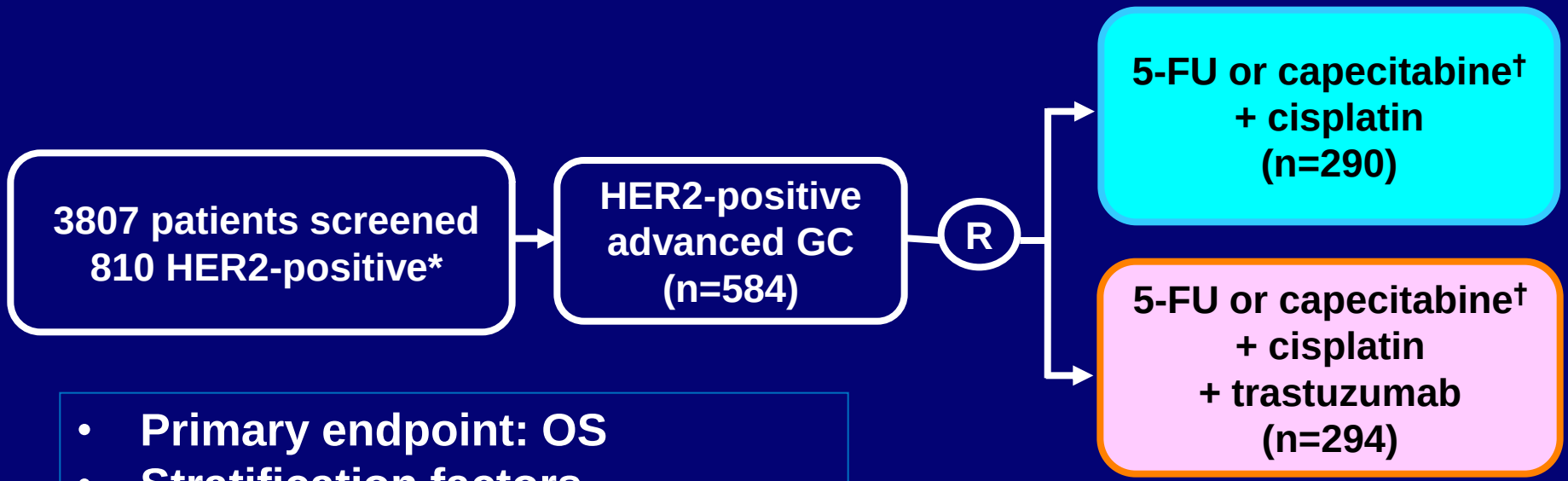
HER2-IHC	0	1+	2+	3+
Intestinal(%) (n=83)	33 (39.8%)	30 (36.1%)	8 (9.6%)	12 (14.5%)
Diffuse (%) (n=137)	98 (71.5%)	29 (21.2%)	6 (4.4%)	4 (2.9%)

HER2 FISH	Not amplified	Amplified
Intestinal(%) (n=83)	69 (83.1%)	14 (16.9%)
Diffuse (%) (n=136)	128 (94.1%)	8 (5.9%)

