Molecular Heterogeneity in Gastric Cancer: Genomic Approaches and Clinical Impact

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esmo.org
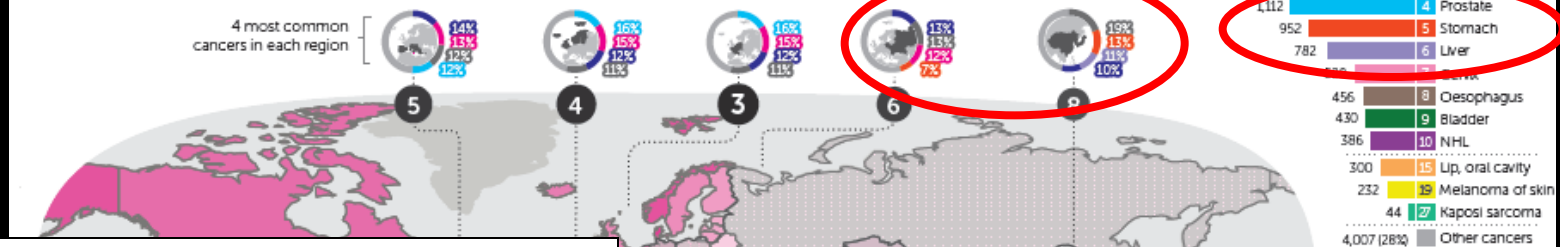
Disclosure slide

- Nothing to Declare

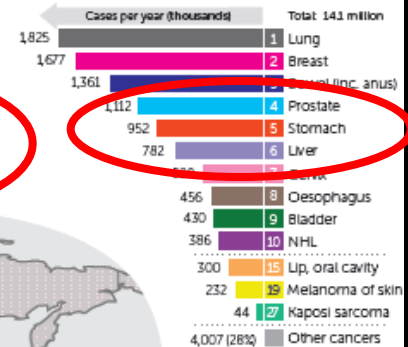# Gastric Cancer : World's 5th Most Common Cancer and 3rd Leading Cause of Cancer Death
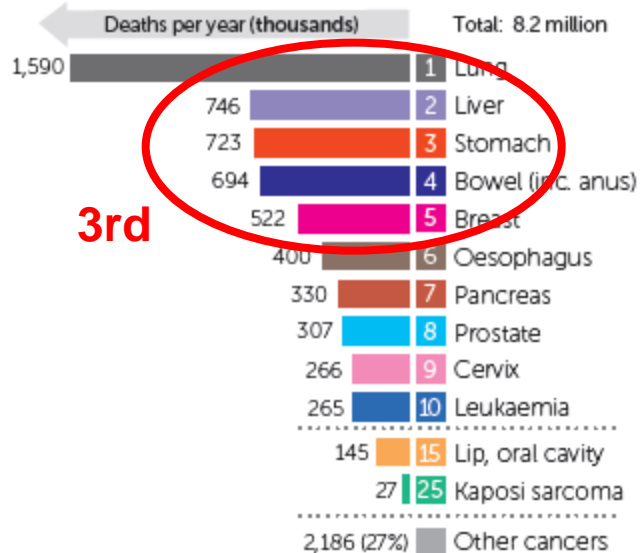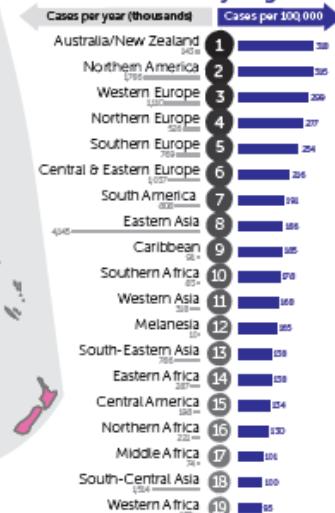
Molecular and Clinical Heterogeneity in Gastric Cancer (GC)
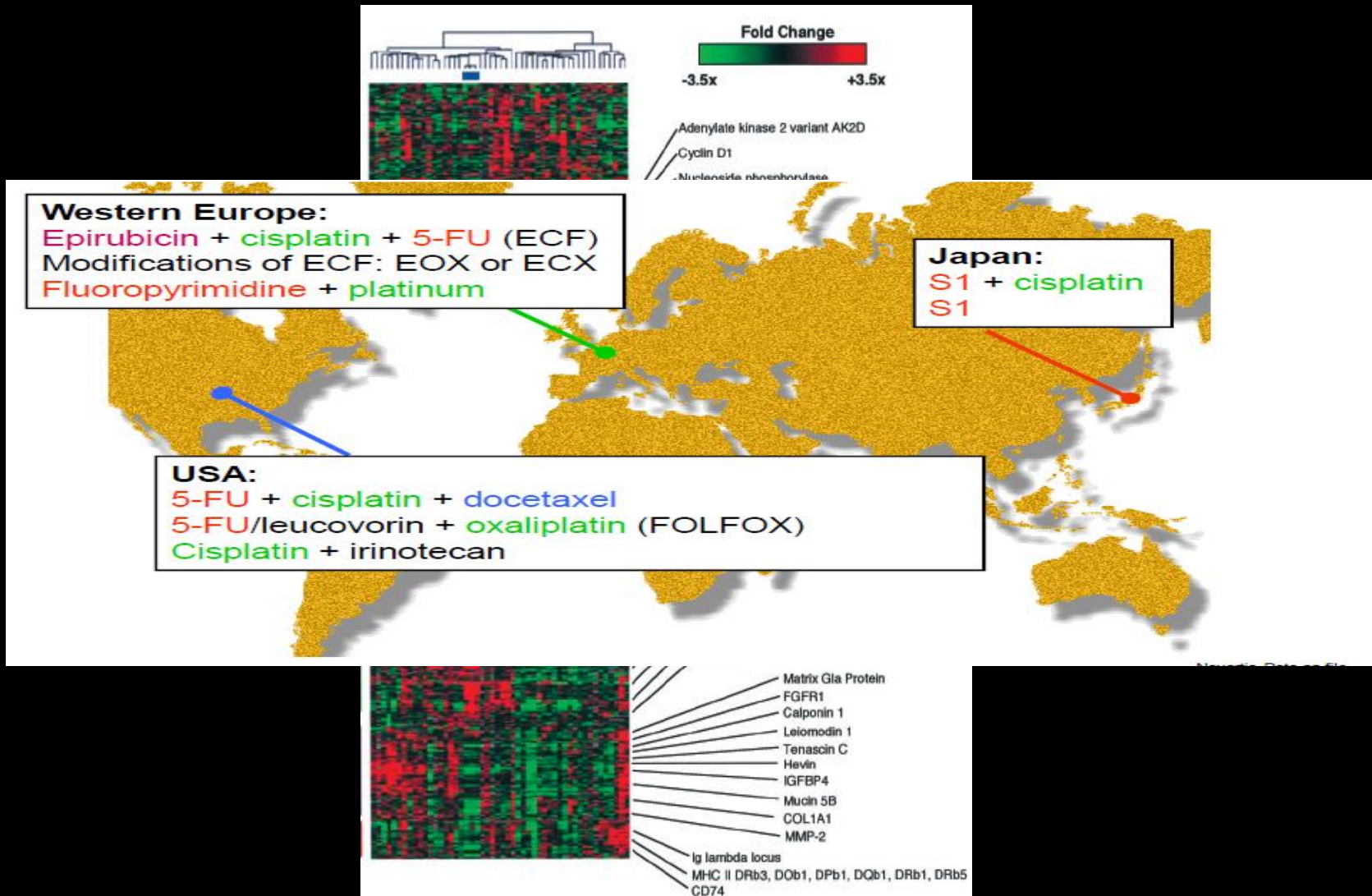
Tay et al., (2003) *Cancer Research*

Can Genomics Improve Gastric Cancer Patient Outcomes?

1) How many GC subtypes exist? What are their <u>driver alterations</u> and pathologic associations?

2) Which GC Subtypes are <u>Clinically Relevant</u>, for Patient Prognosis and Therapy Selection?

3) Are GCs from Asian and non-Asian localities the same?

