

2014 WCG Barcelona

Is gastric cancer different in Asian and Western patients?

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Disclosure

Research funding/advisory board:

Amgen

Merck KGaA

Pfizer

Roche

Phase III Trial in Gastric Cancer

Drugs	Target	study	combination	cases	EP	results
Trastuzumab	HER2	ToGA	XP/FP	584	OS	+
Bevacizumab	VEGF	AVAGAST	XP	760	OS	-
Ramucirumab	VEGFR	REGARD	BSC	355	OS	+
Cetuximab	EGFR	EXPAND	XP	870	PFS	-
Lapatinib	HER2 EGFR	LOGIC	XELOX	454	PFS	-
Panitumumab	EGFR	REAL-3	EOX	730	OS	-
Lapatinib	HER2 EGFR	TYTAN	P	261	OS	-
Everolimus (RAD-001)		GRANITE-1	BSC	633	OS	-
Apatinib	VEGFR		BSC	277	OS	+

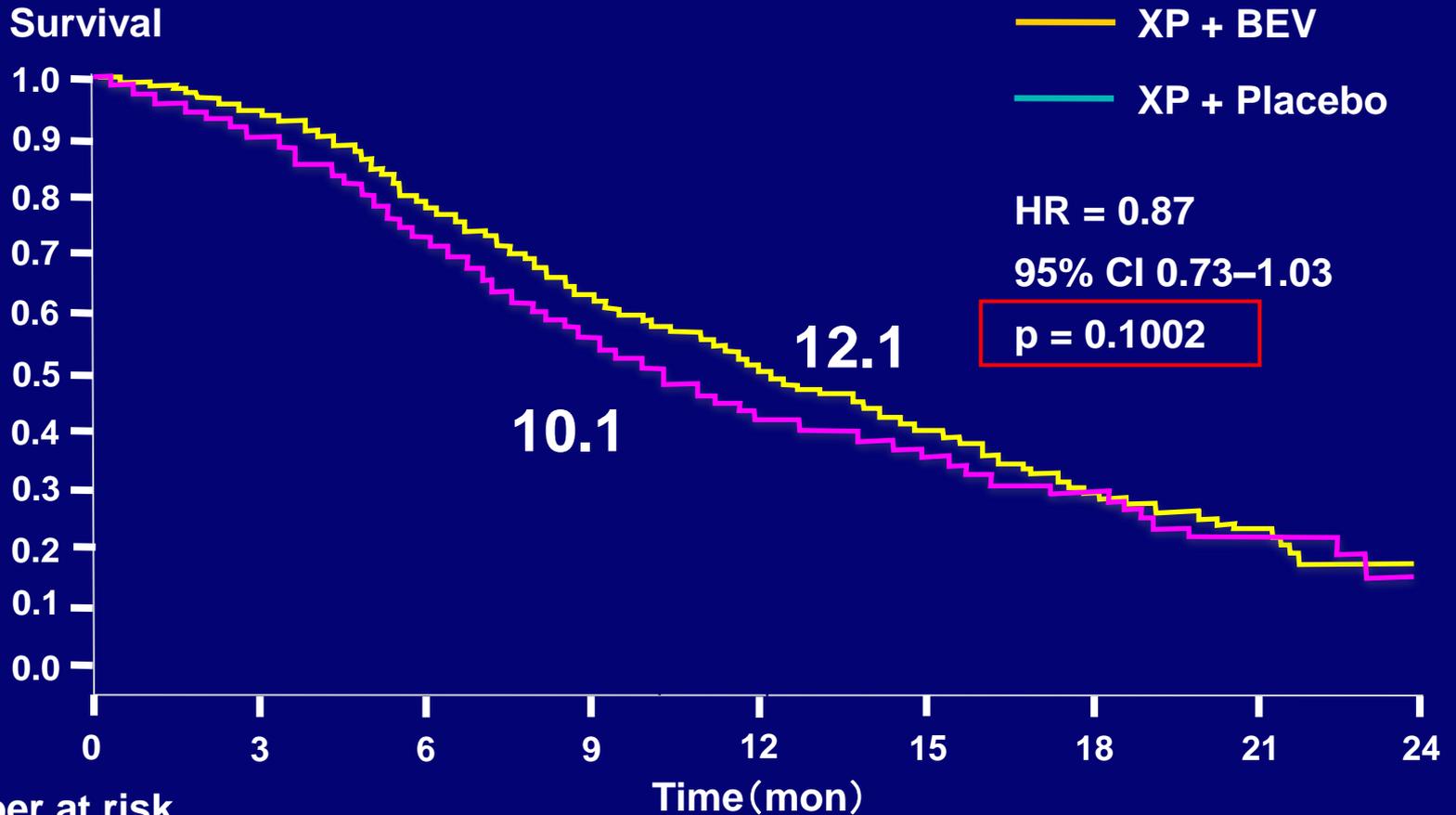
AVAGAST Trial



- **Endpoints**

- **Primary endpoint: OS**
- **Secondary endpoints: PFS, TTP, ORR, safety**

Overall Survival

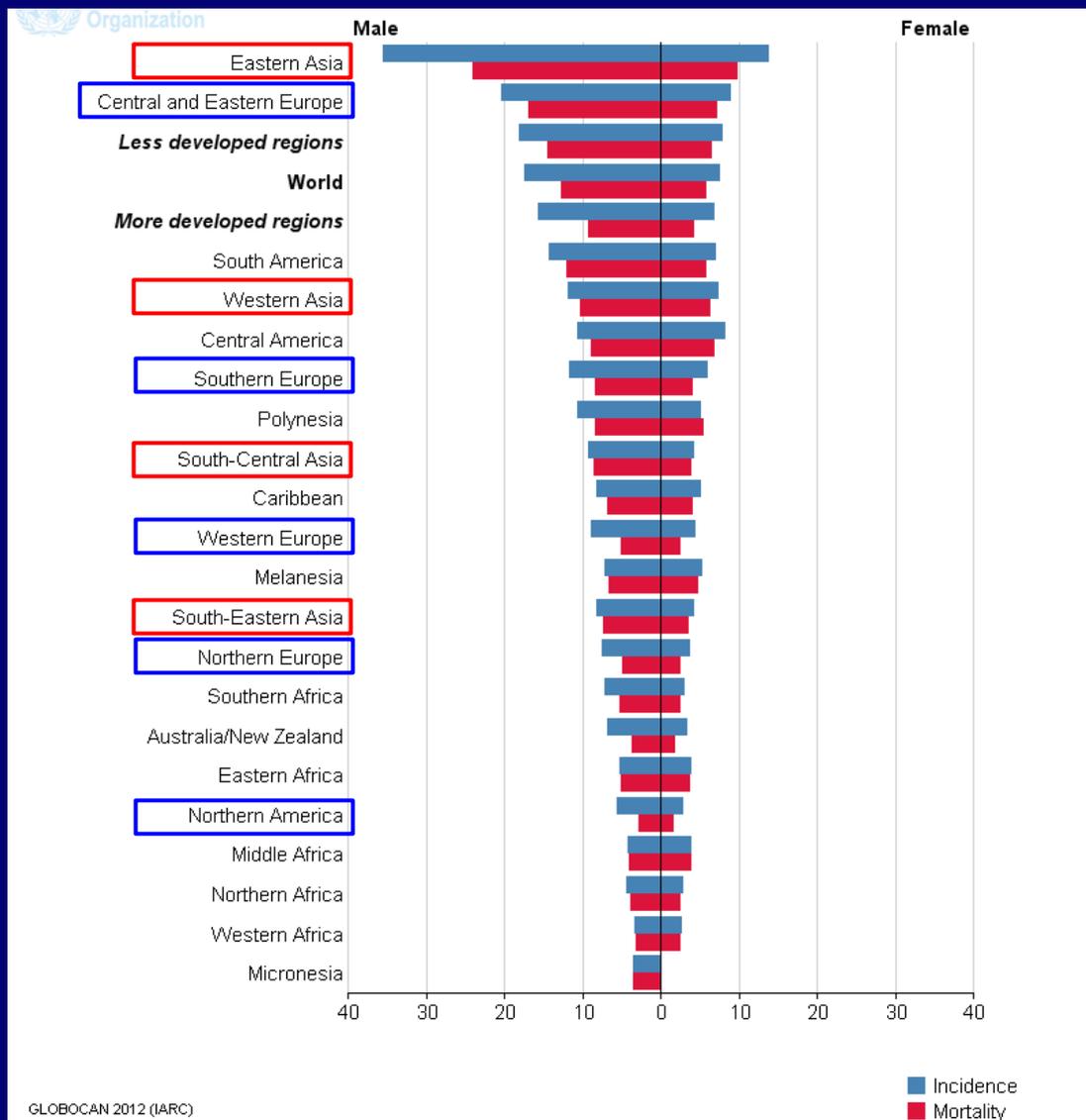


	0	3	6	9	12	15	18	21	24
XP + Placebo	387	343	271	204	146	98	54	15	0
XP + Bev	387	355	291	232	178	104	50	19	0

AVAGAST: Regional Differences in Efficacy

	Region	XP + Placebo Median, mo	XP + Bev Median, mo	Delta, mo	Hazard Ratio	95% CI
OS	Asia	12.1	13.9	1.8	0.97	0.75–1.25
	Europe	8.6	11.1	2.5	0.85	0.63–1.14
	Pan-America	6.8	11.5	4.7	0.63	0.43–0.94
PFS	Asia	5.6	6.7	1.1	0.92	0.74–1.14
	Europe	4.4	6.9	2.5	0.71	0.54–0.93
	Pan-America	4.4	5.9	1.5	0.65	0.46–0.93

GC incidence/mortality vary in the world



The incidence of GC is various:

- between Asia and Western
- Among Asia
- Among Western

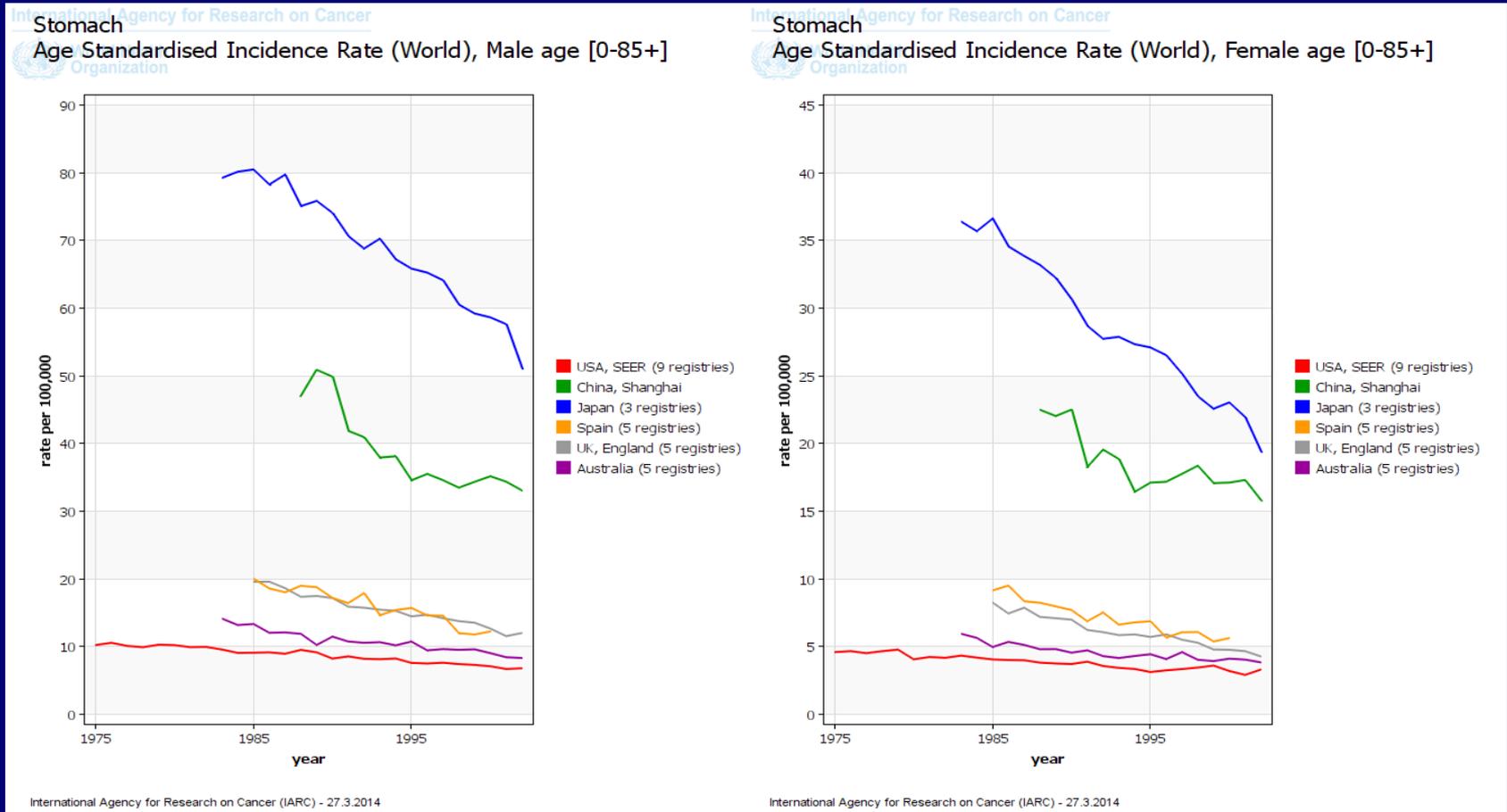
Top 10 tumor type in the world

Estimated number of cancers, all ages in 2008

Tumor Ranking	China	Japan	EU	USA	LATIN AMERICA AND CARIBBEAN
1	Lung	Colorectum	Breast	Prostate	Prostate
2	Stomach	Stomach	Colorectum	Breast	Breast
3	Liver	Lung	Prostate	Lung	Colorectum
4	Colorectum	Prostate	Lung	Colorectum	Lung
5	Esophagus	Breast	Bladder	Bladder	Cervix
6	Breast	Liver	Stomach	Melanoma of skin	Stomach
7	Uterus	Pancreas	Kidney	Kidney	Liver
8	Kidney	Bladder	Pancreas	NHL	NHL
9	Leukaemia	Gallbladder	Melanoma of skin	Leukaemia	Leukaemia
10	other	other	other	other	other

Burden of GC vary in Asia and Western

Trend of GC incidence in Asia and Western



- The incidence of GC is declining world wide

Primary site of GC in Asia and RoW

	Europe	Latin America	Indian subcontinent	North Africa	Asia-Pacific
Site(%)	N=1757	N=1301	N=553	N=439	N=2075
Proximal	12.0	16.6	6.5	18.5	40.0
Antrum	25.7	26.8	15.0	11.8	13.8
Body	20.7	21.3	29.7	12.8	19.3
Entire stomach	41.6	35.4	48.8	56.9	27.9

- Proximal GC is more common in Asia

Europe: Macedonia, Poland, Portugal, Russia, Serbia, Spain, Switzerland, Turkey

Latin America: Chile, Colombia, Mexico, Venezuela

Indian subcontinent: Bangladesh, India, Pakistan

North Africa: Egypt, Tunisia

Asia-Pacific: Korea, Malaysia, Philippines, Taiwan, Thailand

Bang YJ, Asia Pac J Clin Oncol. 2014 Mar;10(1):38-52.

Nashimoto A, Gastric Cancer. 2013 Jan;16(1):1-27.

Wu CX, et al. J Surg Concetp Pract 2008; 13 (1):24-33.

Stages of primary GC in Asia and RoW

	Europe	Latin America	Indian subcontinent	North Africa	Asia-Pacific	Japan	China (Shanghai)
TNM Stage(%)	N=1757	N=1301	N=553	N=439	N=2075	N=12644	N=7342