Im SA, et al. Diagn Mol Pathol 2011

ToGA trial

- Phase III, randomised, open-label, international, multicentre study

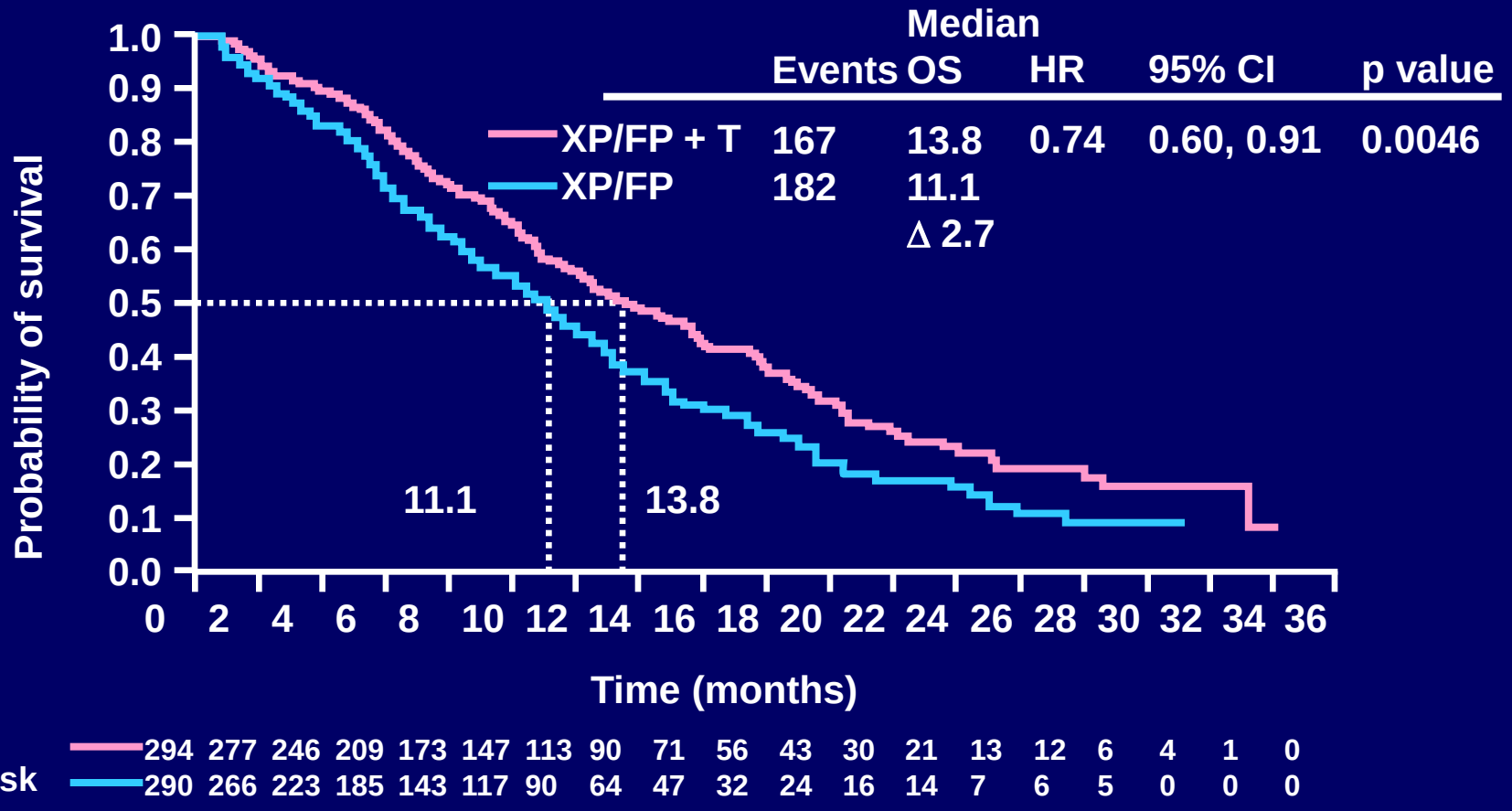


- Primary endpoint: OS
- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

*as defined in the protocol (IHC 3+ and/or FISH+)
†Chosen at investigator's discretion