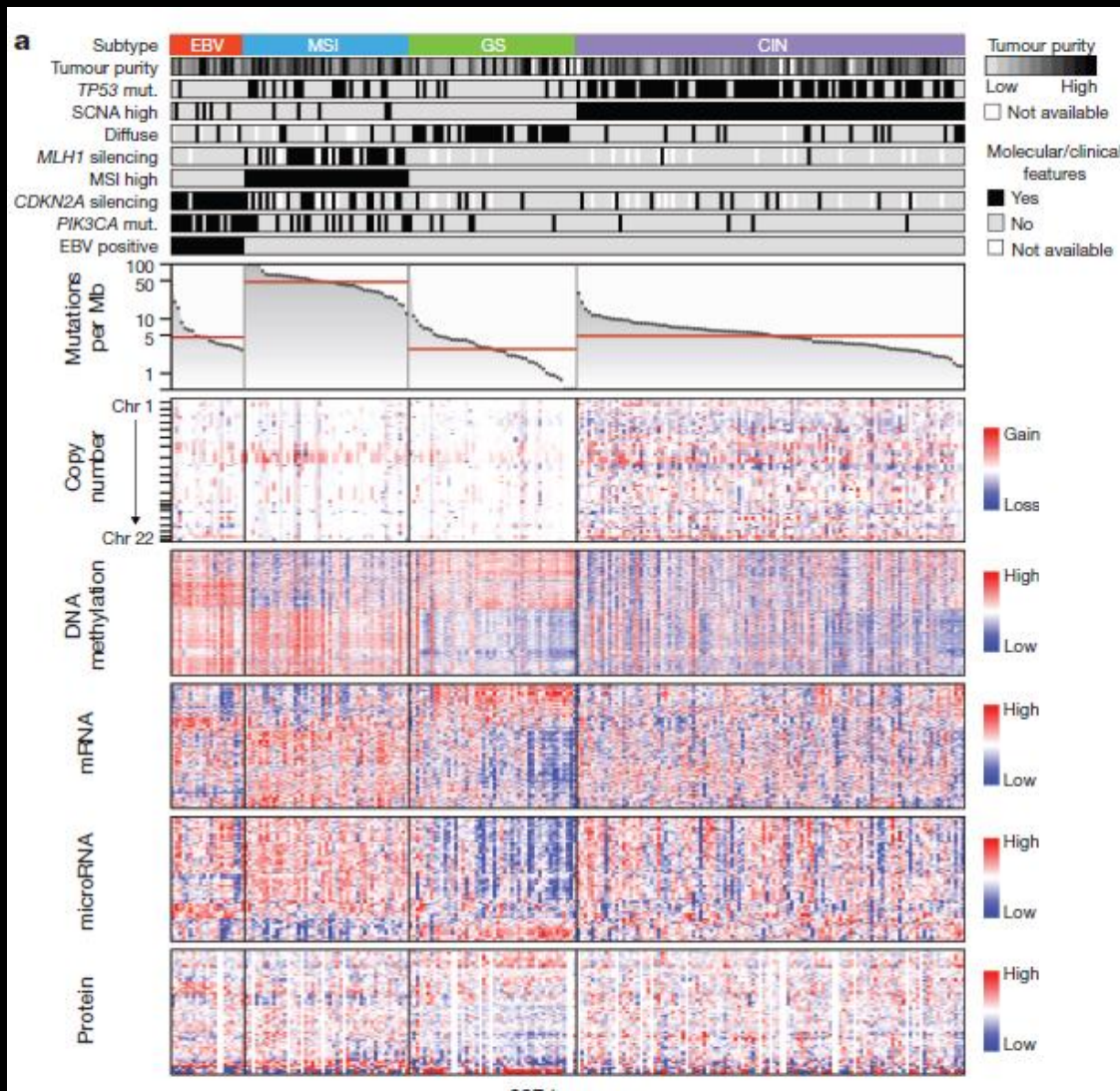# There are ~3-4 Major GC Genomic Subtypes

A) Chromosomal Instability (CIN)

B) Microsatellite Instability (MSI)

C) Genome Stable (GS)

D) Epstein-Barr Virus (EBV)

USA TCGA (2014) *Nature*

GC Genomic Subtypes Show Distinct Molecular and Pathological Characteristics

Chromosomal Instability (CIN) (50%)
- Intestinal-type GCs
- *TP53* mutations
- Focal somatic gene amplifications in RTK/RAS genes

Microsatellite Instability (MSI) (20%)
- Intestinal-type GC `ARID1A, CIMP`
- *TGFBR2, ACVR2A* mutations

Genome Stable (GSS) (20%)
- Diffuse-type GC
- *CDH1, RHOA*** mutations

Epstein-Barr Virus (EBV) (10%)
- Globa `ARID1A, CIMP` on
- *PDL-1/2* Gene Amplification**

Matsusaka et al (2011) *Cancer Res*
Wang et al (2011) *Nat Genetics*
Zang et al (2012) *Nat Genetics*
Nagarajan et al (2012) *Gen Biol.*
Yoon et al (2013) *Genome Res*
Wang et al (2014) *Nat Genetics*
Kakiuchi et al (2014) *Nat Genetics*
USA TCGA (2014) *Nature*

Can Genomics Improve Gastric Cancer Patient Outcomes?

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Singapore Gastric Cancer Consortium Translational Pipeline

Clinical Databases
"Gastronomica"
>250 Tumors

Demographics
Histopathology
Treatment
Survival Outcomes

Experimental Models
"GEMINI"
70 Cell Lines

High-Throughput
Screening
Synthetic Lethality
Cell Based Phenotypes

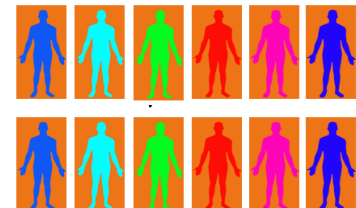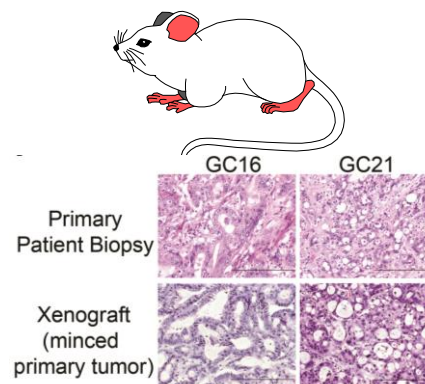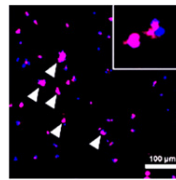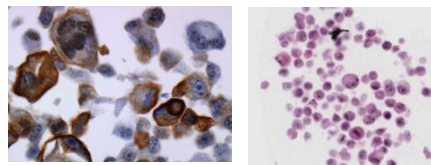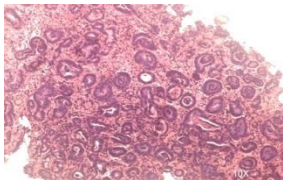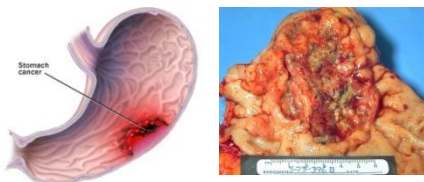## Preclinical Validation
Tumorgrafts
12 Gastric Lines