0-I	12.0	16.6	6.5	18.5	40.0	59.0	15
II	25.7	26.8	15.0	11.8	13.8	11.3	23
III	20.7	21.3	29.7	12.8	19.3	14.7	24
IV	41.6	35.4	48.8	56.9	27.9	15.0	38

- Stages of primary GC is different in Asia and Western
- GC patients in China and Western are often diagnosed in late stage

Europe: Macedonia, Poland, Portugal, Russia, Serbia, Spain, Switzerland, Turkey

Latin America: Chile, Colombia, Mexico, Venezuela

Indian subcontinent: Bangladesh, India, Pakistan

North Africa: Egypt, Tunisia

Asia-Pacific: Korea, Malaysia, Philippines, Taiwan, Thailand

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5-year-OS of GC in Asia and Western

6 th AJCC Stage	MSKCC (USA)	DGCC (Germany)	NCCH (Japan)	SNUH (Korea)	Beijing Cancer hospital	Sun Yat-sen University Cancer Center	Zhongshan Hospital
Sample Size	752	331	6,730	6,314	1,518	1,503	1594
Ia	95%	81%	91.5%	92.6%	96.0%	(96.0%)	93.8%
Ib	85%	61%	84.6%	84.0%	81.0%	(80.0%)	72.7%
II	54%	42%	69.3%	67.4%	60.0%	(68.0%)	(42.0%)
IIIa	37%	28%	50.4%	50.0%	39.0%	(44.0%)	(27.0%)
IIIb	11%	13%	30.6%	30.6%	27.0%	(28.0%)	12.7%
IV	2%	8%	5.4%	13.1%	17.0%	(18.0%)	

The prognosis of GC patients in Asia seems better than western

Some chemotherapy has consistent efficacy around the world

	ML17032 ¹		ToGA ²		EXPAND ³		AVAGAST ⁴		AVATAR ⁵
	Asia	Asia	EU	Asia	White	Asia	EU	Pan-Am	Asia
Regimen	XP	89% XP		XP		95% XP			XP
N	139	164	91	NR	NR	188	124	75	102
OS, m	10.5	13.3	8.9	11.4	9.7	12.1	8.6	6.8	11.4
PFS/TTP, m	5.6	5.7	5.3	5.5	5.7	5.6	4.4	4.4	6.0
ORR, %	46	39.6	28.6	NR	NR	45.5	28.2	36.4	33.7

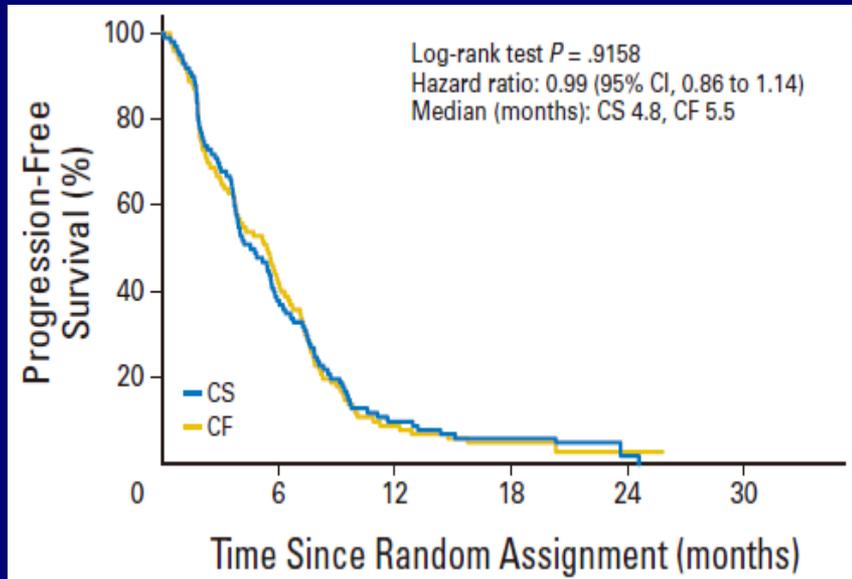
- The Efficacy of 1st line XP regimens in mGC is consistent around the world
- Difference in OS is high likely to be impact by 2nd+ treatment