Bang YJ et al. Lancet 2010

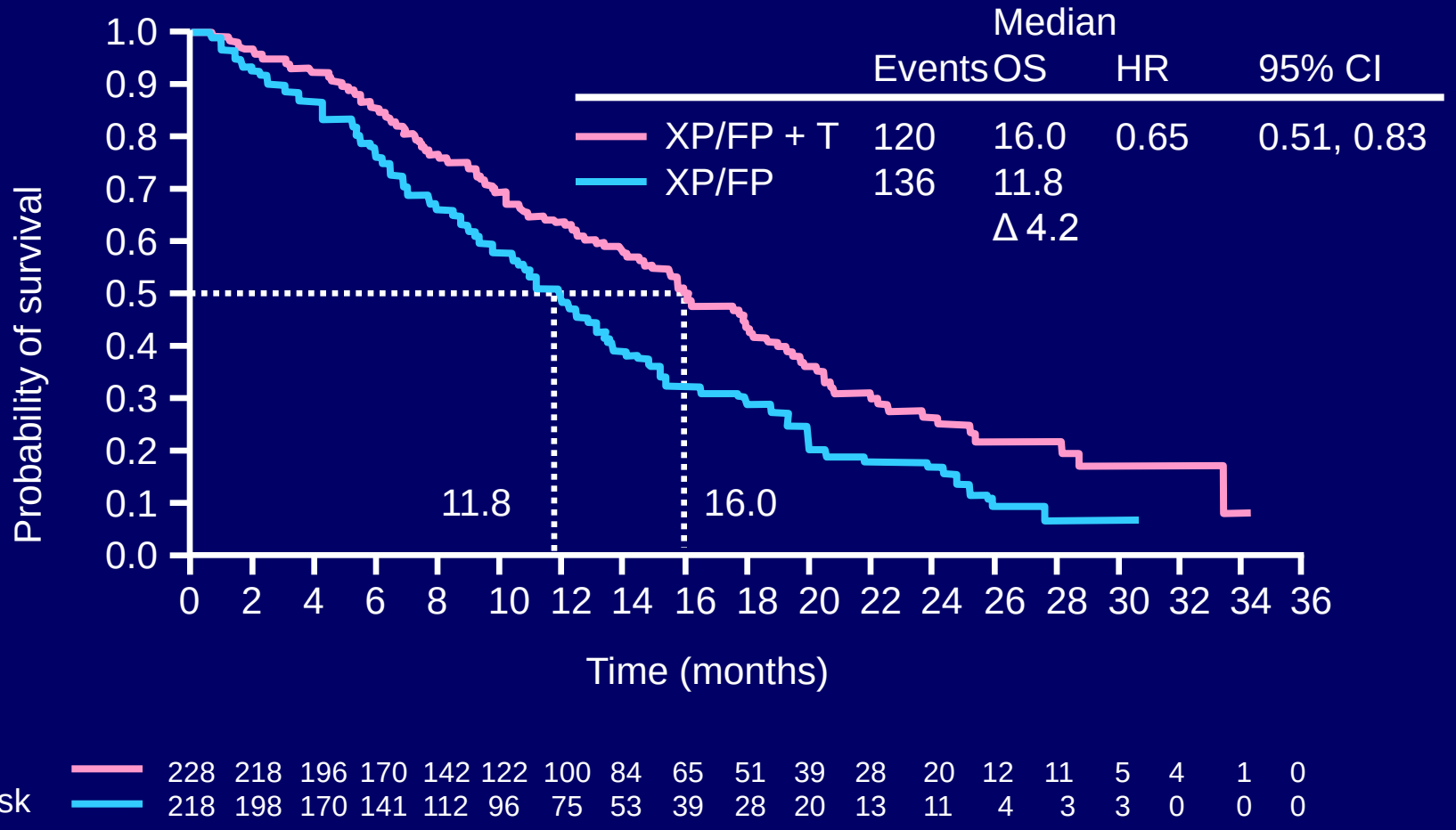
Primary end point : Trastuzumab significantly improved OS