Patient Derived
Xenografts
Tumor Initiating
Cells

Patients
Clinical Trials

Phase I/II
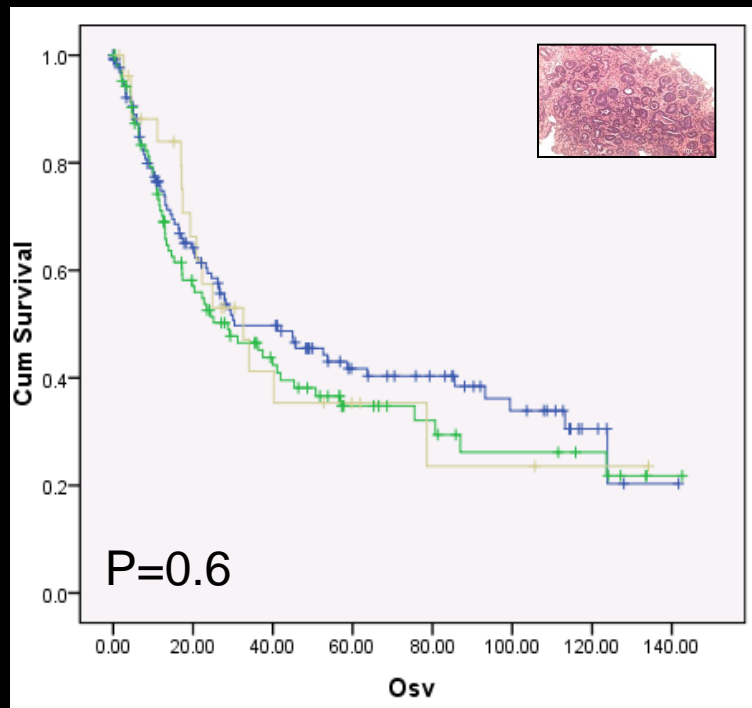Companion
Diagnostics

Genomics as a Bridging Technology

Stomach cancer

Primary Patient Biopsy

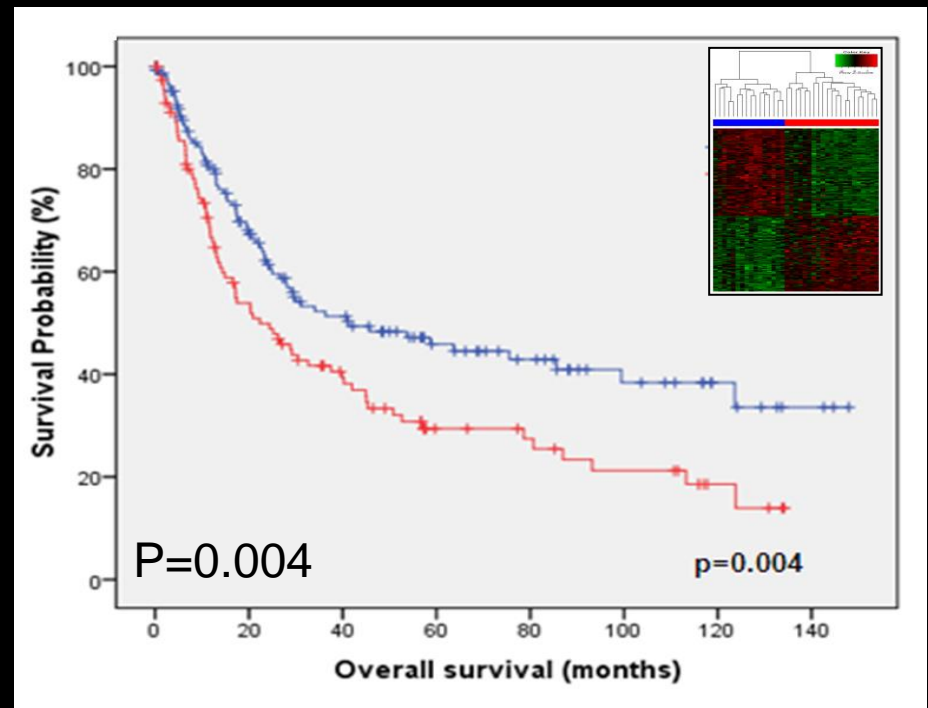Xenograft (minced primary tumor)

GC16   GC21

Patients with *Diffuse-Type* Genomic Signatures and/or Histology Exhibit Poor Prognosis
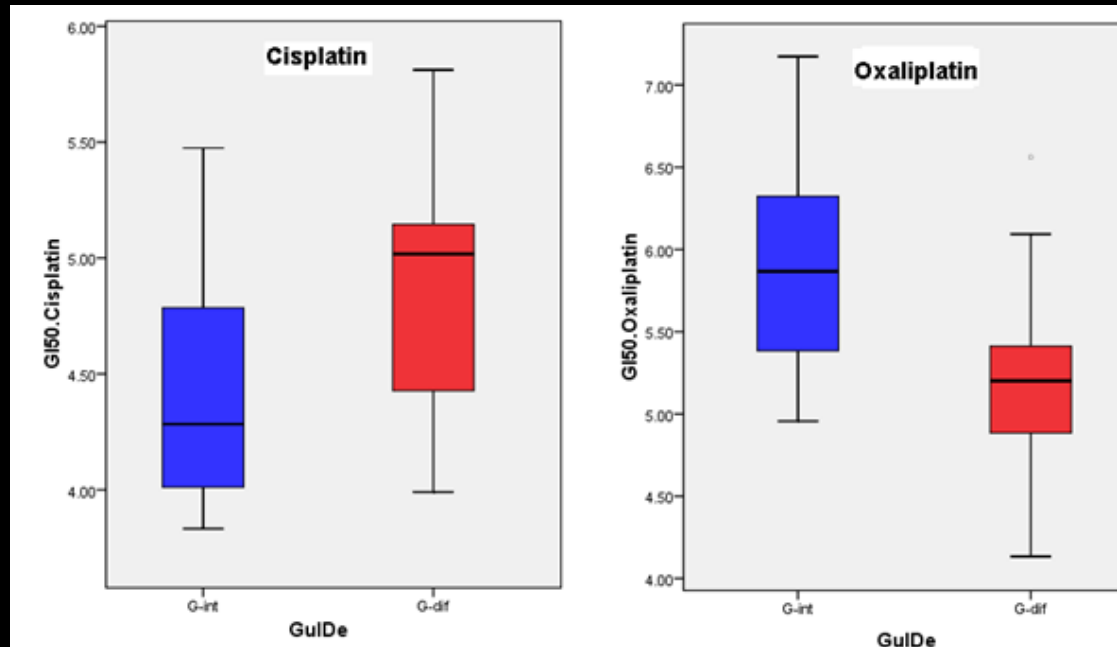

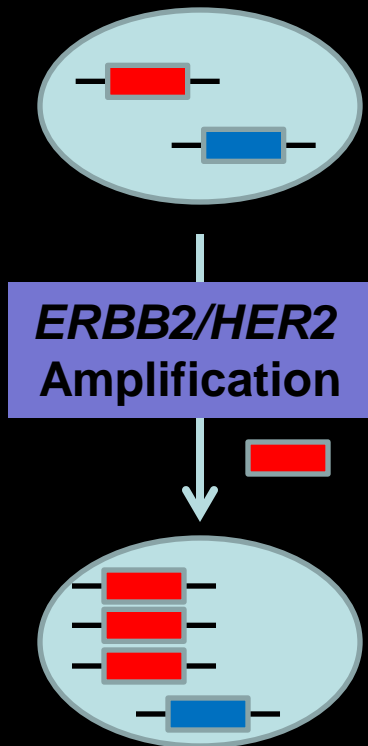Intestinal vs Diffuse (Histopathology)

G-INT vs G-DIF (mRNA signature)

G-INT and G-DIF Cell Lines May Respond Differently to Distinct Platinum Agents

Cisplatin
P=0.03

Oxaliplatin
P=0.02

Tan et al (2011) *Gastroenterology*

Targeted Therapies in Gastric Cancer

ERBB2/HER2 Amplification

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

	Events	Median OS	HR	95% CI
XP/FP + T	120	16.0	0.65	0.51, 0.83
XP/FP	136	11.8		
		Δ 4.2		

11.8   16.0
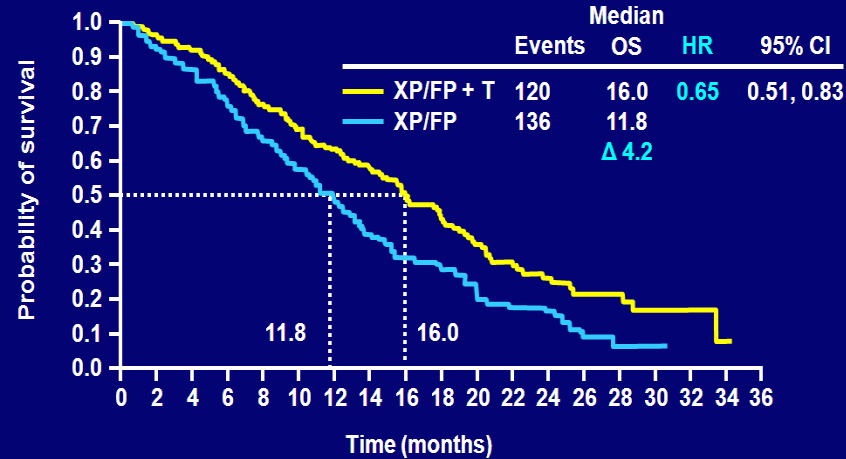
The TOGA Trial

Bang et al (2011) *Lancet*
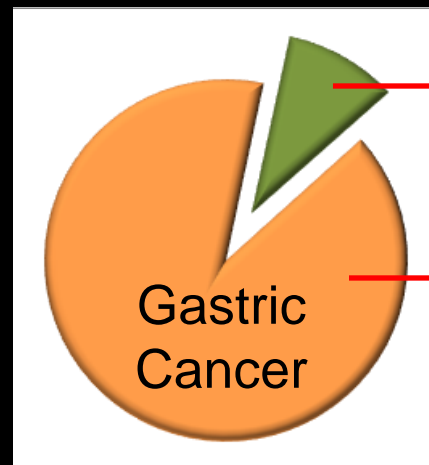
ERBB2 Positive (8-10%)

?????

