

Targeted Therapy in Gastric Cancer

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Outline

GC= gastric, GEJ and (oesophageal) adenocarcinoma

- Introduction
- HER2
- EGFR
- VEGF
- Other molecules in GC
- Future approaches

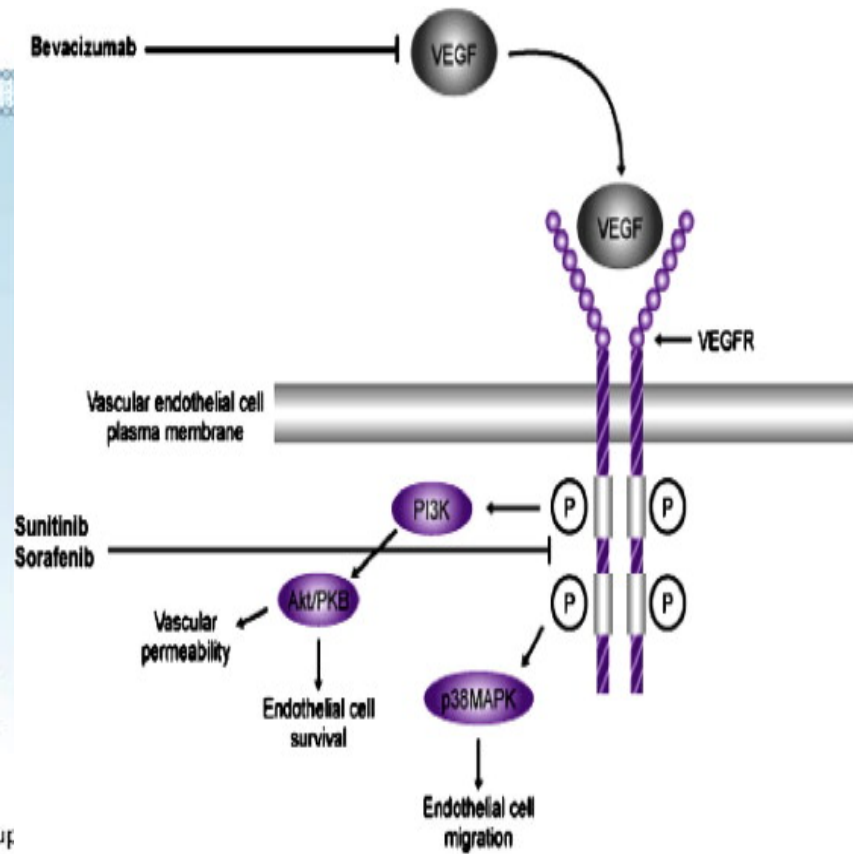
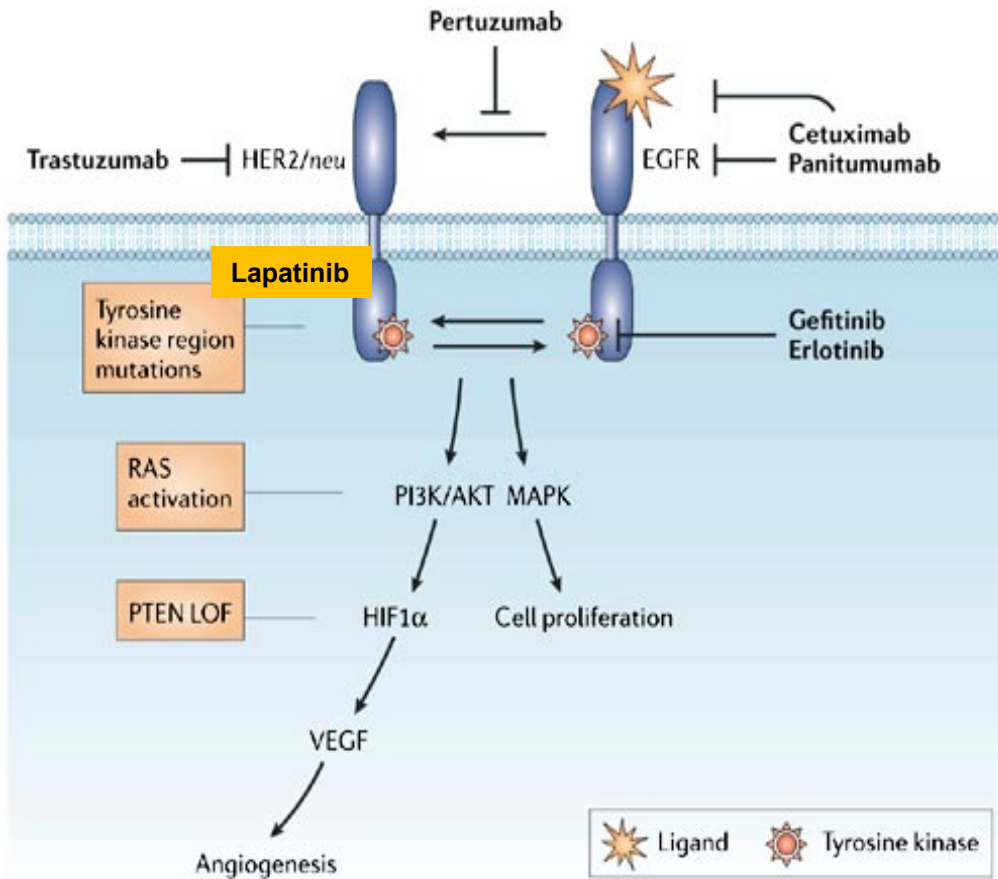
Gastric Cancer (GC)

- GC is the 4th most common cancer globally and 2nd leading cause of cancer mortality
- More than 50% present in advanced stages
- Highest incidence rates of gastric cancers in East Asia
- Growing incidence of GEJ
- Advanced/metastatic GC has a poor prognosis
 - Median OS about 10–11 months
- In the advanced setting, combination chemotherapy results in increased survival of up to 6mths compared to no treatment
- Fluoropyrimidine (5FU/S1/Capecitabine)/Cisplatin-based chemotherapy is mainstay of treatment +/- taxane or epirubicin

1st line combination chemotherapy in adv GC (phase III data)

Regimen	Response rate	Overall Survival
DCF (V325)	37%	9.2 mths
EOX (REAL2)	47.9%	11.2mths
S1-CDDP (SPIRITS)	54%	13 mths
Xeloda-CDDP	41%	10.5mths

Targets to target in GC



HER2/neu

- The HER2 protein (p185, HER2/neu, ErbB-2) is a 185-kDa transmembrane tyrosine kinase (TK) receptor and a member of the epidermal growth factor receptors (EGFRs) family.
- This family is composed of four members: HER1 (also known as the EGFR), HER2, HER3 (also termed ErbB-3), and HER4 (also termed ErbB-4).
- HER2 does not bind to any known ligand, but it is the preferred heterodimerization partner for other members of the HER family.
- In carcinomas, *HER2* acts as an oncogene,

Her-2/neu in GC

Studies	HER2 Overexpression by IHC	HER2 amplification
Japan: Yano et al. (n=200)	23%	27%
Korean: Park et al (n=182)	16%	-
Europe: Gravalos et al. (n=166)	13%	-
UK/Germany: Grabsch et al. (n=924)	<10%	
Lordick et al (n=1527)	22%	
Tan et al. (Singapore)(prelim)	12%	

cf breast ca 10-34%

HER-2 in GC : correlation with pathology and prognosis

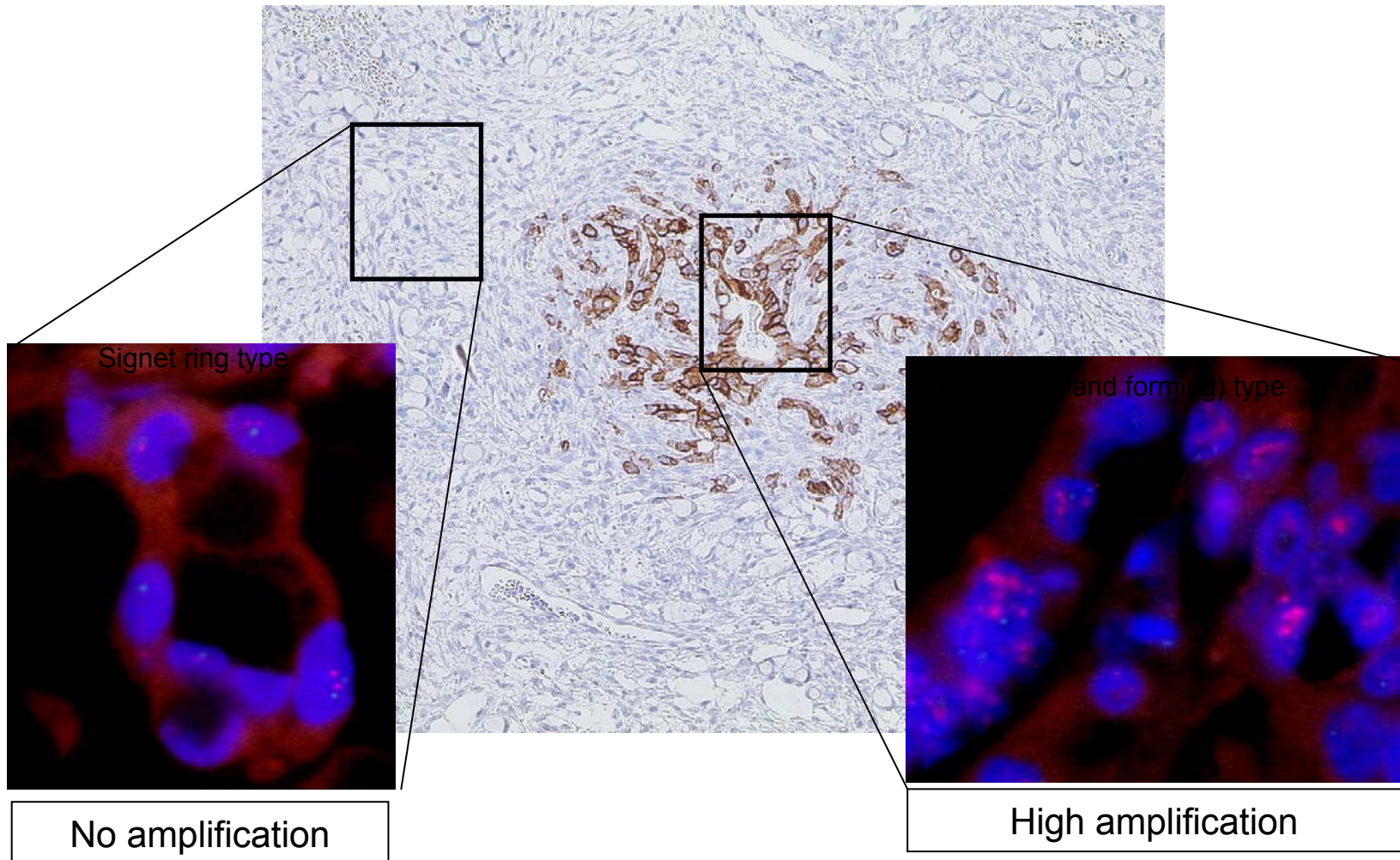
	Intestinal vs Diffuse	GEJ vs Gastric site
Gravalos et al (IHC)	16% vs 7%	25% vs 9.5%
Lordick et al (IHC)	34% vs 5% (vs 20% in mixed)	32% vs 18%
Tanner et al (HER2 amplification by CISH)	21.5% vs 2%	24% vs 12%