ITT population
T = trastuzumab

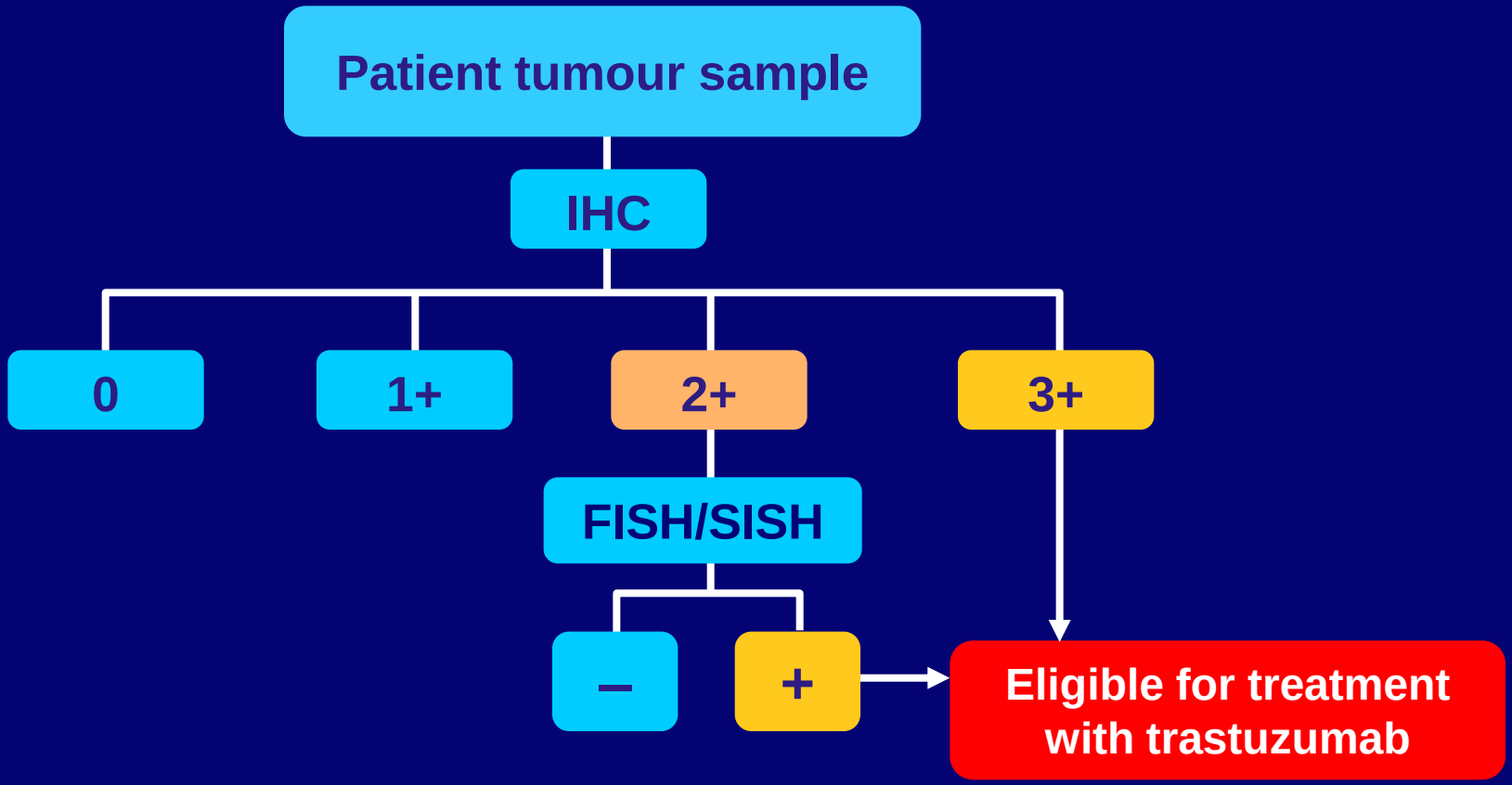
Bang YJ et al. Lancet 2010

OS in IC 2+ / FISH+ or IHC 3+ (exploratory analysis)