NR: not reported

1. Kang YK, et al. Ann Oncol 2009;20:666–73
 2. Bang YJ, et al. Lancet 2010;376:687–97/ ToGA CSR
 3. Tom W, Lancet Oncol. Jun 2013; 14(6): 481–489.
 4. Ohtsu A, J Clin Oncol. 2011 Oct 20;29(30):3968-76.
 5. Shen L, Gastric Cancer. 2014 Feb 21. [Epub ahead of print]

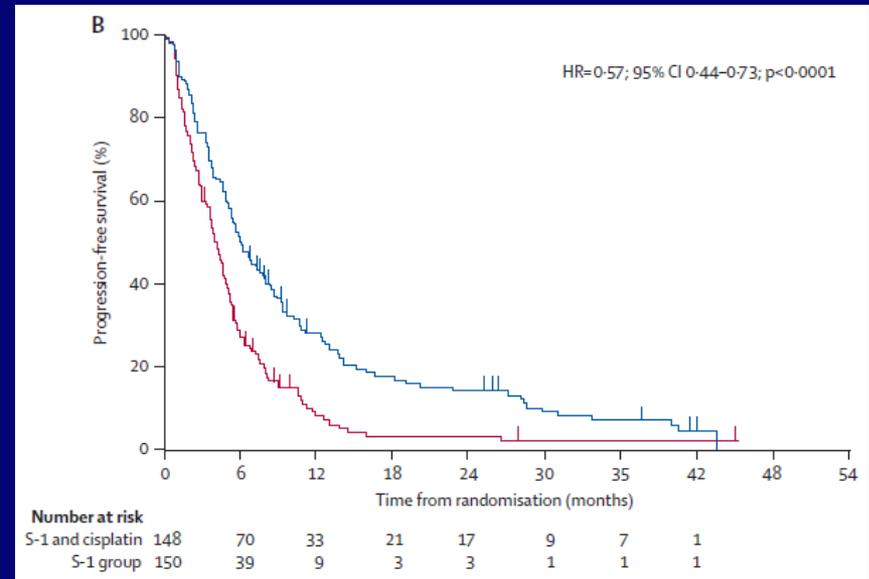
Some chemotherapy has inconsistent efficacy around the world

EU: FLAG: Cisp+S1 vs Cisp+Fu



● mPFS: 4.8m vs 5.5m

JAPAN:SPIRITS: Cisp+S1 vs S1



● mPFS: 6.0m vs 4.0m

Adjuvant Chemotherapy

For those without pre-operation chemotherapy, adjuvant chemotherapy are recommended.

Regimens include:

S-1

XELOX

FOLFOX

ECF

EU :

ECF

XELOX

FOLFOX

2nd line treatment summary

	Germany		Korea		UK	
	CPT-11	BSC	TXT/CPT-11	BSC	TXT	BSC
N	21	19	133	69	84	84
PS,% (0-1/2)	81/19	74/26	100/0	100/0	73/17	86/14
mOS (m)	4.0	2.4	5.3	3.8	5.2	3.6

- 2nd line therapy extends survival in advanced gastric cancer and is an appropriate standard of care
- 1st line study should consider the impact of difference 2nd line treatment in different regions

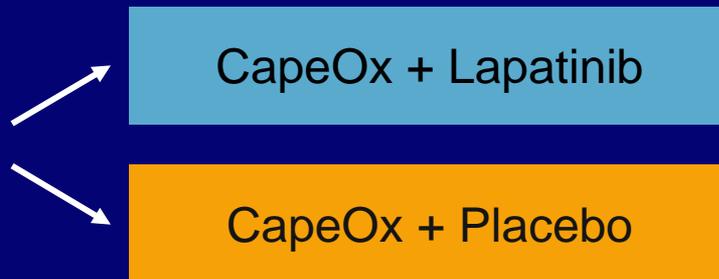
AVAGAST: Subsequent Lines of Therapy by Region

Region	Patients entered	Patients receiving second-line treatment	%
Asia	376	248	66
Europe	249	78	31
Pan-America	149	32	21