Gastric Cancer

Exclusive RTK/RAS Amplifications in GC

FGFR2   ERBB2   EGFR   MET

KRAS

Proliferation, survival ...

ositive
%)

=72/193 (37.3%)

■ FGFR2 ■ KRAS ■ ERBB2 ■ EGFR ▨ MET
■ RTK/RAS Absent
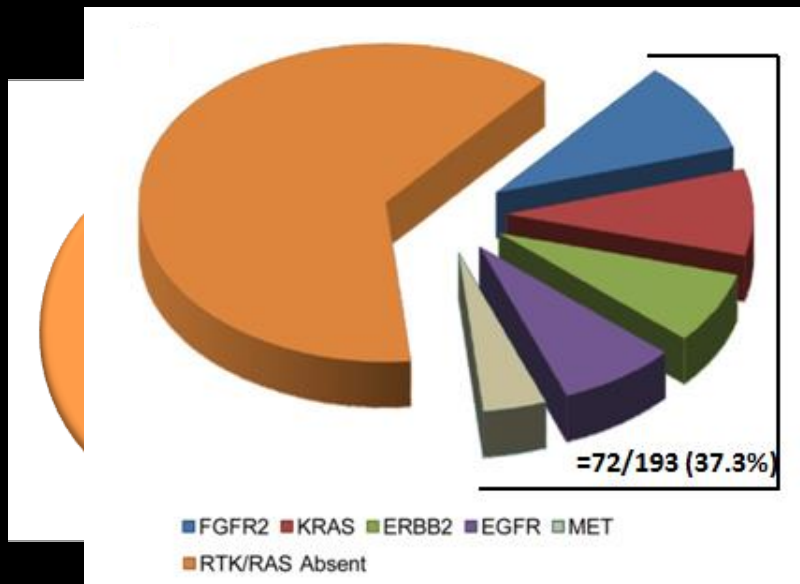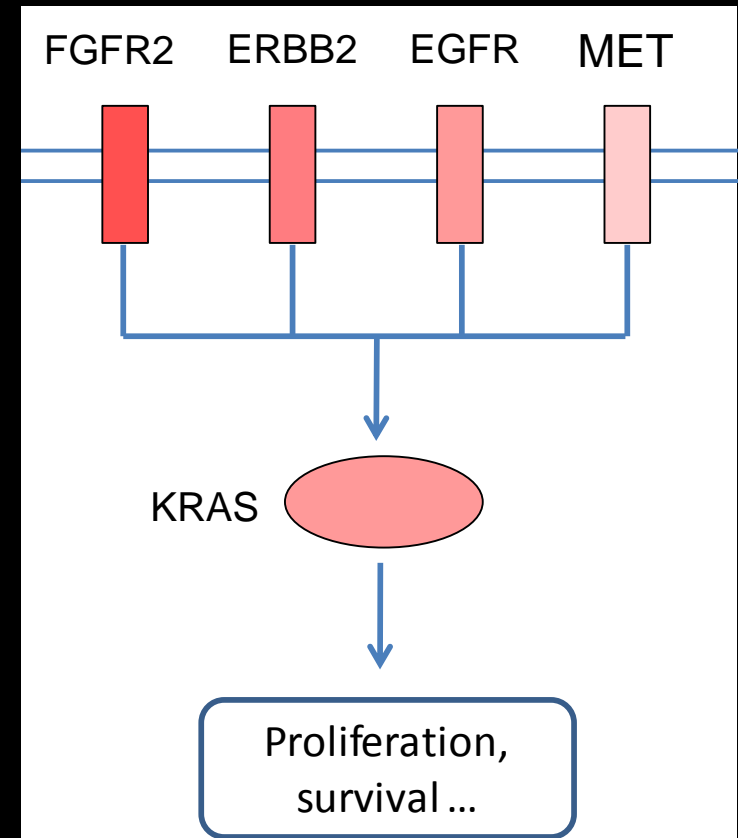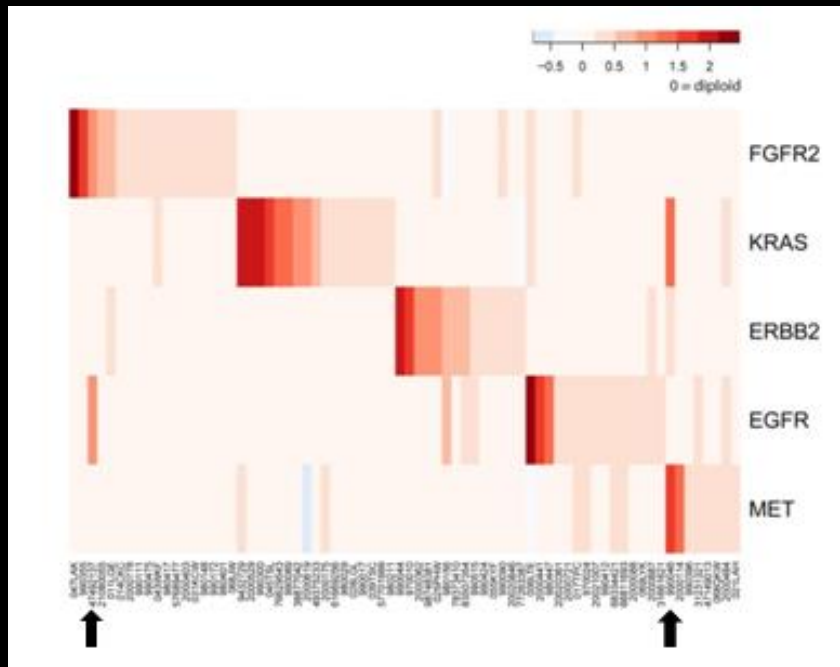
Deng et al (2012) *Gut*

Gastric CpG Island Methylator (CIMP) – A Targetable Epigenetic Phenotype?

DNA Methylation Clustering

Impact of DNA Demethylating Agents on Gastric CIMP Tumors

G-CIMP Lines

Decitabine (5-aza-2'deoxycytidine)

Inhibitor of DNA Methyltransferase
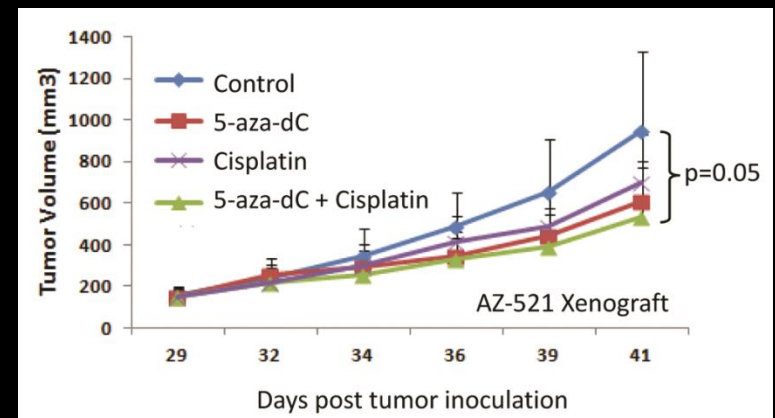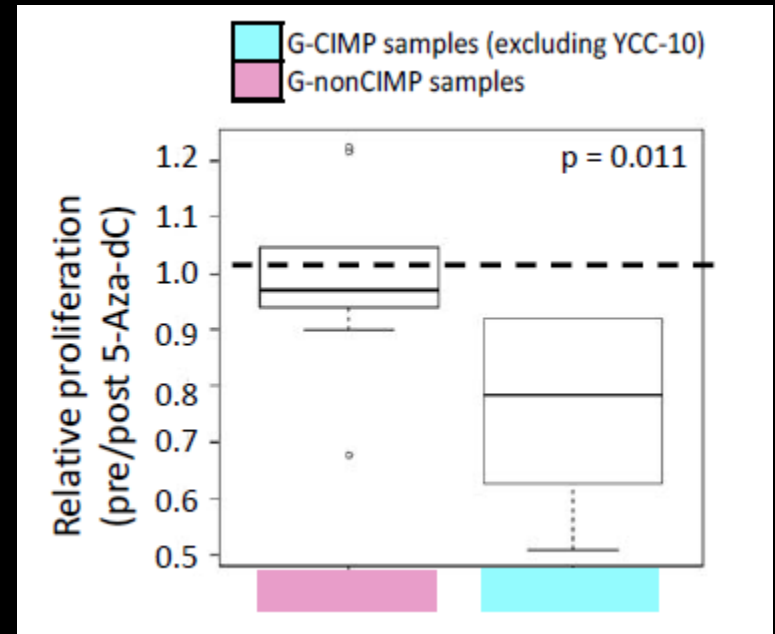
Zouridis et al., (2012) *Sci Trans Med*