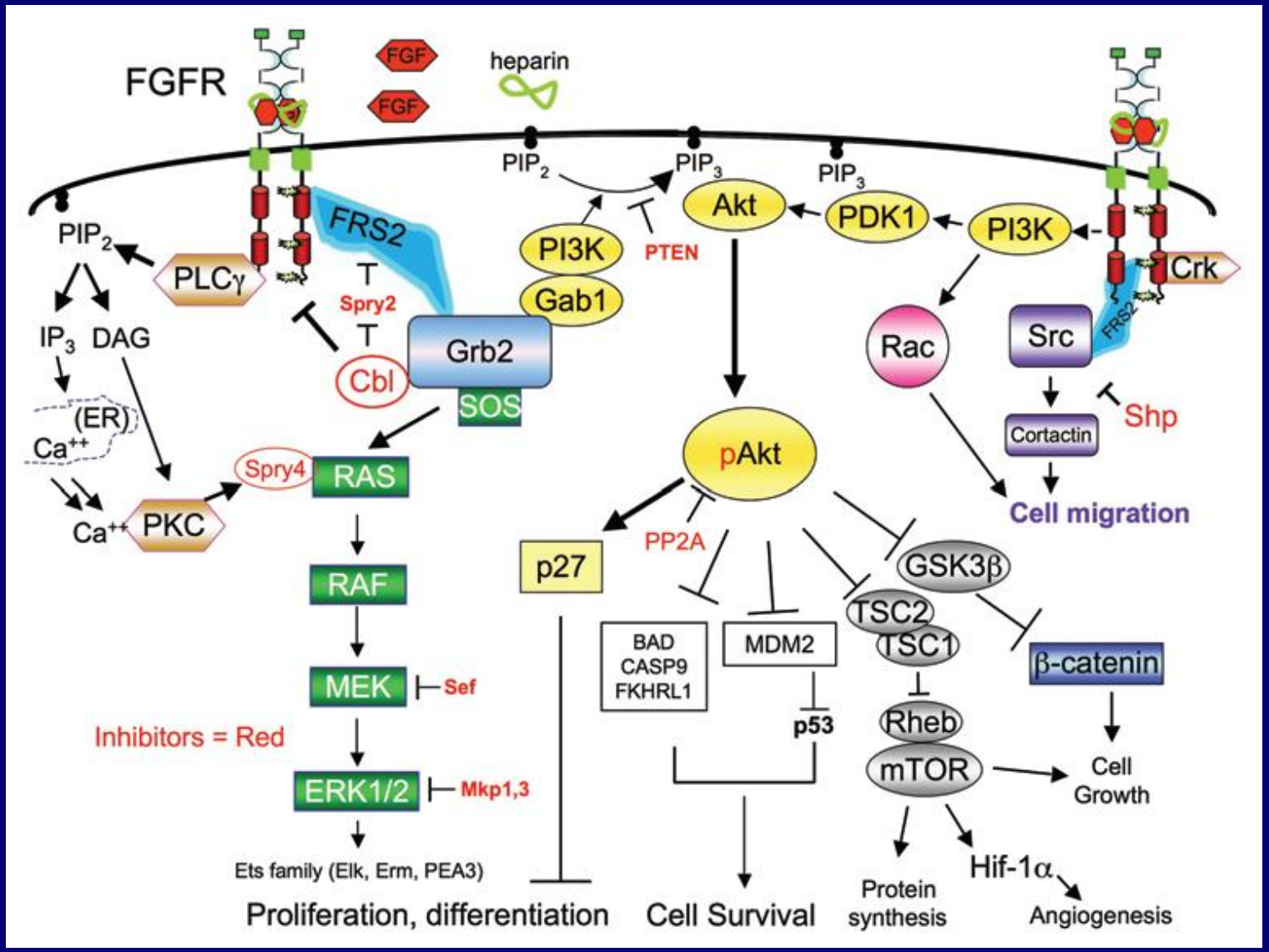
Bang YJ et al. Lancet 2010

Recommended HER2 testing algorithm*



*According to the European Medicines Agency license
SISH = silver in situ hybridisation