- HER2 over-expression and amplification has been associated with poorer survival
- HER2 gene amplification is inversely related to E-cadherin mutations which are typical for diffuse type GC
- A recent study (n=924) by Grabsch *et al* found that HER2 expression in GC is rare, heterogenous and of no prognostic value: <10% HER2+; of which 91% were intestinal type. And had no correlation with survival or stage of disease

Concordance between HER2 overexpression by IHC and gene amplification by FISH

- Controversial
- Earlier studies showed poor concordance
- Later studies:
 - Yano et al.: found a concordance rate between IHC and FISH in the HER2-protein overexpression cases of 87% (58.5% for 2+ and 88% for 3+).
 - ToGA trial, the concordance was 87% and differences were largely due to FISH-positive cases that were IHC 0/1
- In breast cancer , concordance rate up to 98%

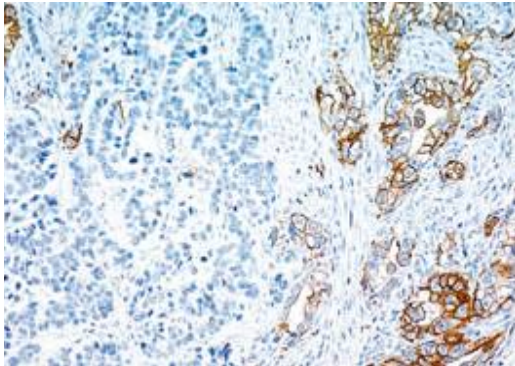
Tumour heterogeneity is more common in gastric cancer



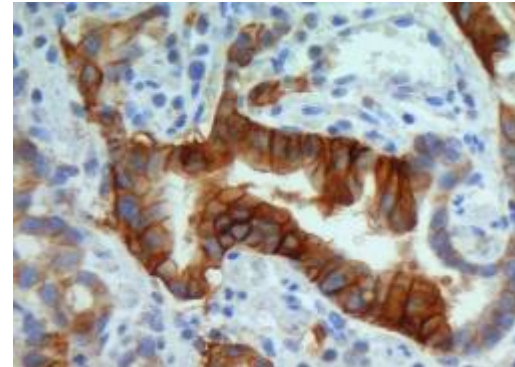
Differences in HER2 testing in breast and gastric cancers

- Histological differences between gastric and breast cancers necessitate modifications to the HER2 scoring system for gastric cancer
- Discrepancies bet IHC and FISH results mainly due to:

1. Tumour heterogeneity is more common in gastric cancer



2. Glandular tumour cells with incomplete (basolateral) membrane staining with IHC



Thus, modified HercepTest used in GC

Hofmann M, *et al. Histopathology* 2008; 52:797–805.

Breakdown of successful HER2 IHC and FISH screening

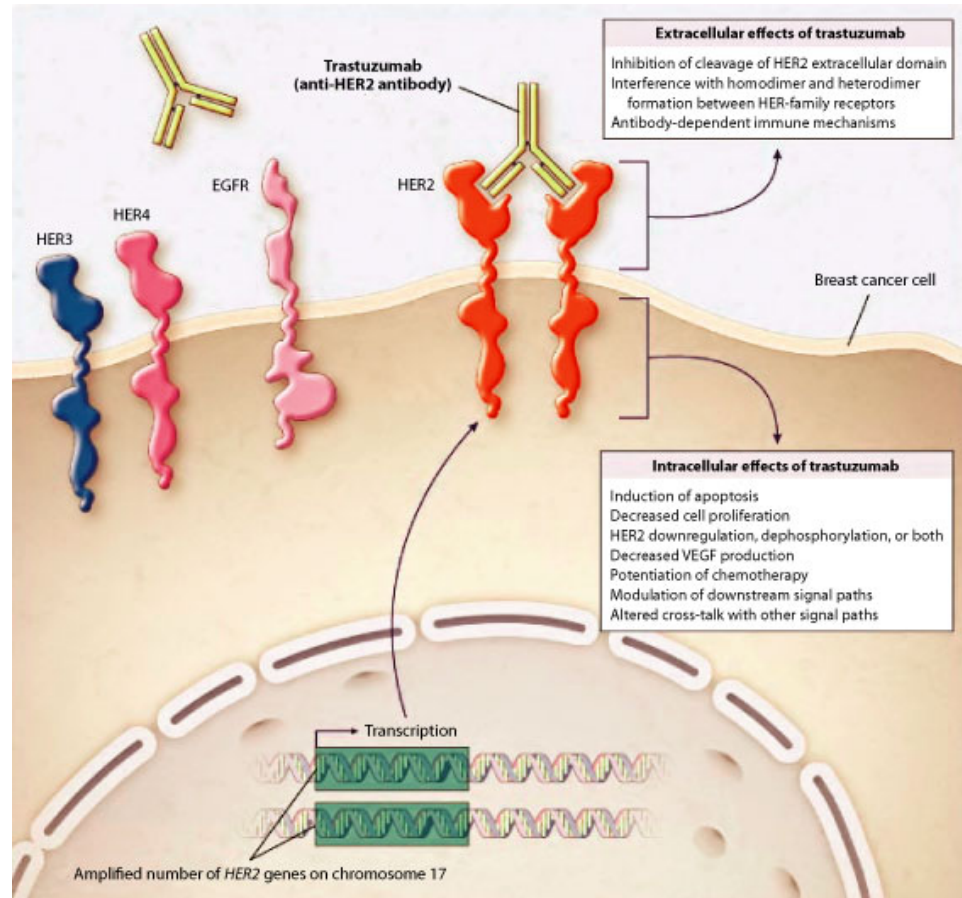
HER2 status of cases with both IHC and FISH results (n=3280)

	IHC 0 n (%)	IHC 1+ n (%)	IHC 2+ n (%)	IHC 3+ n (%)	Total n (%)
FISH+	94 (4.9)	96 (15.7)	212 (54.6)	354 (94.9)	756 (23)
FISH-	1815 (95.1)	514 (84.3)	176 (45.4)	19 (5.1)	2524 (77)
Total	1909 (100)	610 (100)	388 (100)	373 (100)	3280 (100)

Out of 2519 IHC 0/1+ cases, 7.5% scored FISH+
Out of 761 IHC 2+/3+ cases, 74.4% scored FISH+

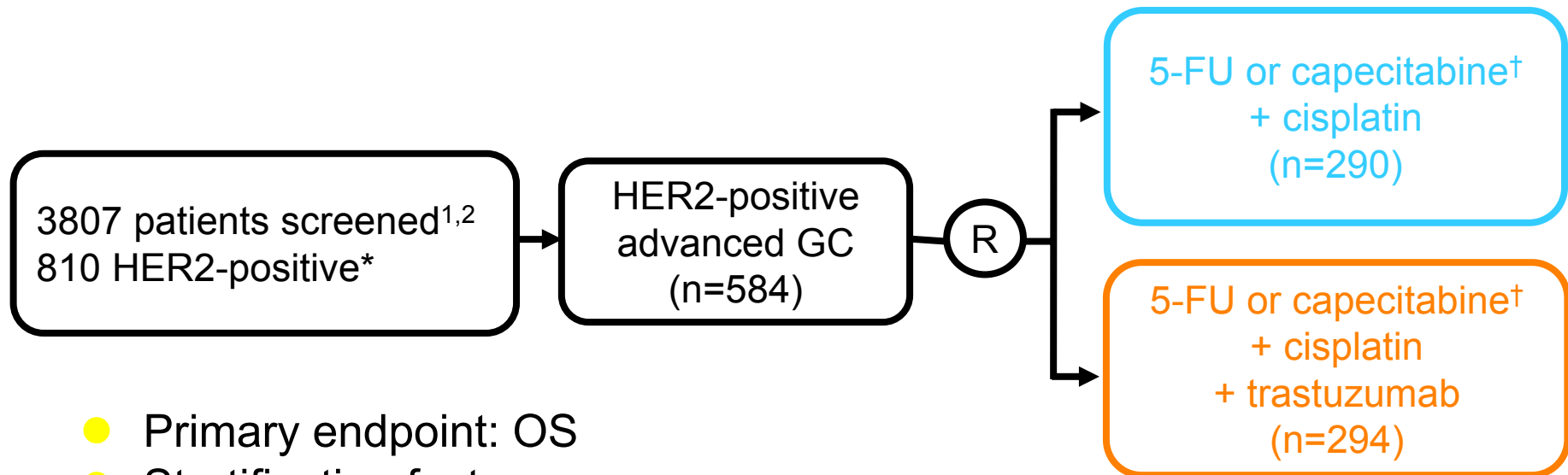
Trastuzumab in GC

- Trastuzumab is a human IgG moAb against HER2/neu receptor, which acts by binding the extracellular domain
- Effects on apoptosis, cell proliferation, angiogenesis and potentiation of chemotherapy
- Indication for trastuzumab in adv GC comes from positive results of the phase III ToGA trial



ToGA trial design

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

1. Bang *et al.* ASCO 2009; Abstract 4556.
2. Chung *et al.* ECCO-ESMO 2009; Abstract 6.511.

Main patient selection criteria

Inclusion criteria

- **Adenocarcinoma** of stomach or GEJ
- Inoperable locally advanced and/or metastatic disease
- Measurable disease (RECIST), or non-measurable evaluable disease
- HER2-positive tumour (centrally assessed)
 - **IHC 3+ and/or FISH+**
- Adequate organ function and ECOG performance status ≤ 2
- Written informed consent