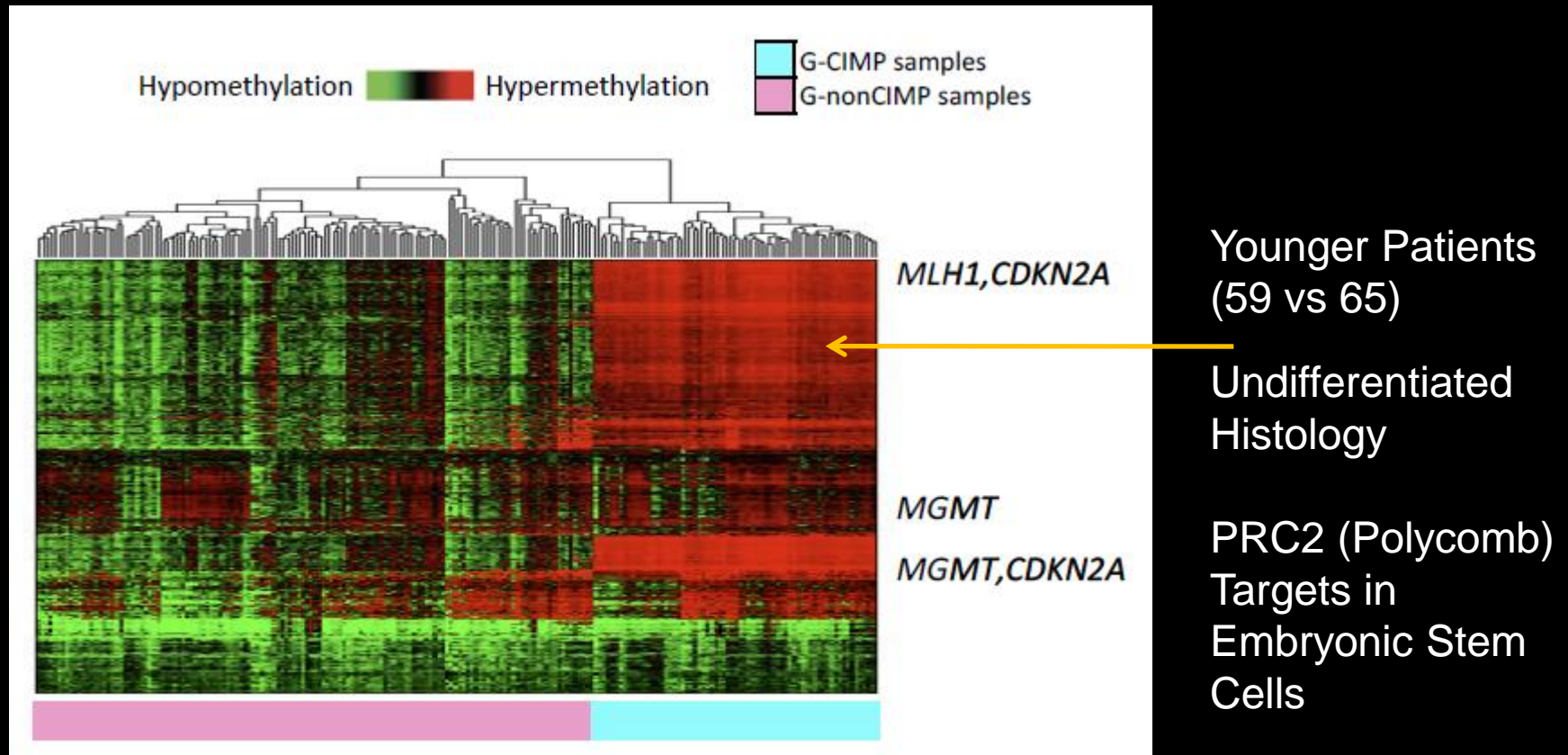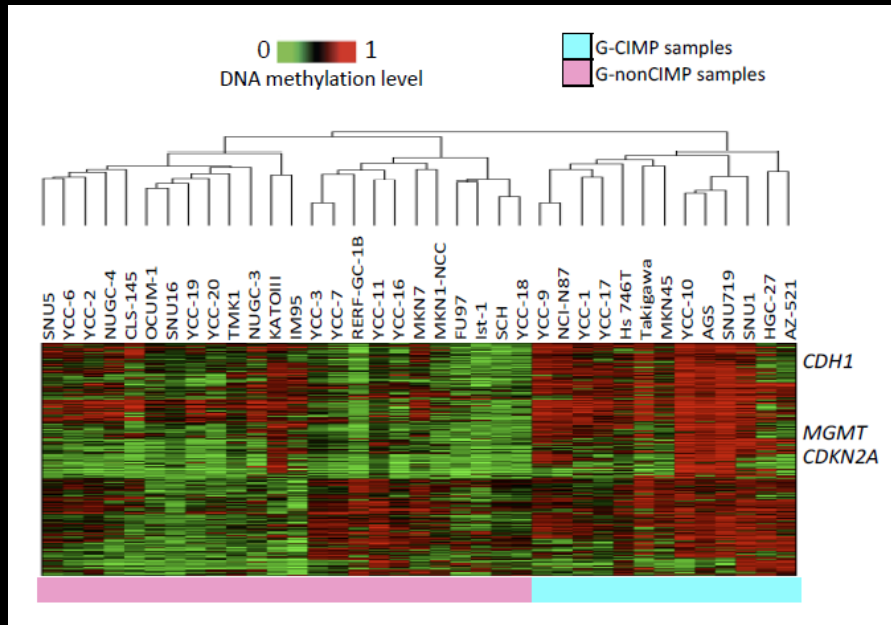# Can Genomics Improve Gastric Cancer Patient Outcomes?

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Somatic Alterations (eg Amplifications) Between Asian and Non-Asian GCs Appear Similar
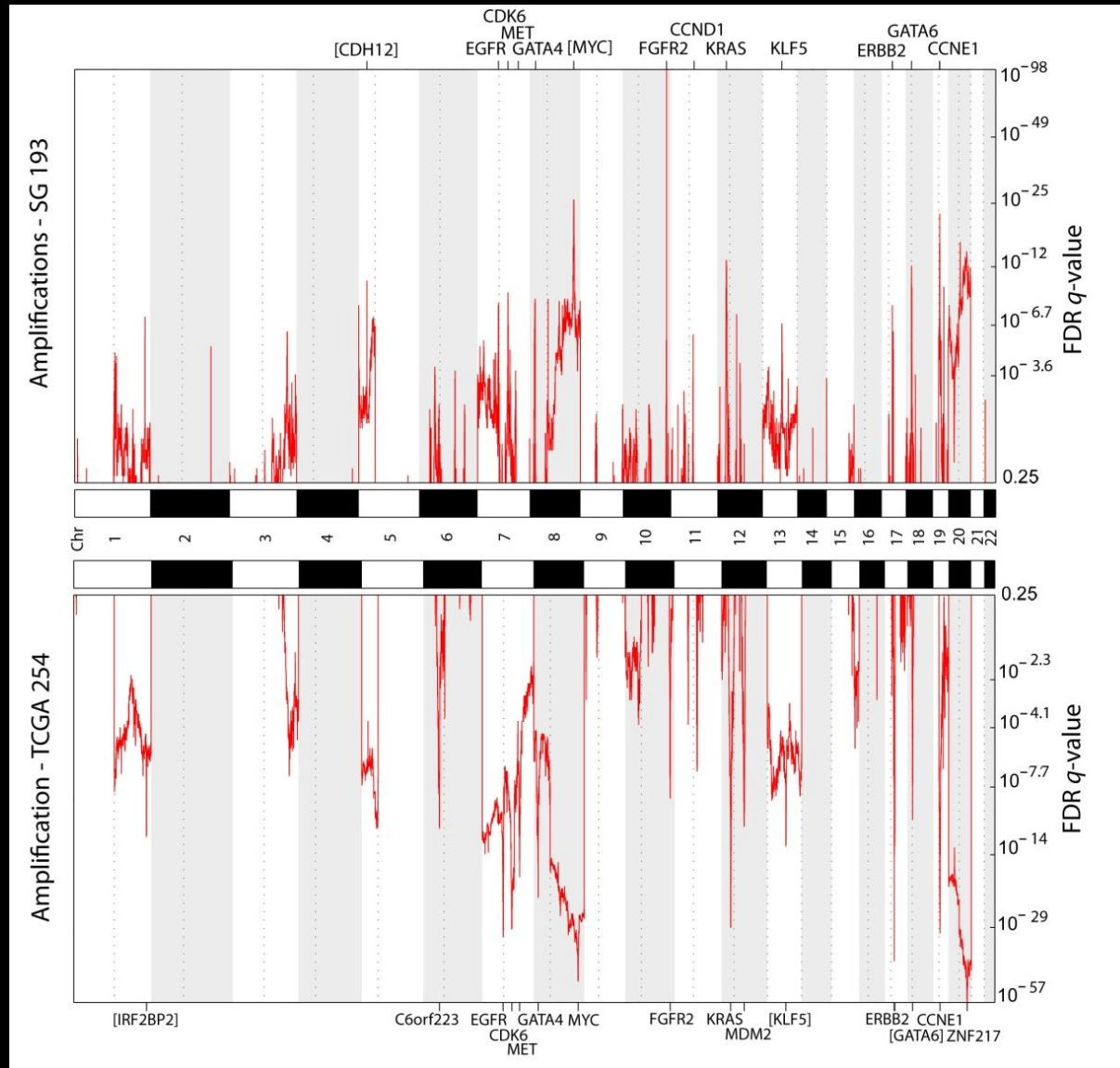
Singapore Cohort