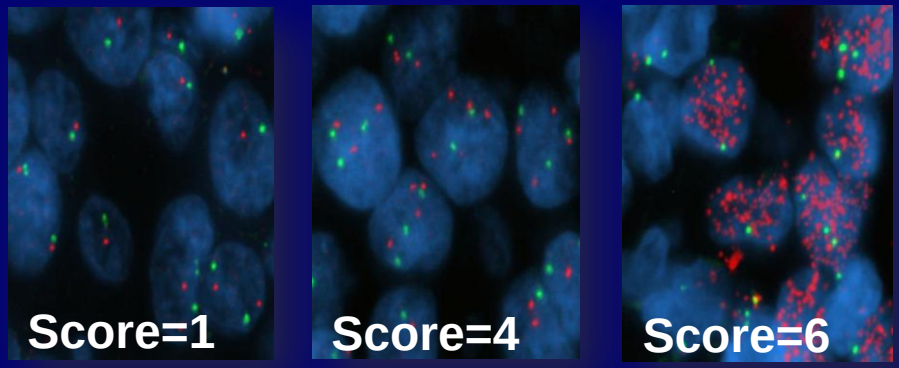
Intracellular signalling pathways downstream of FGFRs



Acevedo VD et al. Cell Cycle 2009

FGFR2 amplification in gastric cancer

FISH score		Korean GC (n=356)	Caucasian GC (n=408)
1	Disomy	53% (190)	35% (142)
2	Low Trisomy	18% (63)	16% (65)
3	High Trisomy	3% (12)	7% (28)
4	Low Polysomy	18% (66)	21% (87)
5	High Polysomy	3% (10)	14% (56)
6	Gene Amplification	4.2% (15)	7.4% (30)