Exclusion criteria

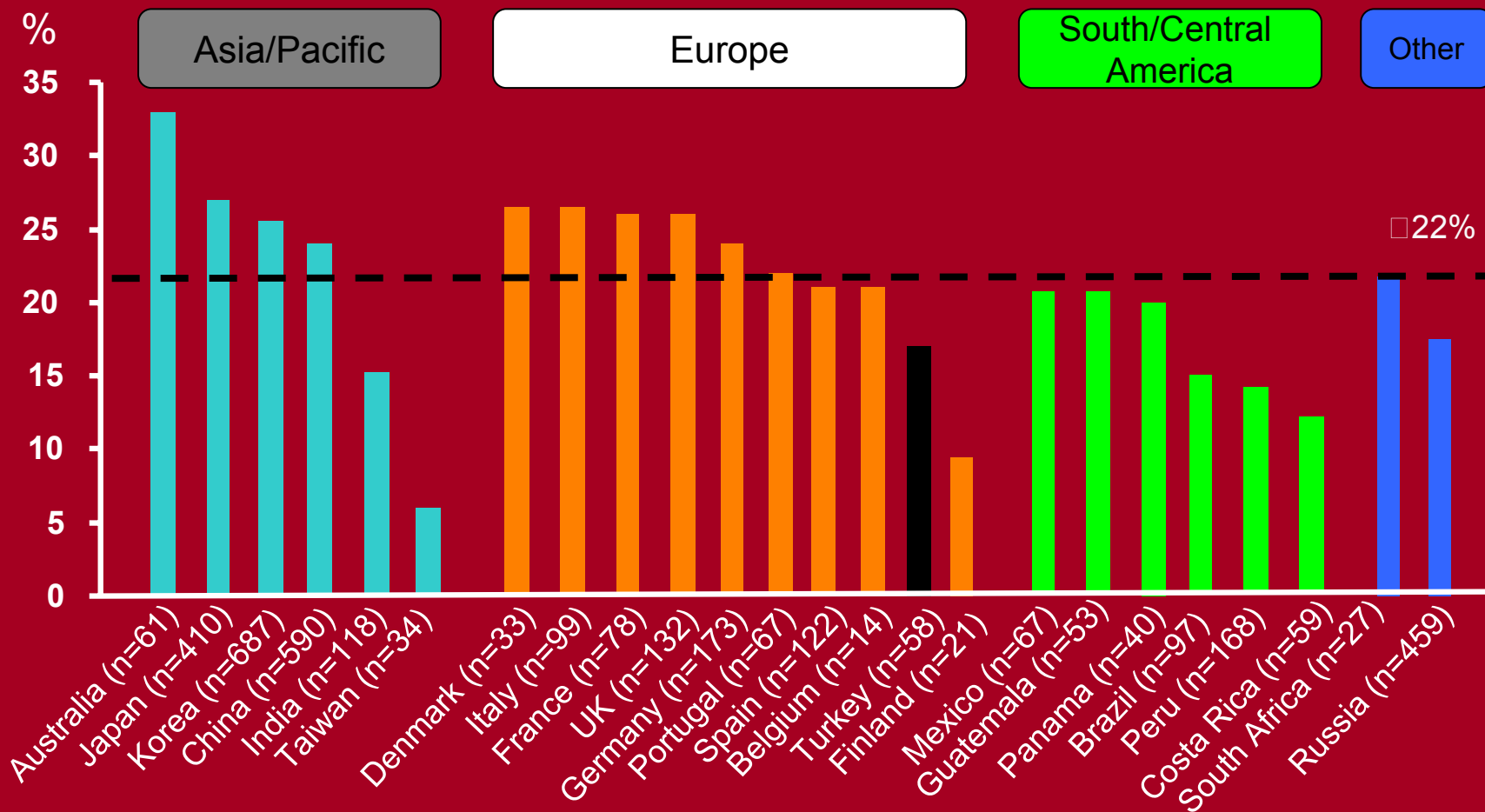
- Previous adjuvant chemotherapy within 6 months
- Chemotherapy for advanced disease
- Congestive heart failure or baseline LVEF $< 50\%$
- Creatinine clearance < 60 mL/min

Breakdown of all HER2-positive cases (n=810)

	IHC 0	IHC 1+	IHC 2+	IHC 3+	No IHC
FISH+	94	96	212	354	10
FISH-	—	—	—	19	—
No FISH result	—	—	—	25	—

- 810 cases (out of 3667 successfully tested for HER2) were HER2-positive according to the ToGA protocol (~22%)
- 610 cases had high HER2 protein expression (~16%)
- 594 patients fulfilled the protocol eligibility criteria and were randomised in ToGA

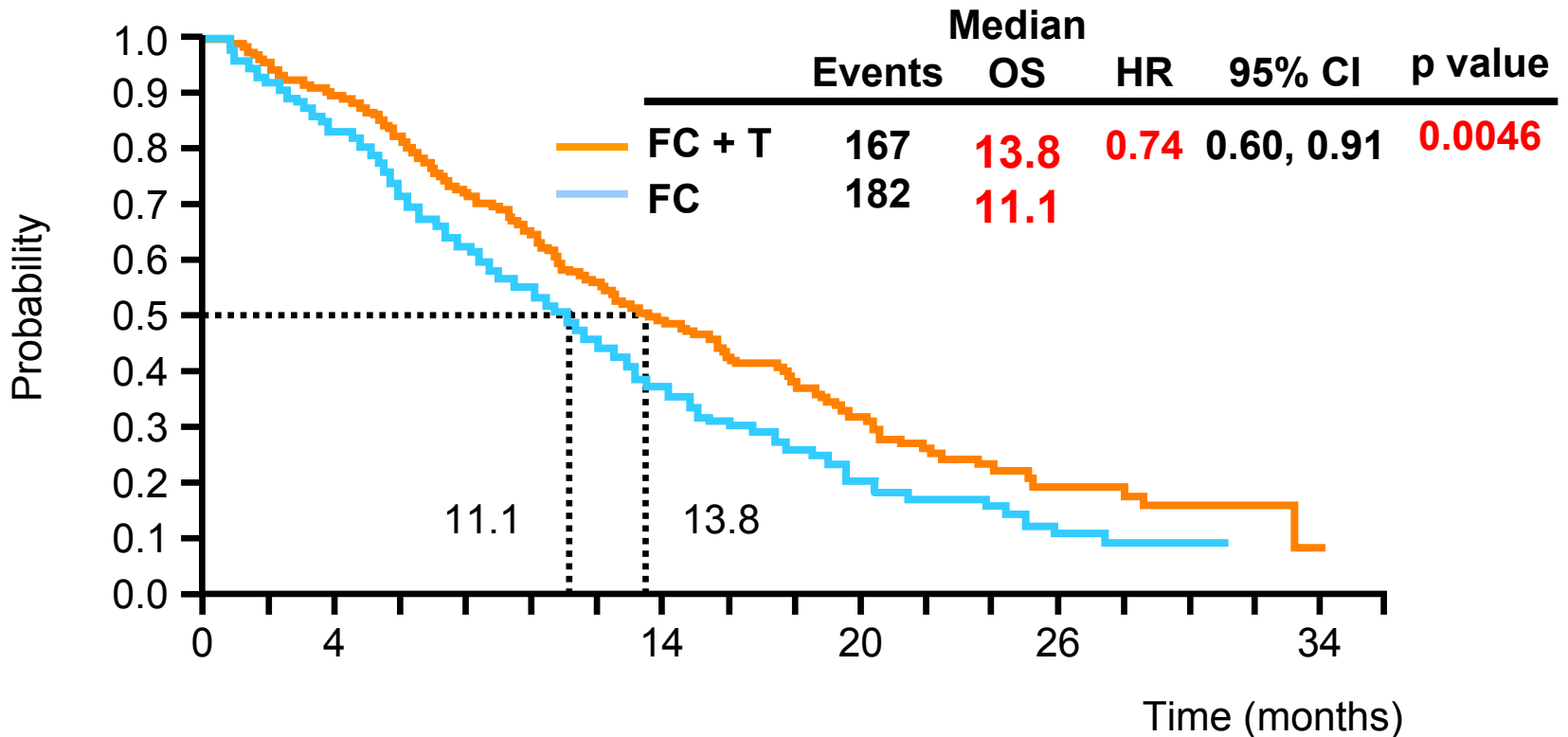
Patients with IHC 3+ or FISH+ disease



Patient demographics and baseline characteristics

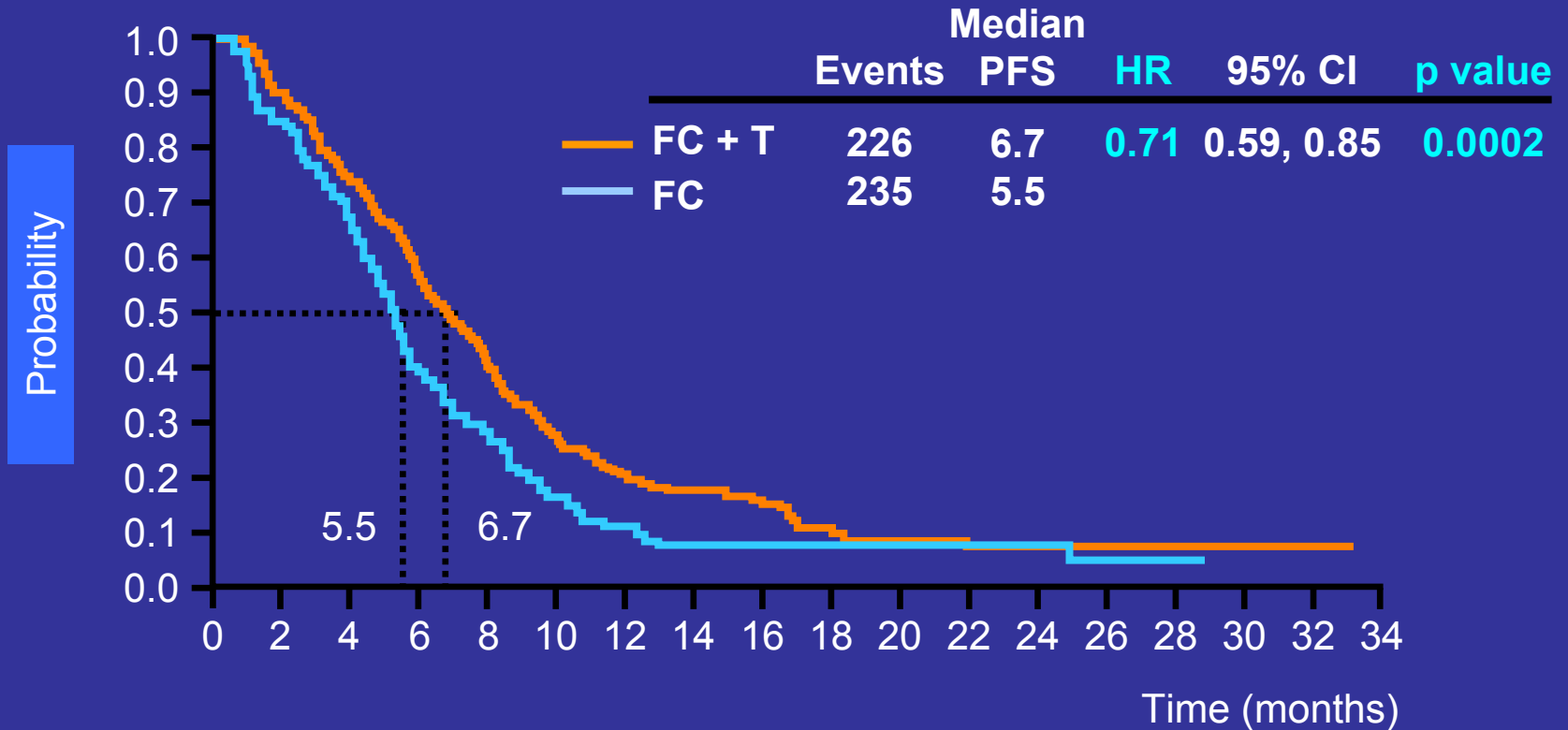
Characteristic	F+C n=290	F+C + trastuzumab n=294
Sex, %		
Male / Female	75 / 25	77 / 23
Age, median (range) years	59.0 (21–82)	61.0 (23–83)
Weight, median (range) kg	60.3 (28–105)	61.5 (35–110)
Region, n (%)		
Asia	166 (56)	158 (53)
C/S America	26 (9)	27 (9)
Europe	95 (32)	99 (33)
Other	9 (3)	14 (5)
Type of GC (central assessment)		
Intestinal	74.2 ^a	76.8 ^b
Diffuse	8.7 ^a	8.9 ^b
Mixed	17.1 ^a	14.3 ^b
Prior gastrectomy	21.4	24.1