TCGA Cohort (USA)

Phase III GC Clinical Trials Reveal an Association between Geography and Clinical Outcome

Comparing Asian and Non-Asian GCs Analysis of 1,600 Gastric Tumors

mRNA Profiles (>1000)

9 expression profiling studies (n=1,016)
- 6 studies of Asian origin (n = 890)
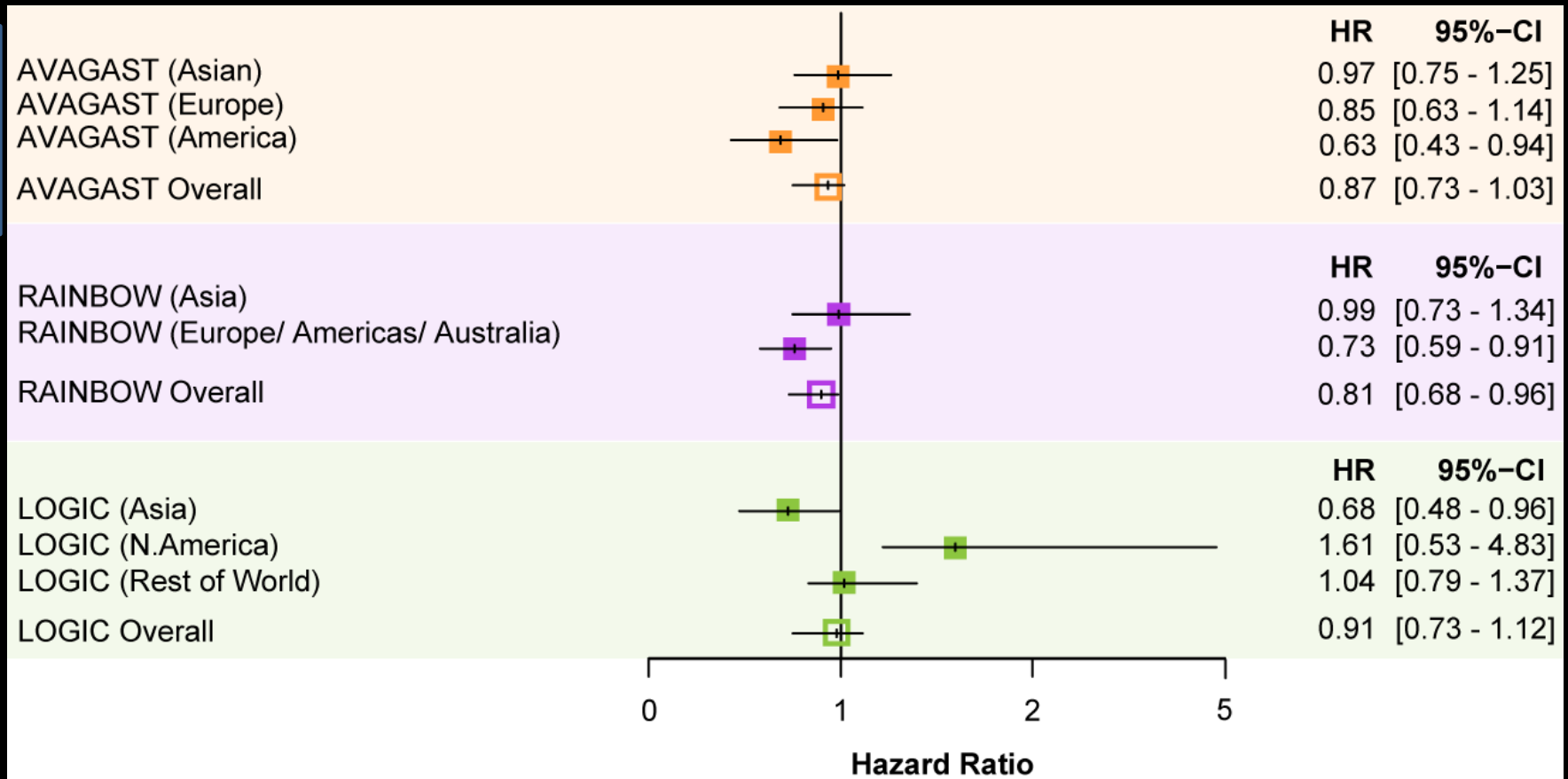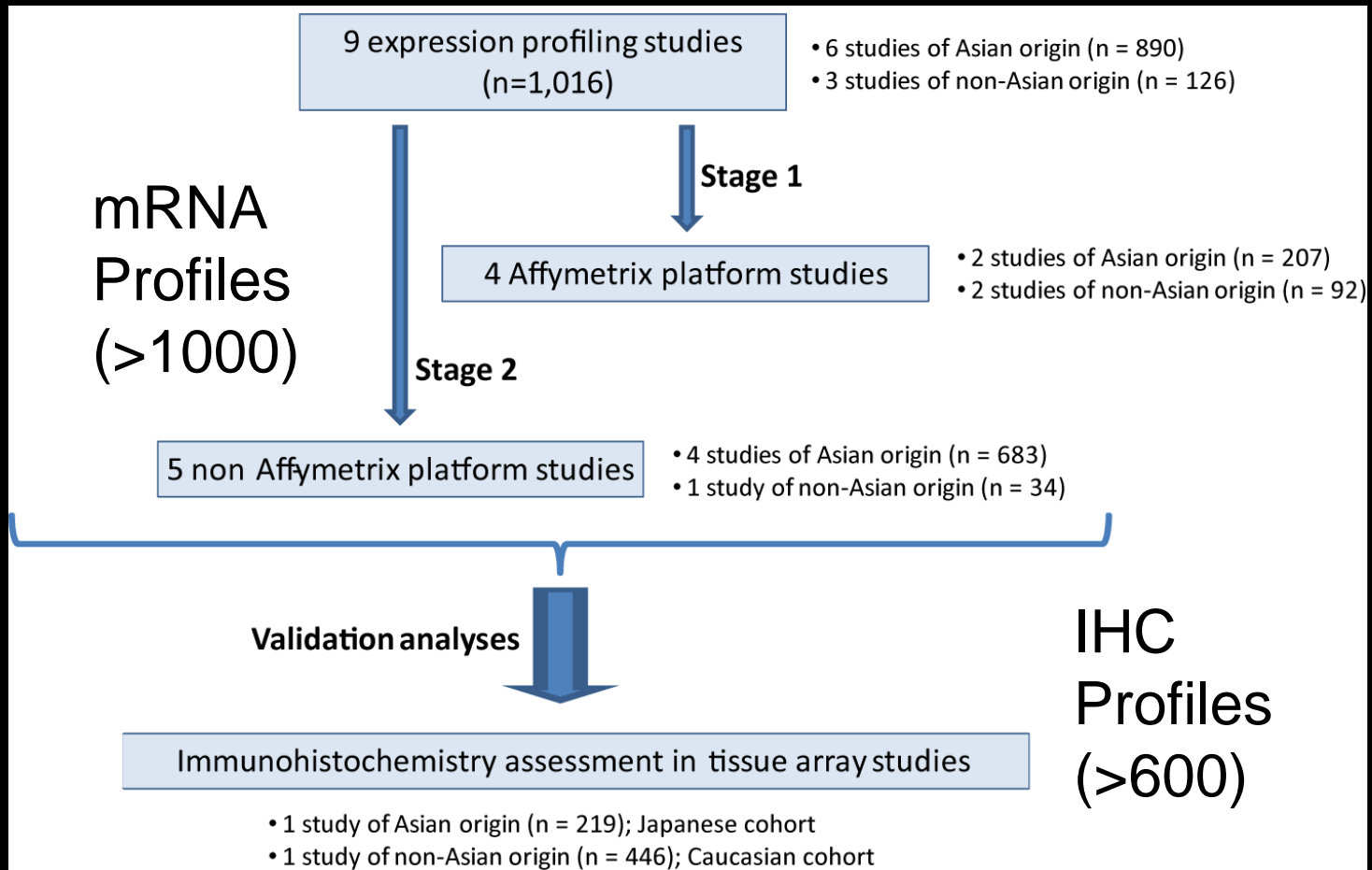- 3 studies of non-Asian origin (n = 126)