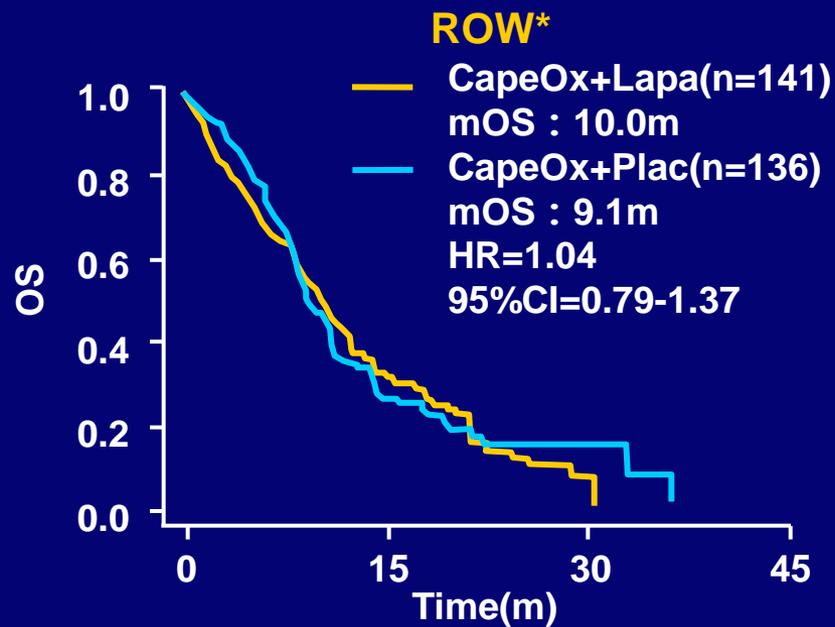
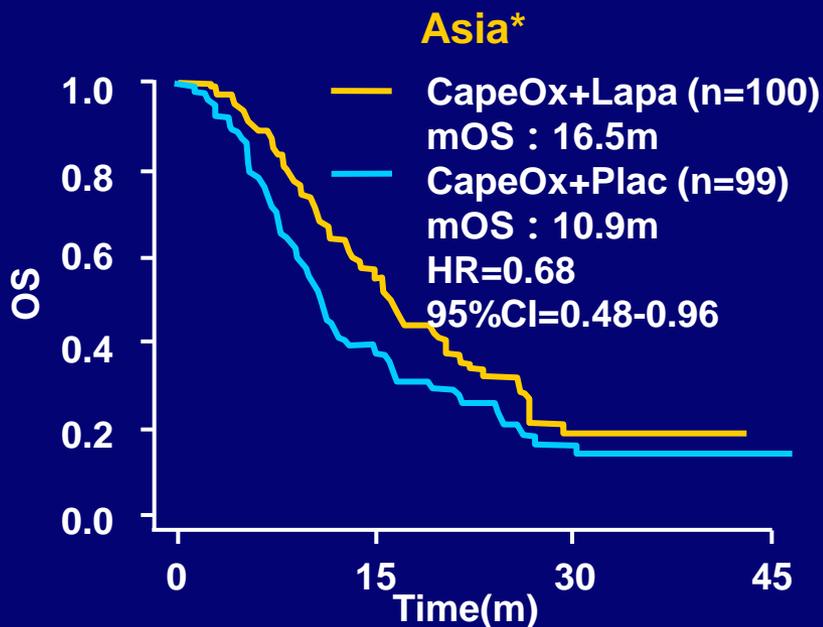
LOGiC:

The efficacy of target drug seems different in different regions

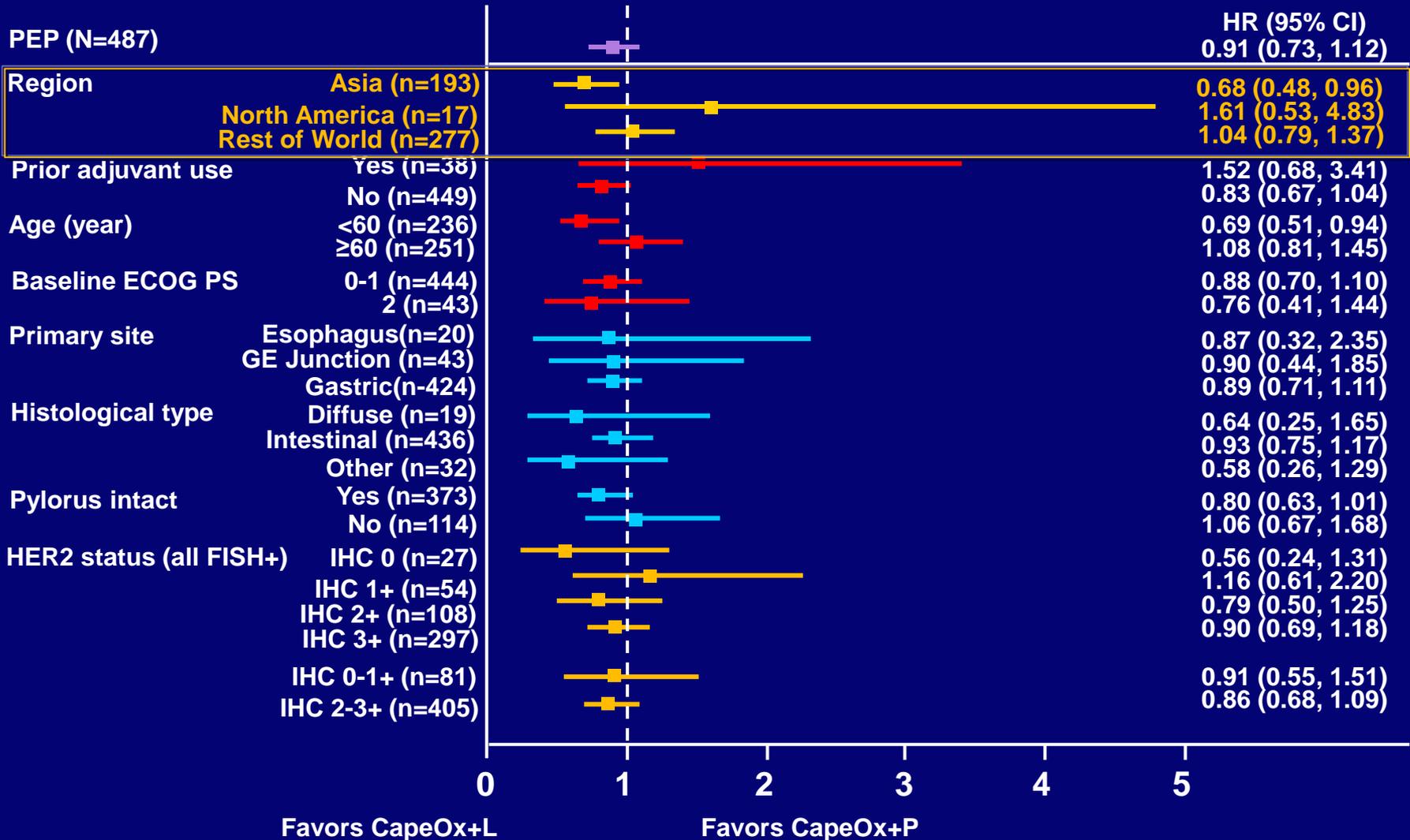
Patients with HER2-amplified locally advanced, unresectable, or metastatic gastric, esophageal, or GEJ cancer



(N = 545, primary endpoint: OS)