Primary end point: OS



No. at risk	0	4	8	12	16	20	24	28	32
FC + T	294	209	113	56	21	12	6	1	0
FC	290	185	90	32	14	6	0	0	0

Secondary end point: PFS

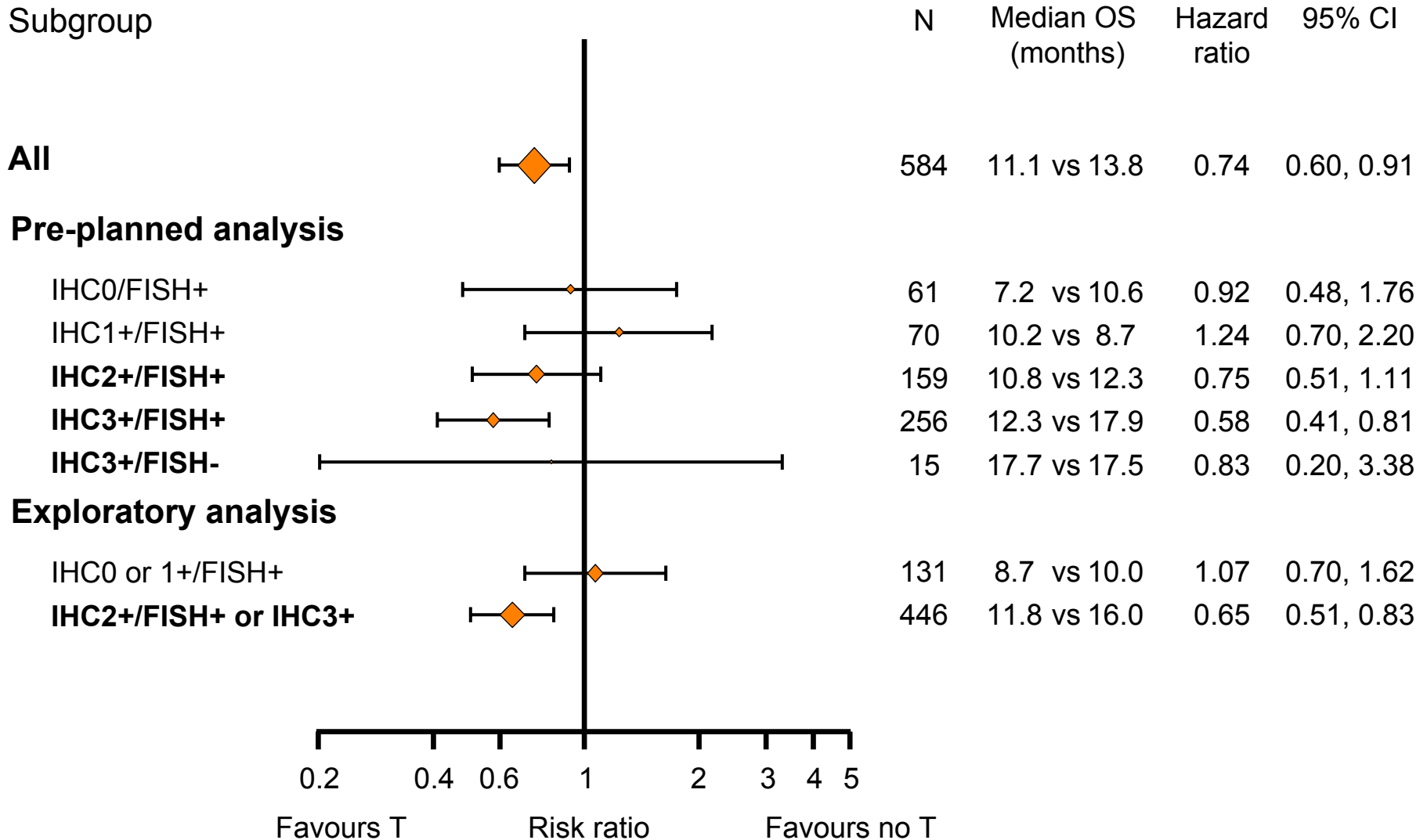


No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
FC + T	294	258	201	141	95	60	41	28	21	13	9	8	6	6	6	4	2	0
FC	290	238	182	99	62	33	17	7	5	3	3	2	2	1	1	0	0	0

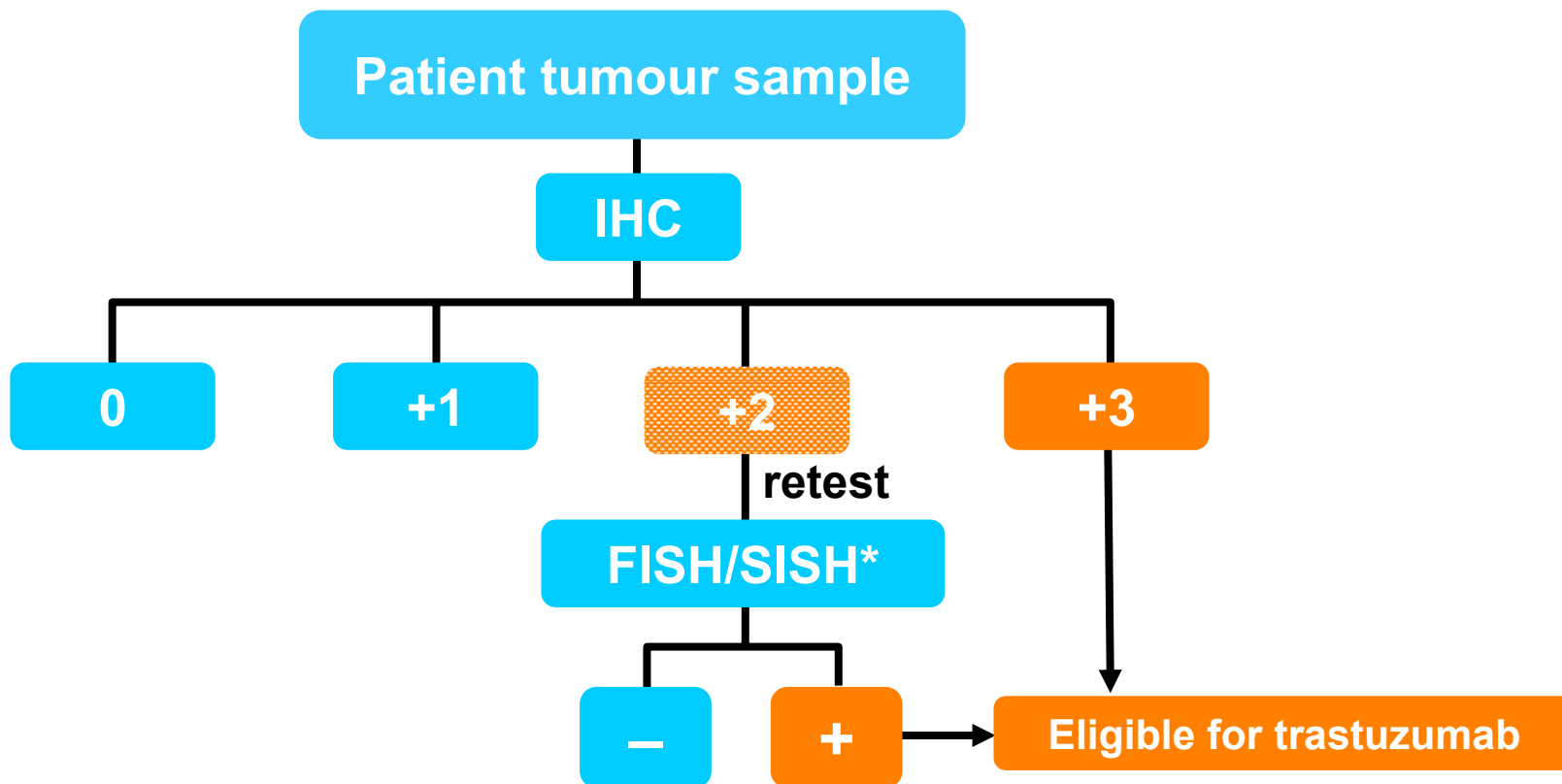
Efficacy end points

Endpoint	F+C n=290	F+C + trastuzumab n=294	HR (95% CI)	p-value
OS, median months	11.1	13.8	0.74 (0.60, 0.91)	0.0046
PFS, median months	5.5	6.7	0.71 (0.59, 0.85)	0.0002
TTP, median months	5.6	7.1	0.70 (0.58, 0.85)	0.0003
ORR, %	34.5	47.3	1.70* (1.22, 2.38)	0.0017
Patients with measurable disease	37.4	50.9	1.74* (1.23, 2.46)	0.0017
DoR, median months	4.8	6.9	0.54 (0.40, 0.73)	<0.000 1
Clinical benefit rate, %	69.3	78.9	1.66 (1.14, 2.41)	0.0081

Efficacy: OS by HER2 status



Suggested HER2 testing algorithm in GC/GEJ cancer



*cut off for FISH, SISH = HER2:CEP17 ratio ≥ 2

Safety: non-haematological AEs

AE, %	F+C n=290		F+C + trastuzumab n=294	
	All	Grade 3/4	All	Grade 3/4
Nausea	63	7	67	7
Vomiting	46	8	50	6
Fatigue	28	2	35	4
Diarrhoea	28	4	37	9
Constipation	32	2	26	<1
Asthenia	18	3	19	4
Stomatitis	15	2	24	<1
Weight decrease	14	2	23	2
Abdominal pain	14	1	16	1

Safety: haematological AEs

AE, %	F+C n=290		F+C + trastuzumab n=294	
	All	Grade 3/4	All	Grade 3/4
Neutropenia	57	30	53	27
Febrile neutropenia	3	3	5	5
Anaemia	21	10	28	12
Thrombocytopenia	11	3	16	5

No unexpected toxicities in the trastuzumab-containing arm including symptomatic heart failure