Stage 1

4 Affymetrix platform studies
- 2 studies of Asian origin (n = 207)
- 2 studies of non-Asian origin (n = 92)

Stage 2

5 non Affymetrix platform studies
- 4 studies of Asian origin (n = 683)
- 1 study of non-Asian origin (n = 34)

Validation analyses

IHC Profiles (>600)

Immunohistochemistry assessment in tissue array studies
- 1 study of Asian origin (n = 219); Japanese cohort
- 1 study of non-Asian origin (n = 446); Caucasian cohort
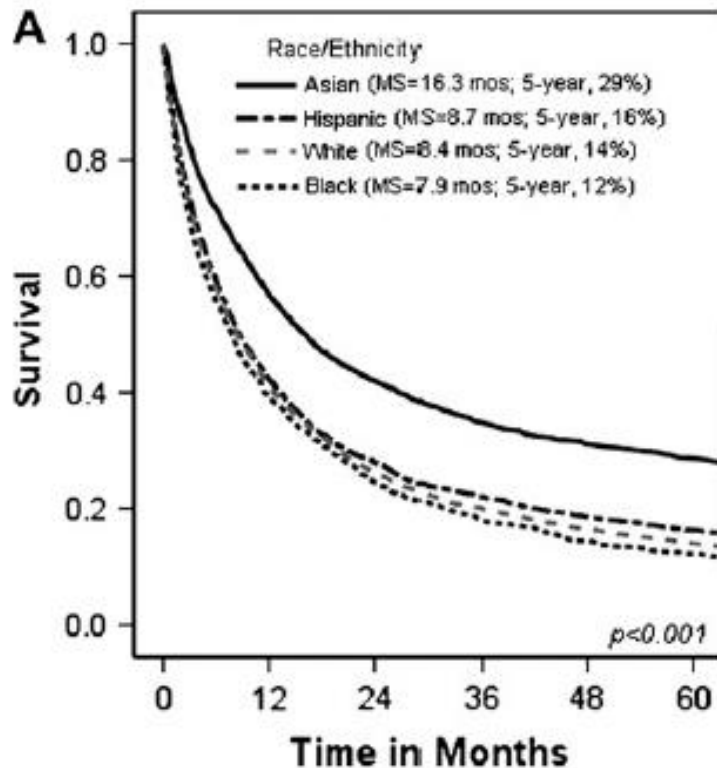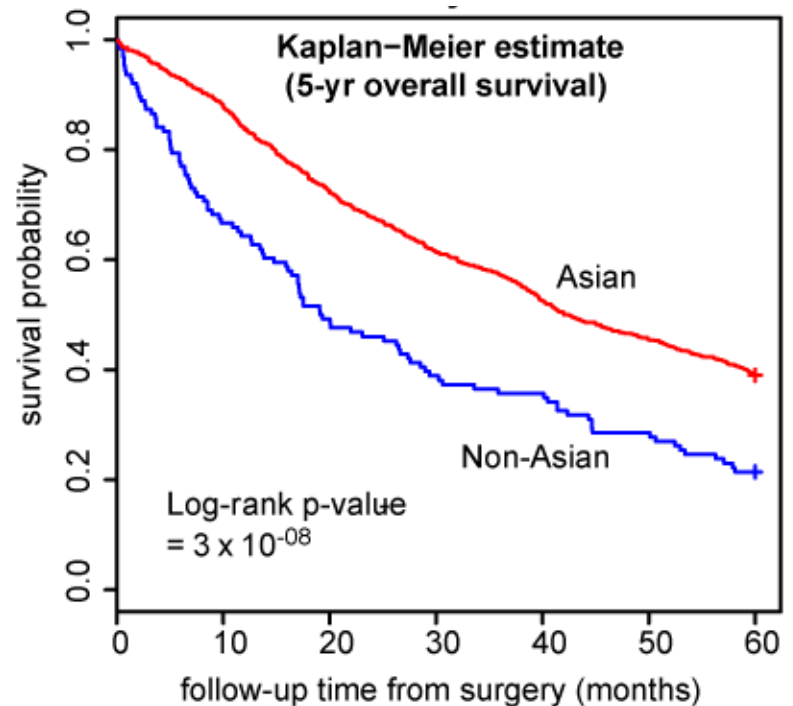
Collaboration : Johann A. Gagnon-Bartsch
Terry Speed, UC Berkeley
RUV algorithm : *Nature Biotechnology* (2014)

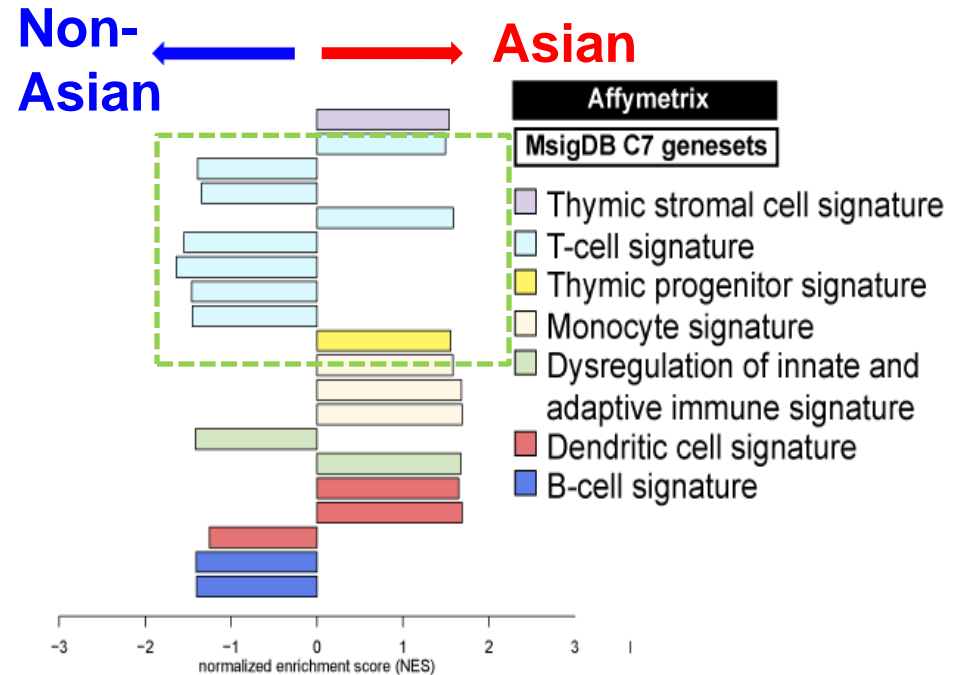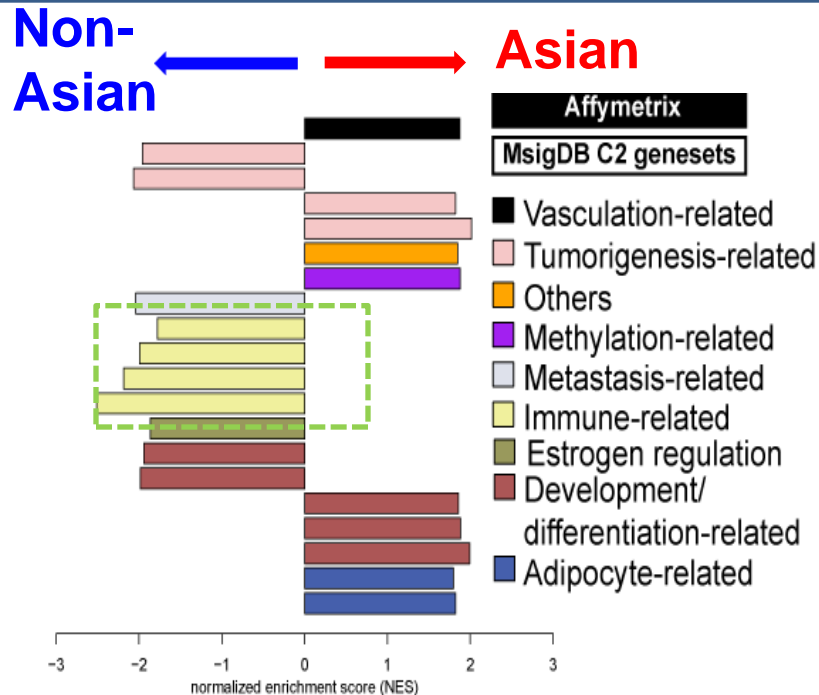# GC Expression Cohorts Recapitulate Well Known Geographic Differences in 5-yr Overall Survival
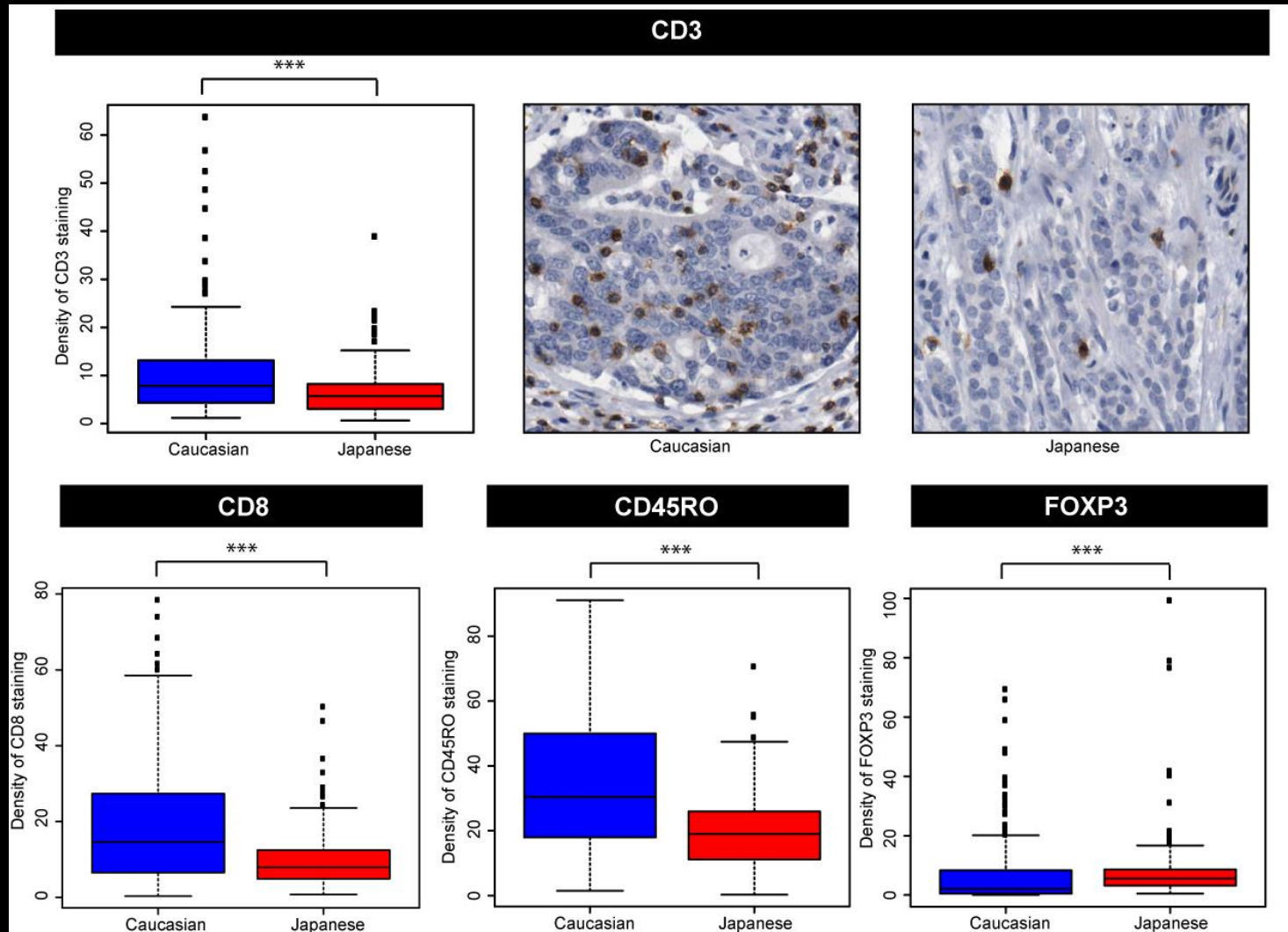