LOGiC: OS subgroup analysis



IPASS: High incidence of EGFR mutation in Chinese population

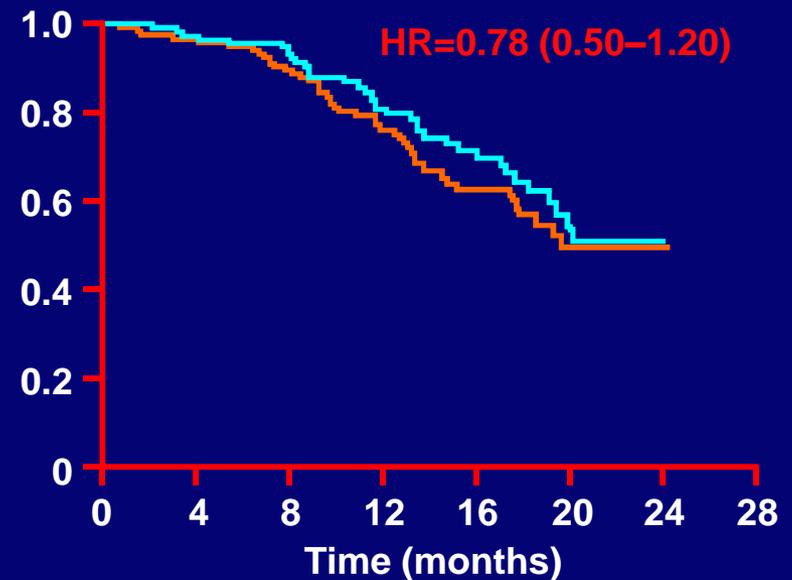
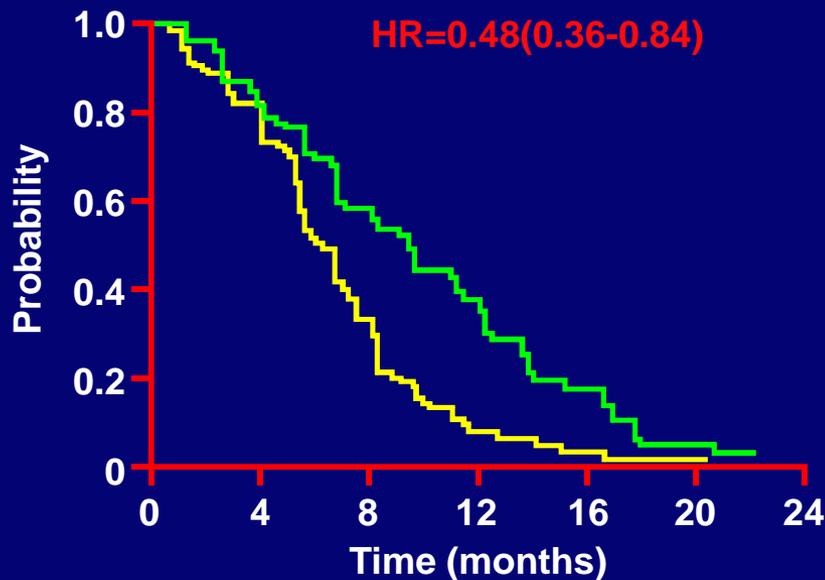
EGFR mutation-positive*

PFS

OS

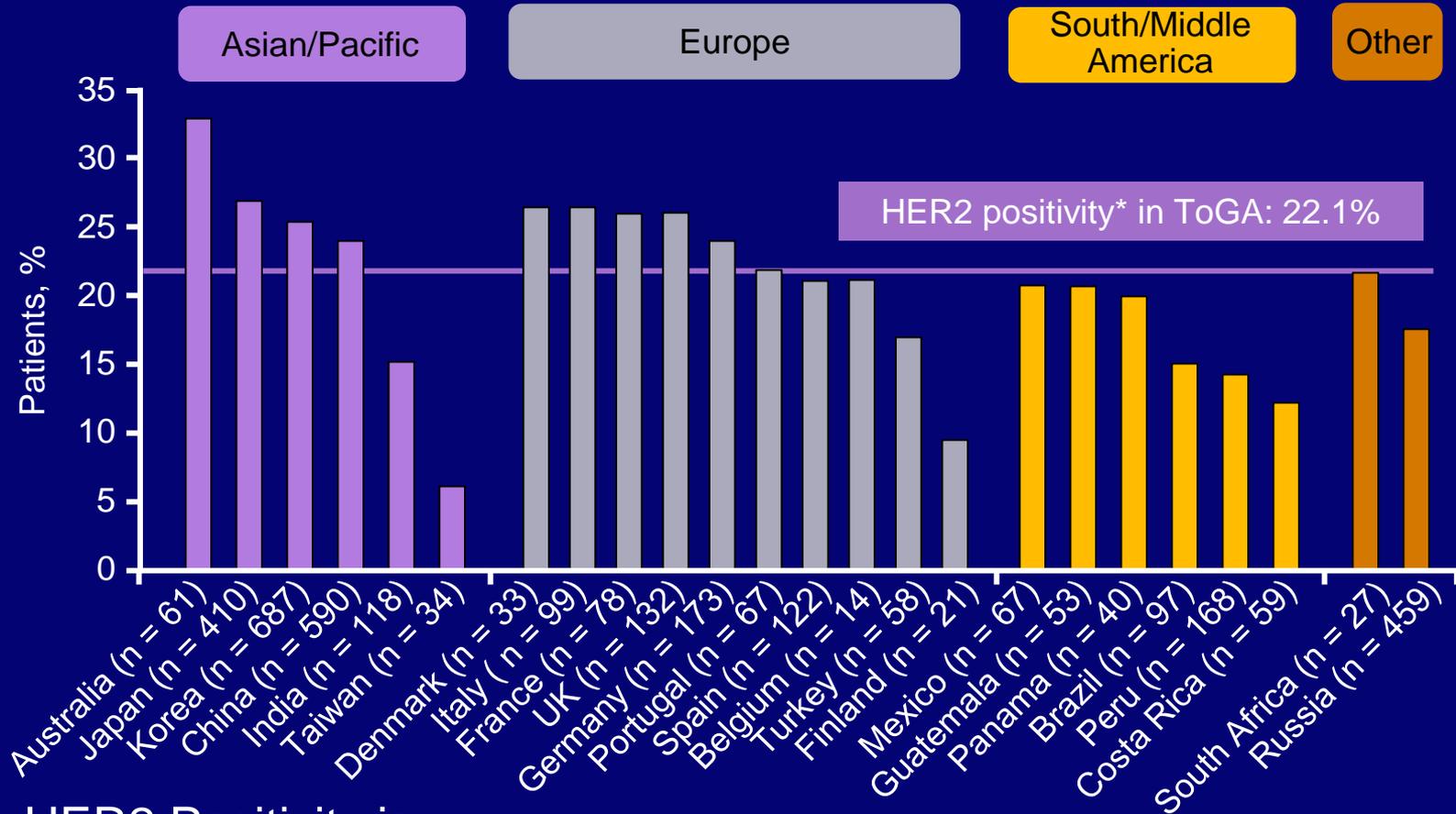
Gefitinib (n=132)
CP (n=129)