Safety: cardiac AEs

Cardiac event, n (%)	F+C n=290		F+C + trastuzumab n=294	
	All	Grade 3/4	All	Grade 3/4
Cardiac AEs, total	18 (6)	9 (3)	17 (6)	4 (1)
Cardiac failure	2 (<1)	2 (<1)	1 (<1)	1 (<1)
LVEF drops*				
<50%		2 (1.1)		14 (5.9)
<50% and by ≥10%		2 (1.1)		11 (4.6)
Cardiac AEs leading to death		2 (<1) Cardiac arrest; cardio-respiratory arrest		2 (<1) Acute MI; cardiac failure

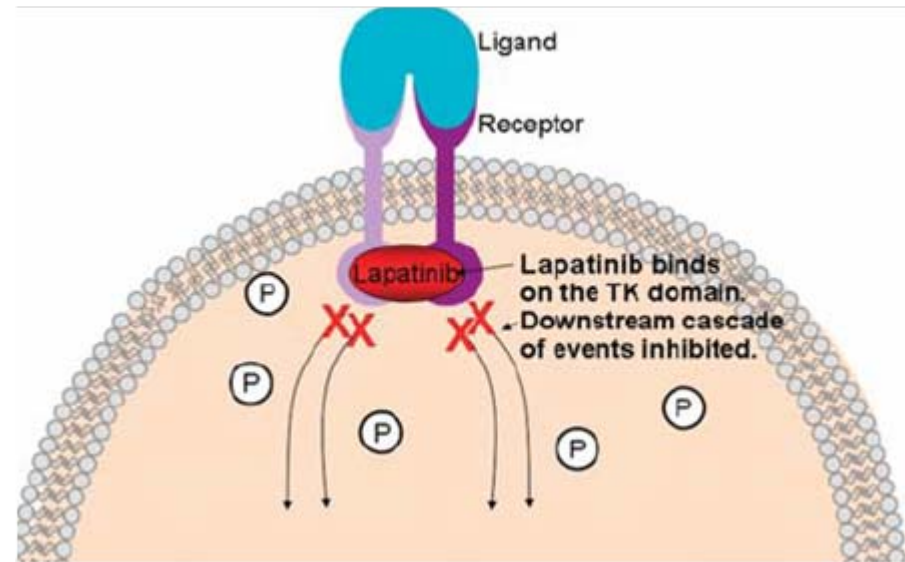
Except Asymptomatic decrease in LVEF

Summary of ToGA Trial

- Trastuzumab reduced the risk of death by 26% when combined with a reference chemotherapy (HR 0.74)
- Prolonged the median survival by nearly 3 months (11.1 to 13.8 months; $p=0.0046$) in patients with HER2-positive advanced gastric/GEJ cancer
 - Increased survival with trastuzumab (16.0 months vs 11.8 months; HR 0.65) in patients with high HER2 protein expressing tumours (IHC 2+/FISH+ or IHC 3+)
- All secondary efficacy parameters were also significantly improved
- Addition of trastuzumab to chemotherapy was well tolerated and has become a new option for GC patients with HER2 +

Lapatinib in GC

- Lapatinib is an oral TKI that has activity against EGFR and Her-2/neu



Lapatinib in Met GC

	Subjects	Response rates	Overall Survival
Iqbal 07 Phase II 1 st line	N=47; unselected gastric adenoca	7%	5 mths
Hecht 08 Phase II refractory	N=25 oeso and GEJ adenoca; EGFR+ and/or HER2+	0%; SD in 2 patients for 5 and 9 mths	
Galsky 09 refractory	N=16 GEJ adenoca; HER2 amplified	1 CR	-

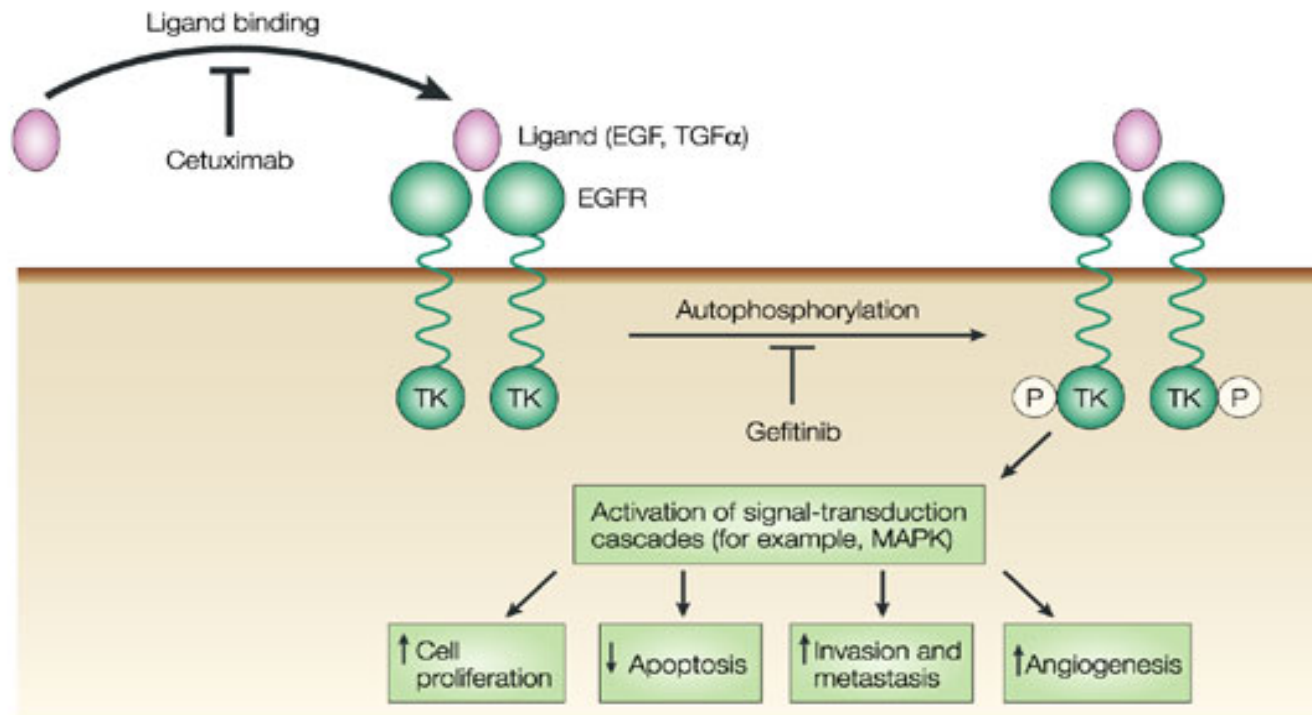
Phase III LOGiC trial evaluating capecitabine/oxaliplatin +/- lapatinib as 1st line therapy in HER2 overexpressing GC..

EGFR in Gastric Cancer

- EGFR overexpression
 - 86% of stomach and 60% of GEJ tumors by IHC; 60% of gastric adenocarcinomas by PCR
 - Associated with advanced stage and poorer prognosis
 - Is more common in SCC than in adenocarcinoma
- EGFR initiates signal transduction cascades which promote cell division, migration, angiogenesis and inhibits apoptosis
- EGFR mutations that have been detected in NSCLC are rarely present in GC
- Cetuximab, matuzumab, gefitinib and erlotinib have been combined with chemotherapy in GC- phase II trials
- EGFR expression does not correlate with treatment efficacy

EGFR inhibitors: mAbs and TKIs

Cetuximab most extensively studied in GC to date



Nature Reviews | Drug Discovery

Cetuximab in Locally Advanced GC

- At least 6 trials to date, mostly in abstract form
- Some in combination with RT
- pCR rates 13-40% for pre-operative trials
- In 1 published study, 49 patients treated with C + paclitaxel+ carboplatin + RT resulted in: CR70% and pCR 27% after surgery
 - Main toxicities were skin tox and oesophagitis
-

Cetuximab as 1st line in Metastatic GC

Regimen	Ph	n	Site/Histo	Better ORR	Overall survival
<i>Pinto et al:</i> C + Folfiri	II	38	11% GEJ; 89% gastric adenoca	44%	12mths
<i>Kanzler et al:</i> C+FUFIRI	II	49	31%GEJ; 69% gastric adenoca	42%	16.6mths
<i>Han et al.:</i> C+ Folfox6	II	38	100% Gastric adenoca	50%	9.9mths
Yeh et al C+CI5FU/LV/Cis	II	35	100% Gastric adenoca	69%	14.5mths
<i>Kim et al:</i> C + Xelox	II	44	Only 1 patient GEJ	52%	11.8mths
<i>Moehler et al</i> C + FU/FA/Irinotecan	II	49	31% GEJ 69% gastric	42% (+ SD 73%)	16.6mths
<i>Lordick et al:</i> C+ FUFOX	II	52	60% EGFR+ but no correlation with outcome	65%	9.5mths

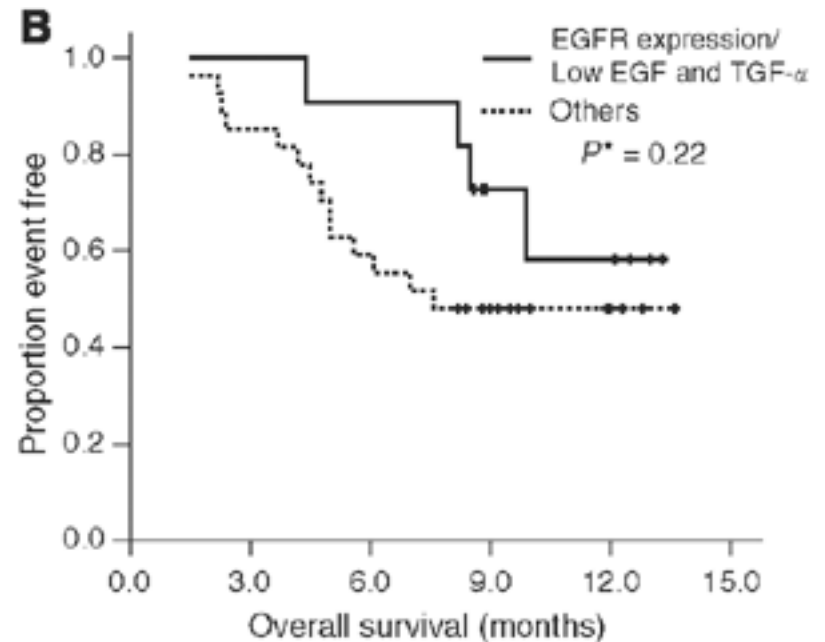
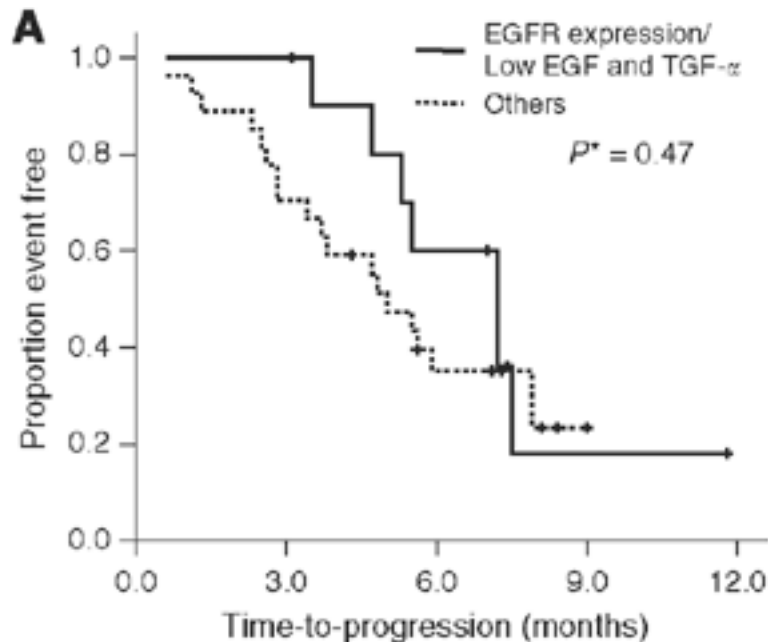
Cetuximab in Metastatic GC