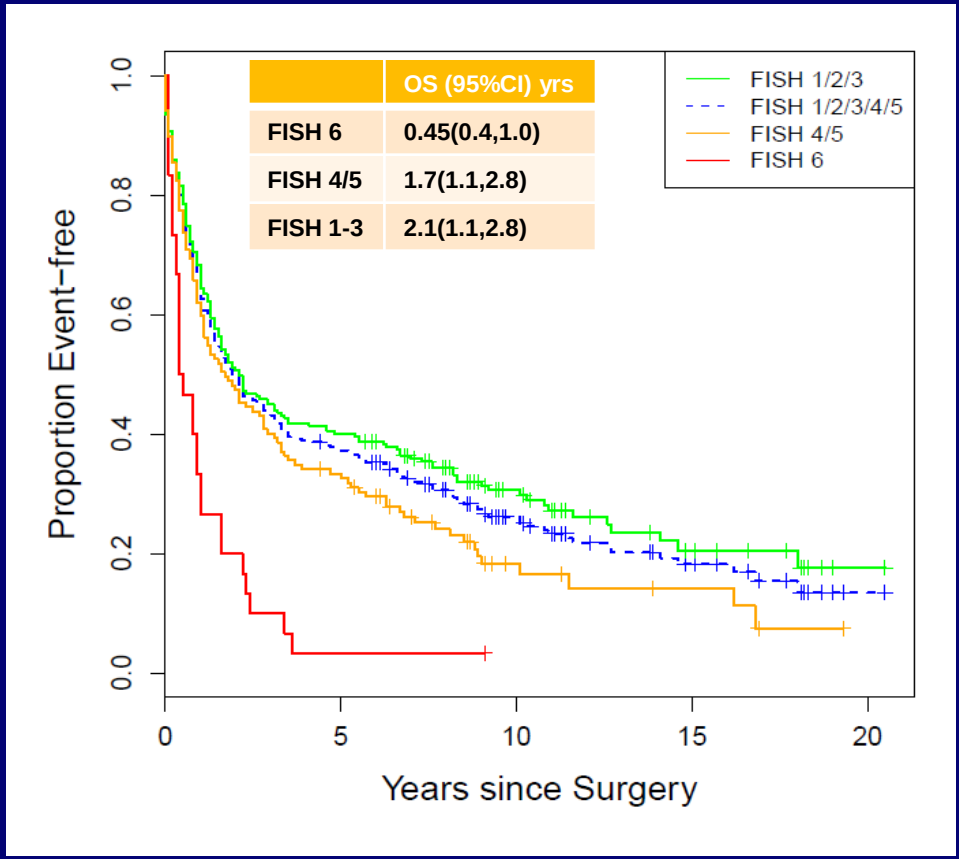


- Prevalence of FGFR2 amplification (FISH 6) was 4.2% in Korean cohort & 7.4% in Caucasian cohort

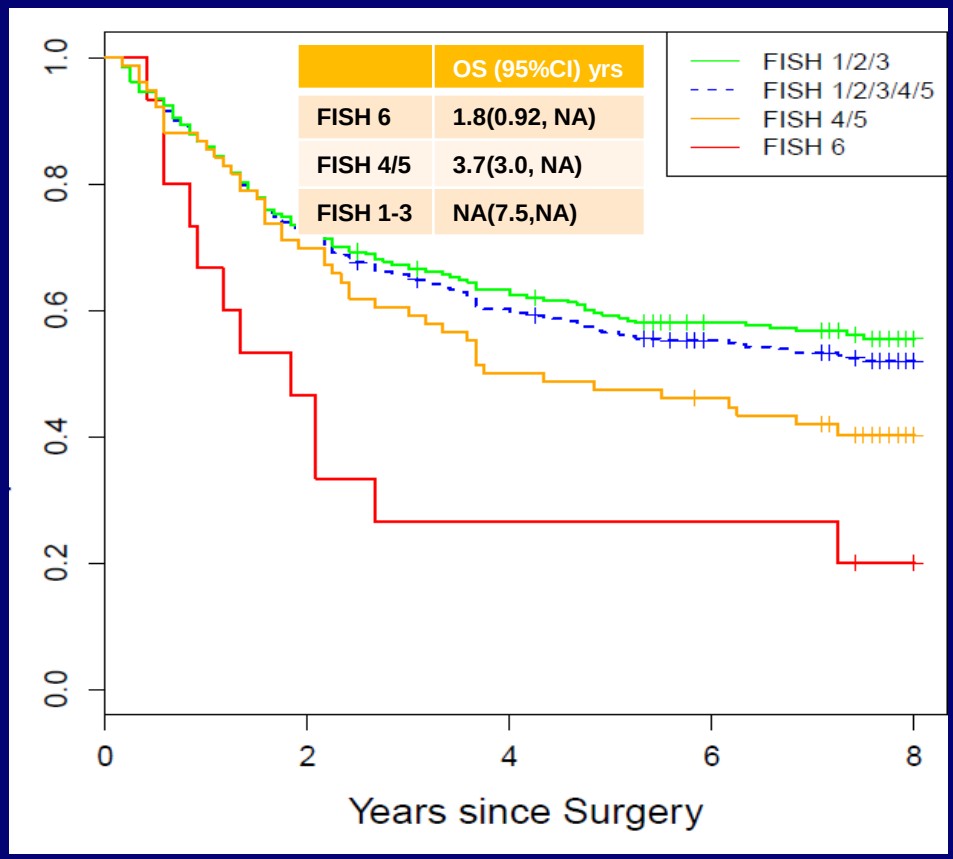
Kilgour E, Bang YJ, Kim WH et al. ASCO 2012

FGFR2 amplification is prognostic

Caucasian cohort



Korean cohort



Kilgour E, Bang YJ, Kim WH et al. ASCO 2012