Gefitinib
CP



*60% of population

HER2 Positivity Worldwide



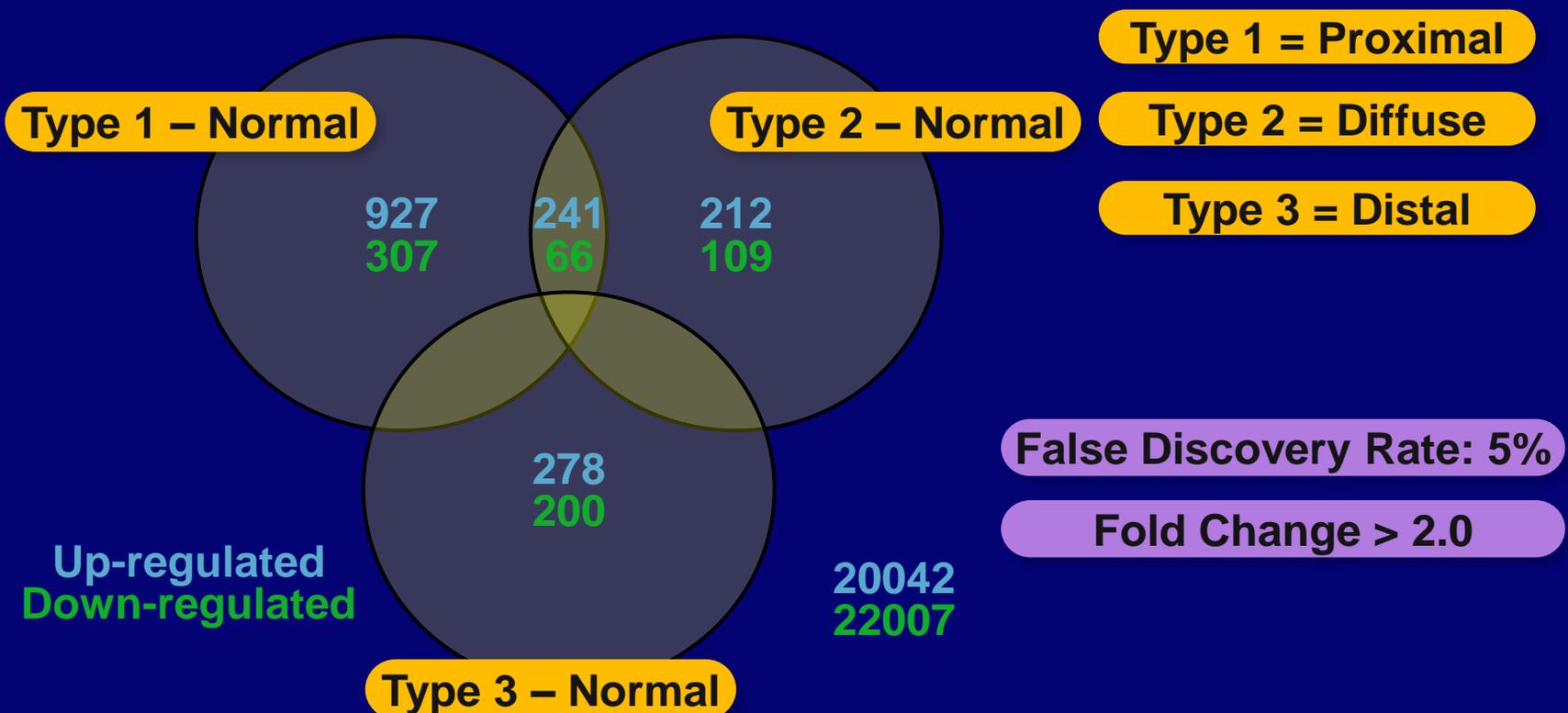
HER2 Positivity is:

consistent in different region level
various in country level

*HER2 positivity: IHC 3+ or FISH +

Gastric Cancer Subtypes Differ From Normal and From Each Other

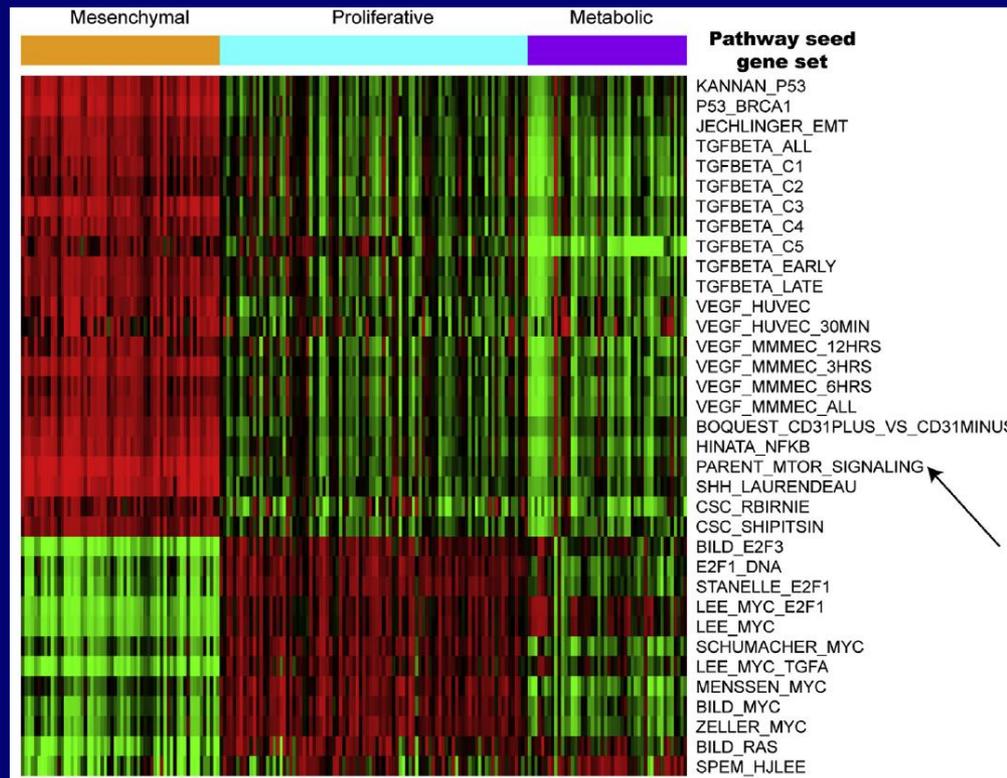
Samples : 36 from MSKCC



Probes that are significantly different between
NORMAL stomach and GC subtype

Molecular Subtypes of Gastric Cancer

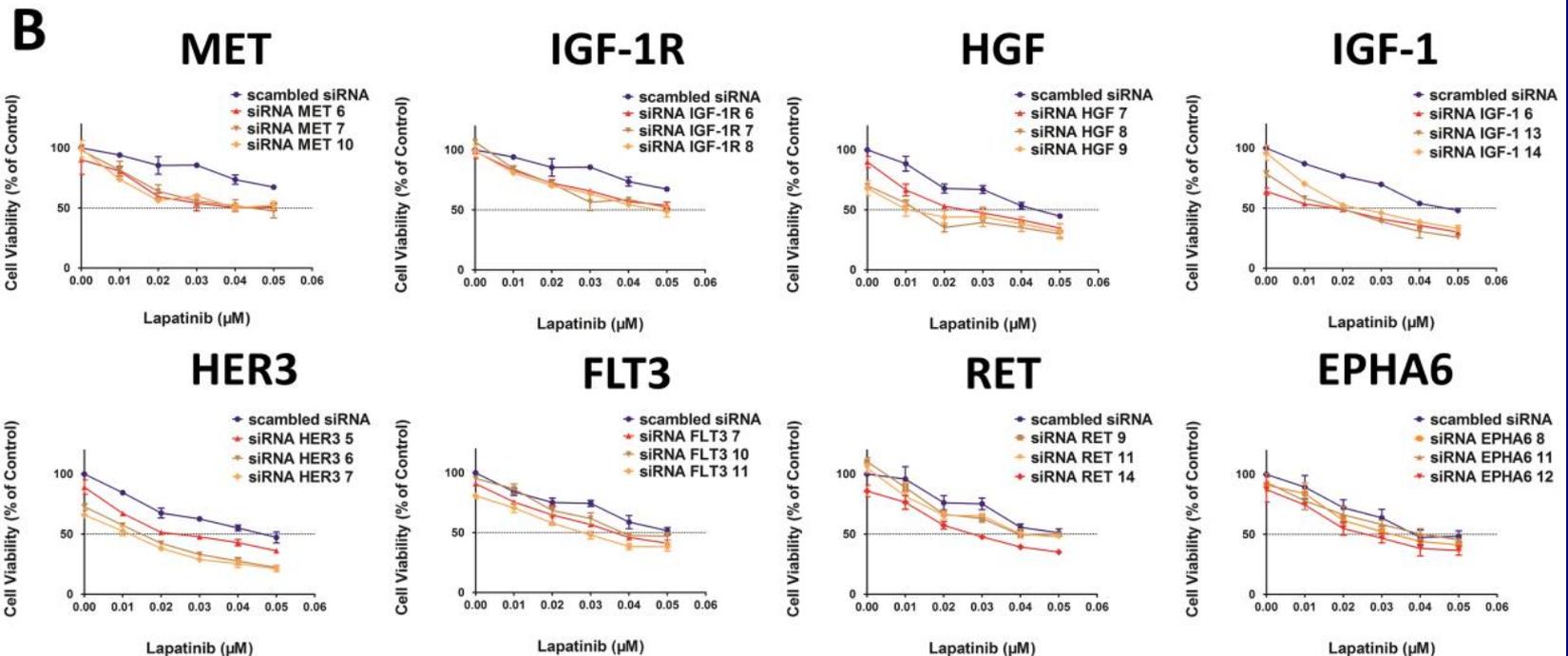
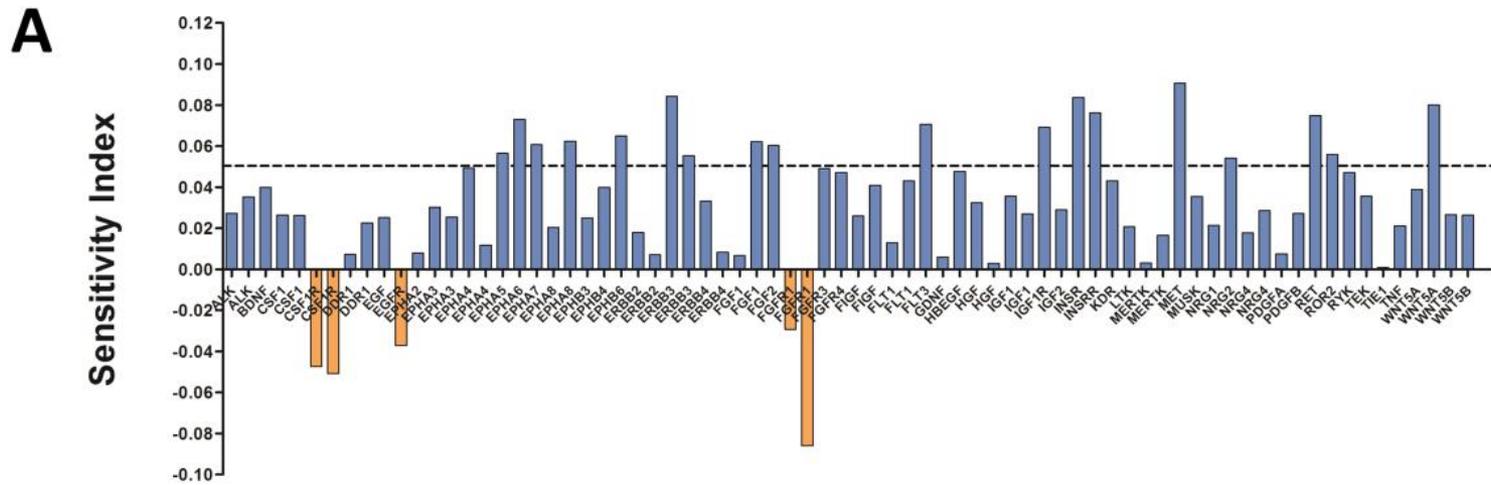
Samples : 248 from Singapore and Australia



3 subtypes of gastric adenocarcinoma based on gene expression patterns:

proliferative, metabolic, and mesenchymal

shRNA screen to identify lapatinib sensitizers in the library representing RTK receptors and related growth factors.



Summary

- **Gastric cancer is different in the molecular subtype**
- **The relationship between region and molecular subtype need further study**

- **Recommend for further clinical study:**
 - **Choose regimen with consistent efficacy around the world as control**
 - **Consider the impact of different 2nd even 3rd line treatment in the study**
 - **Consider the potential difference in expression of biomarker in different region**

THANK YOU FOR YOUR ATTENTION!