- Numerous phase II trials using Cetuximab in combination with chemo in 1st line setting: ORR 40-69%; OS 9.5 to 17 mths
- Expected toxicities due to C
- Relationship between EGFR exp and response to C is unclear. At least 2 phase II studies show no correlation
- As 2nd line monotherapy, at least 4 trials. Results disappointing

Cetuximab + mFolfox6 in adv GC

Han et al BJC 2009

- N=38
- No patient had EGFR amplification or Kras mutations
- 11 patients with EGFR expression by IHC and low levels of major (competing) ligands serum EGF and TGF- α showed 100% RR (vs 37% in the rest)
- Elevation in ligand levels at disease progression imply that ligands may play an important role in cetuximab resistance



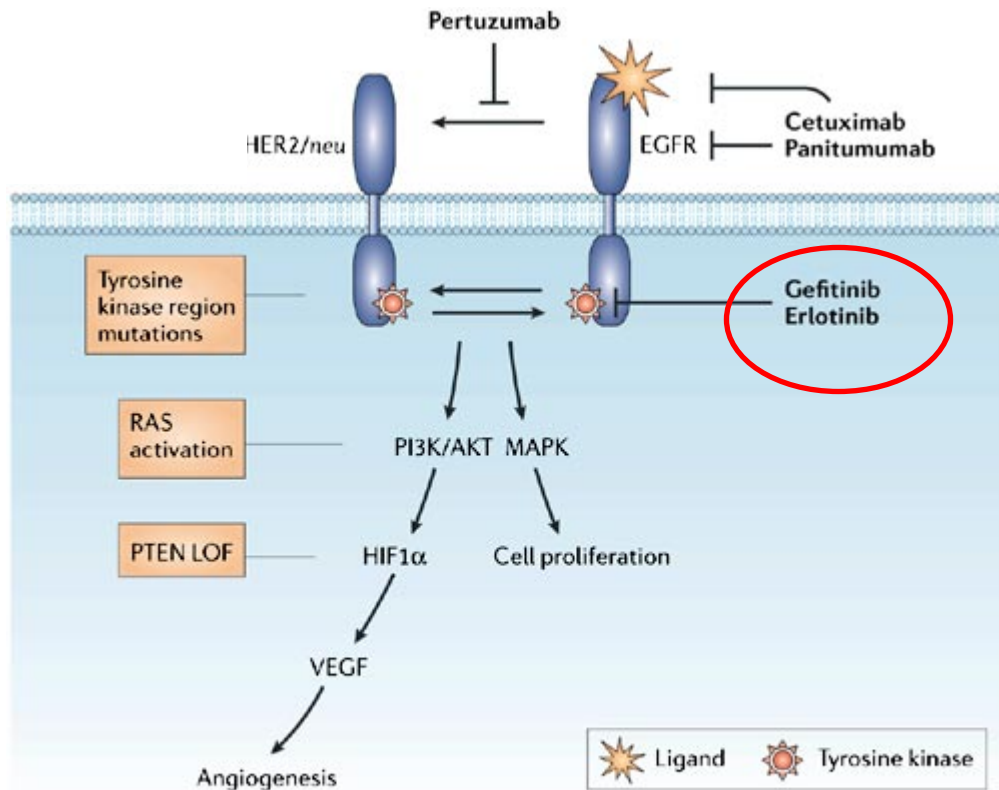
Cetuximab in GC

- The incidence of Kras mutation and its relationship to Cetuximab therapy response in GC is still not known
- As salvage therapy in heavily pretreated patients, C +irinotecan had tumor control rate of 62%
- EXPAND trial: Phase III comparing XP vs XP + Cetuximab- ongoing
 - Target n= 870, 1st line gastric and GEJ adenoca
- CALGB trial: randomized phase II ECF or CPT11/CDDP or folfox +/- C

Other EGFR MoAb

- Matuzumab and panitumab in phase I
- REAL-3 trial in adv GC
 - EOX +/- panitumab
- MATRIX in adv GC
 - ECX +/- matuzumab

EGFR TKIs in GC



- Oral small molecules which inhibit ATP binding within TK domain leading to complete inhibition of EGFR autophosphorylation and signal transduction

Gefitinib and Erlotinib in GC

	n	Histo/site	ORR	OS
Ferry et al Phase II Gefitinib 500mg/d	27; prior chemo	Oesophageal adenoca	11% PR; 26% SD	4.5mths
Janmaat et al Phase II Gefitinib 500mg/d	36; prior chemo	72% oesophageal adenoca	3% PR; 28% SD	5.5mths
Dragovich et al Phase II Erlotinib 150mg/d	70; 1 st line	All adenoca; 37% gastric; 63% GEJ	1 CR; 7% PR; 12% SD all in GEJ only	GEJ 6.7mths; Gastric 3.5mths

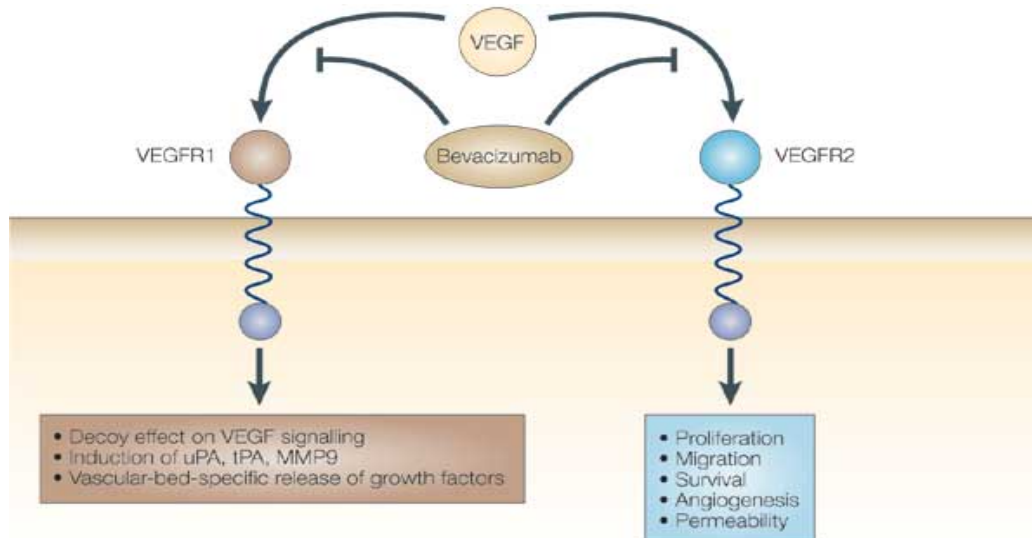
VEGF in GC

- VEGF is upregulated in Barretts oesophagus, the precursor of oesophageal adenocarcinoma
- Elevated serum and tumor VEGF are associated with poor prognosis in patients with resectable gastric cancer
- Two main strategies for inhibiting the VEGF pathway: humanised mAb against VEGF (e.g Bevacizumab) and small molecule TKIs directed to receptors of VEGF, Flt-1 and Flk-1/KDR (e.g Sunitinib)

Maeda 1996; Yamamoto 1998; Kanai 1998;
McCarty 2004

Bevacizumab in GC

- In preclinical studies, bevacizumab showed enhanced inhibitory effects on GC cells when combined with chemotherapy
- Synergy with docetaxel shown *in vitro*



Phase II trials using Bevacizumab in GC

				Response rates	Clinical Outcome	G3/4 Toxicities
El Rayes et al. Ann Oncol 2010	Bev + Docetaxel/ Oxaliplatin	N=38; 1 st line	45% Gastric 55% GEJ adenoca	CR 5%;PR37%; SD 37% (DCR79%)	PFS 6.6mths OS 11.1mths	Perforation in 3 patients
Shah et al. JCO 2006	Bev + Cis/CPT11	N=47; 1 st line	51% Gastric 49% GEJ adenoca	CR4%; PR42%; SD26% (DCR72%)	TTP 8.3mths OS 12.3mths	Perforation in 2 patients; MI in 1;
Kelsen et al. JCO 2009	Bev + modified docetaxel/ Cis/5FU	N=44; 1 st line		67%	TTP 12mths; OS 16.2mths	Perforation in 1 patient; Thrombosis 31%
Enzinger et al. ASCO 06 (study ongoing)	Bev+ docetaxel/ Cis/CPT11	N=20; 2nd line	5 Gastric; 4 GEJ; 10 oesophageal ; 1 oeso SCC	Of 17 pts, PR24%; SD38%	-	Bleed 12%; Arterial thrombosis 8%

Ongoing trials

AVAGAST trial

- A phase III RCT of bevacizumab in combination with capecitabine and cisplatin vs placebo + capecitabine and cisplatin as 1st line therapy in advanced GC
- N=760
- Negative study
- Results will be presented at ASCO 2010

MAGIC-B trial

- Perioperative ECX+/- Bev

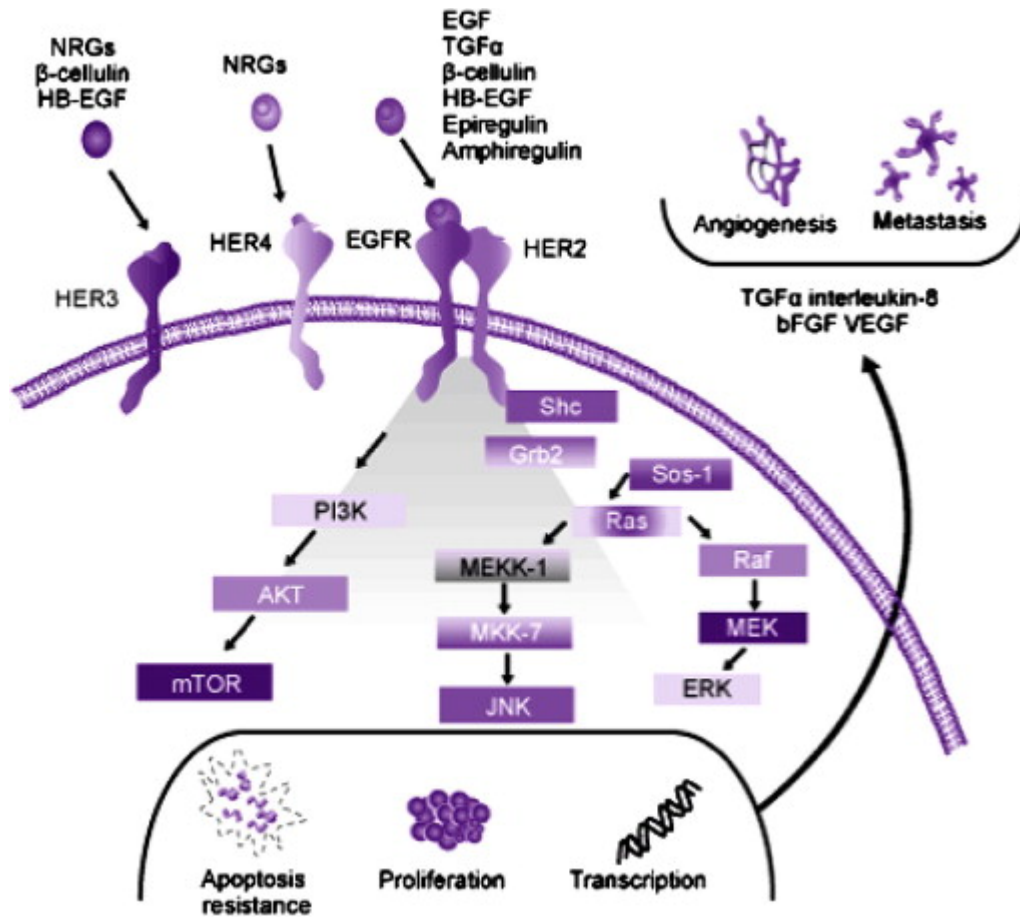
Anti-VEGF TKIs in GC

- Sunitinib
 - In a phase II trial, 42 patients with prior chemo, sunitinib resulted in 5% PR; 36% SD Median OS 12.5mths
- Sorafenib
 - 2 phase II trials: encouraging results so far

<i>Sun et al.</i> Soraf + Docetaxel/Cis	N=44	ORR 38.6% (1 CR)	TTP 5.8mths; OS 14.9 mths
<i>Kim et al</i> Soraf + Capecitabine/Cis	N=21	ORR 62.5%	PFS 10mths

Other novel agents in GC

Agent	Pathway	Patients	Response rates	Survival	Author
Everolimus	mTOR	N=53 refractory	SD 55%	PFS 2.7mths; Estimated OS 72% at 9mths	Yamada et al
Celecoxib + Cis/CPT11 and RT	COX-2	N=36 locally advanced (30 Adeno, 6 SCC)	11 pCR	NK	Enzinger et al.
Other studies : c-met inhibitors ; HSP-90 inhibitors; matrix metalloproteinase inhibitors (halted)					

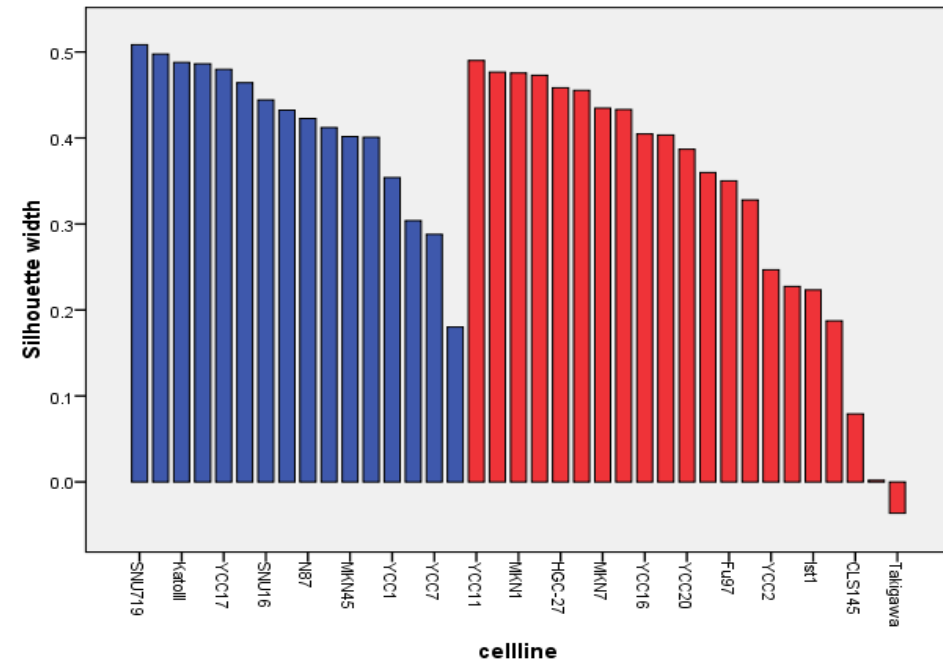
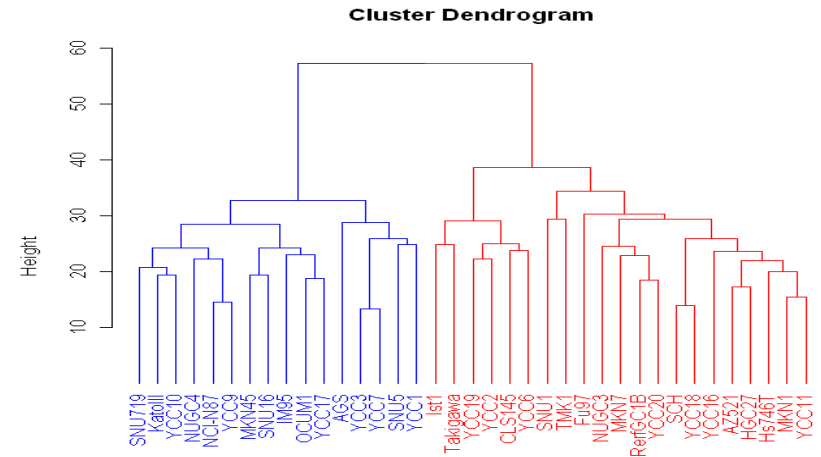
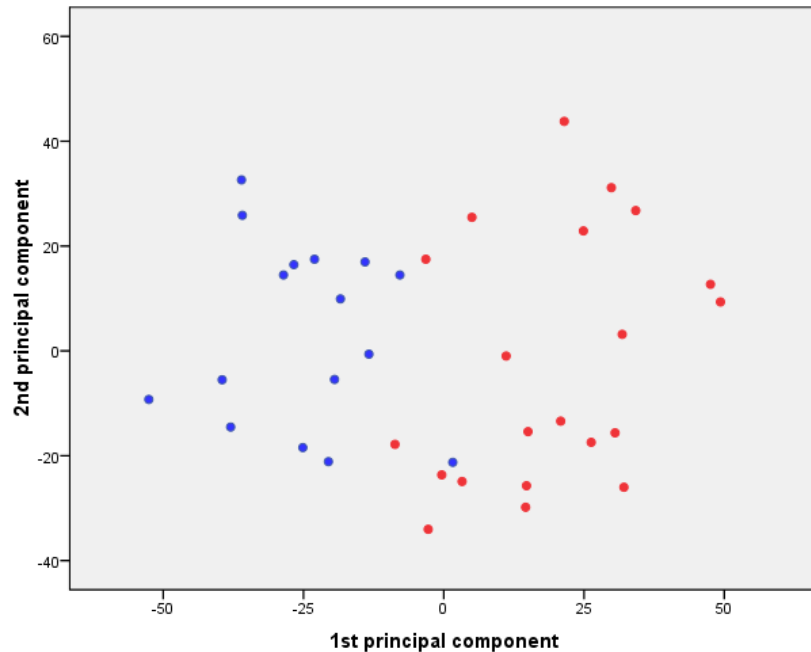


Challenges using targeted therapy in adv GC

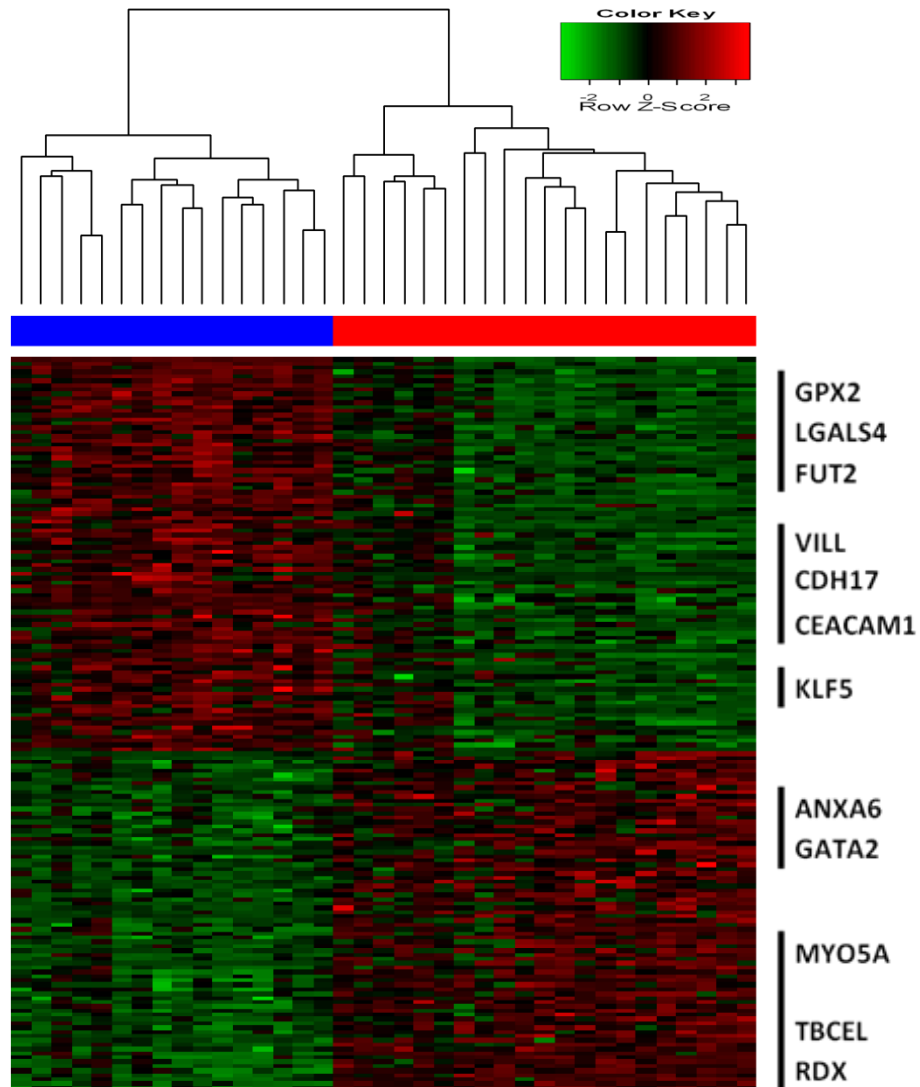
- No doubt there is activity with targeted therapy in GCs especially with positive results from the ToGa study
- Role of continuing therapy beyond progression (cf breast cancer)
- Identifying potential biomarkers that can help select the right patients for the right targeted therapy
 - Using histology and tumor site to determine patient eligibility in clinical trials may be too simplistic
 - Can we identify the right pathway that is aberrant in the individual patient?

2 major subclasses of Gastric cancer cell lines – G1&G2

Courtesy of Dr Iain Tan/Patrick Tan
National Cancer Centre Singapore

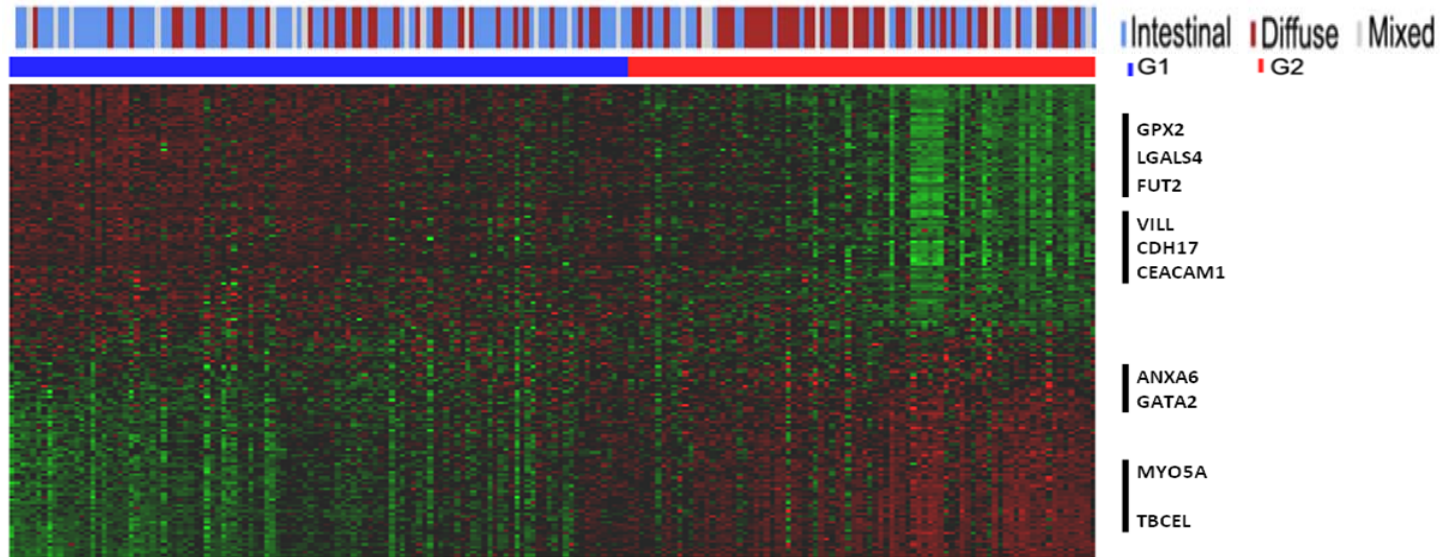


G1 / G2 are distinguished by 171 genes

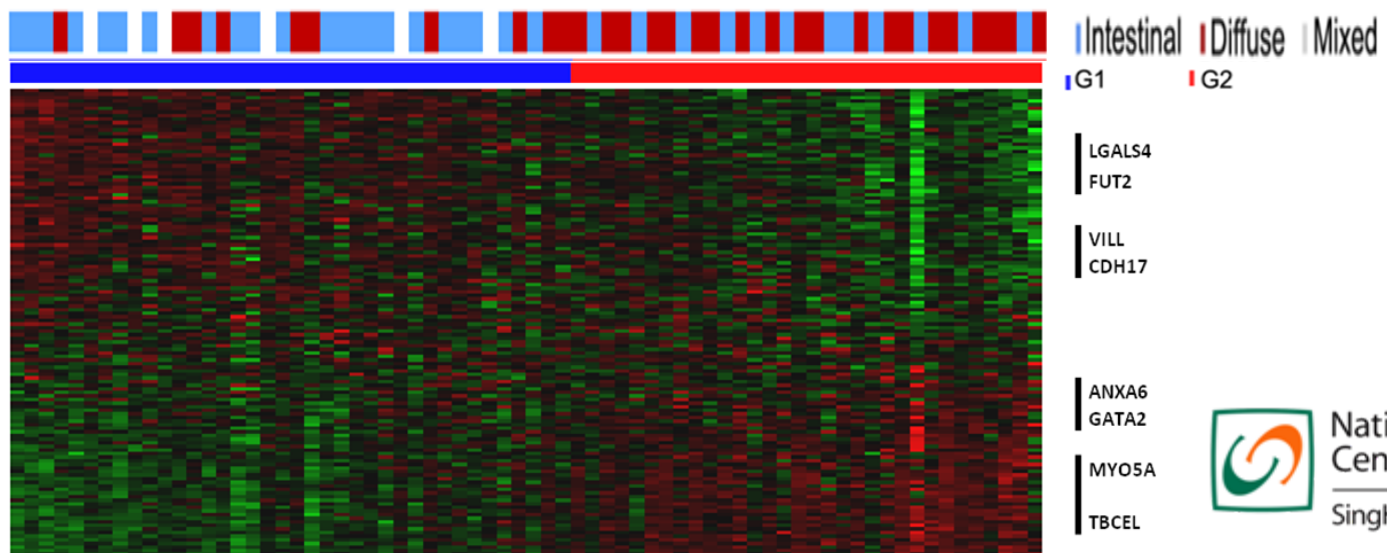


G1/G2 are related to Intestinal and Diffuse respectively: $p < 0.01$, concordance: 65%

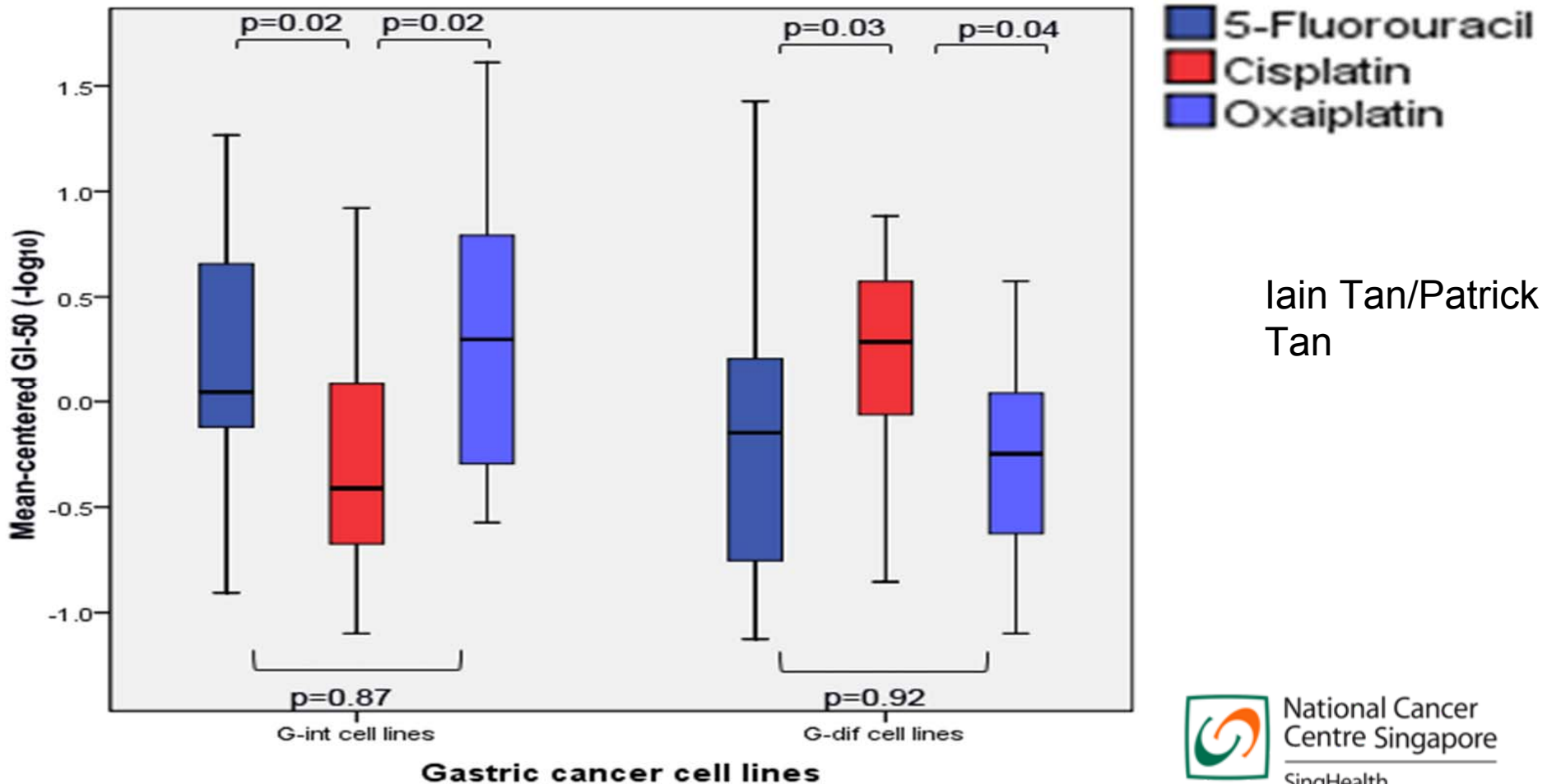
SG
($n=200$)



AU
($n=70$)



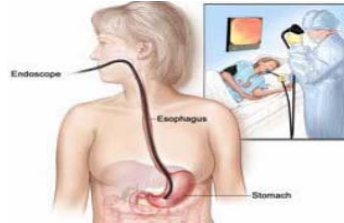
G1/G2 cell lines display differential response to 5FU, oxaliplatin and cisplatin



Iain Tan/Patrick Tan

3G trial

Treatment naïve
Advanced Gastric
Cancer (primary in
situ)



OGD guided Bx



Expression
profile



Ascertain G1/G2

~ 5-7 working days

G1 : S1/ oxaliplatin

G2 : S1/ cisplatin

In conclusion

- Trastuzumab is the first targeted agent to improve survival when added to conventional chemotherapy in HER2+ gastric cancer
- There are many ongoing large scale clinical trials using various targeted agents
- Perhaps there is a need for a change in trial design and approach to better optimise efficacy of targeted agents
- Role of targeted therapy in early stage GC still to be determined

Thank You