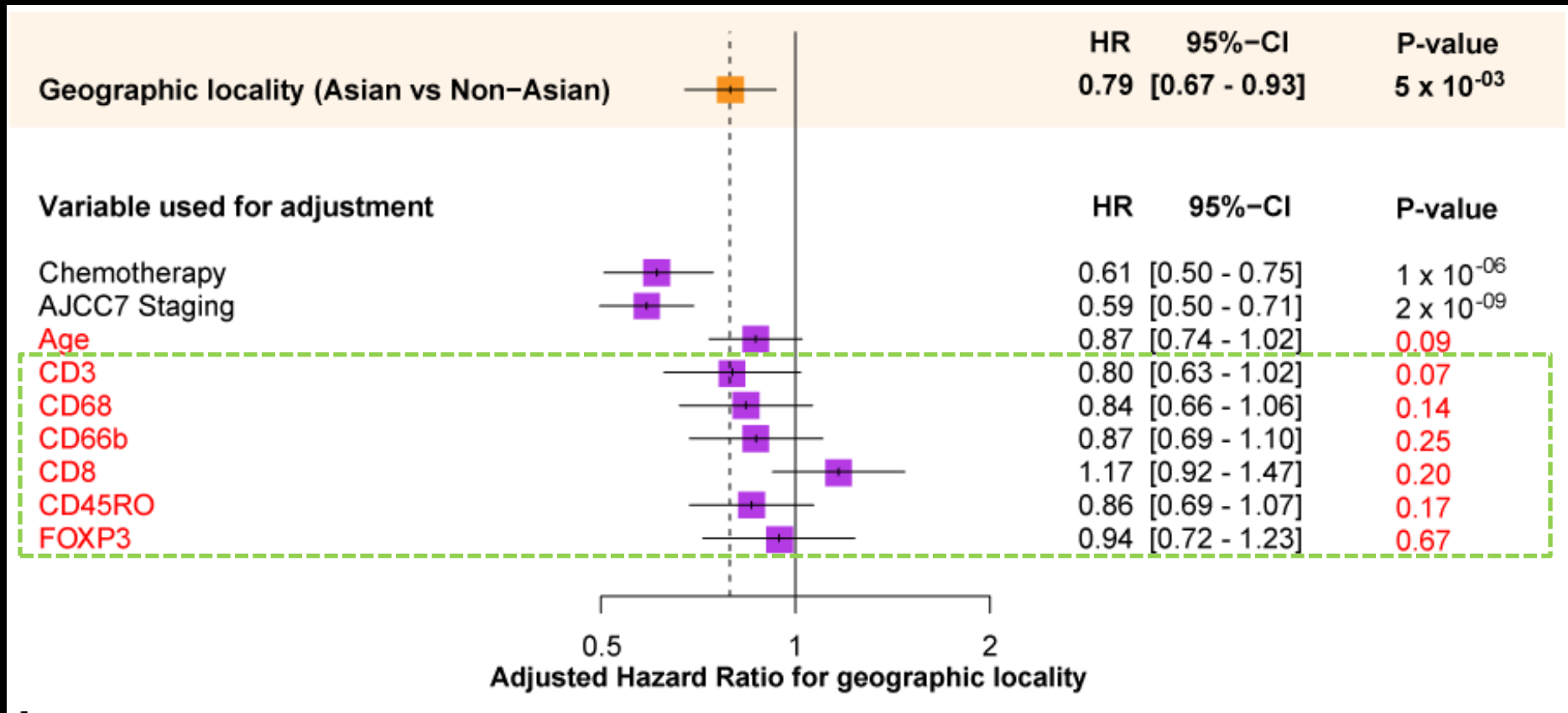Kim et al (2010) *Annals of Oncology*

Non-Asian GCs are Enriched in T-cell Gene Signatures Relative to Asian GCs

Immunohistochemistry Validation of T-cell Signatures in Non-Asian GCs

Adjusting for T-cell Signatures Impacts Geographic Differences in Overall Survival

	HR	95%-CI	P-value
Geographic locality (Asian vs Non-Asian)	0.79	[0.67 - 0.93]	5 x 10^-03

Variable used for adjustment	HR	95%-CI	P-value
Chemotherapy	0.61	[0.50 - 0.75]	1 x 10^-06
AJCC7 Staging	0.59	[0.50 - 0.71]	2 x 10^-09
Age	0.87	[0.74 - 1.02]	0.09
CD3	0.80	[0.63 - 1.02]	0.07
CD68	0.84	[0.66 - 1.06]	0.14
CD66b	0.87	[0.69 - 1.10]	0.25
CD8	1.17	[0.92 - 1.47]	0.20
CD45RO	0.86	[0.69 - 1.07]	0.17
FOXP3	0.94	[0.72 - 1.23]	0.67

0.5 1 2

Adjusted Hazard Ratio for geographic locality

Conclusions and Discussion

- Large-scale expression analysis reveals differences in the <u>tumor microenvironment</u> between Asian vs non-Asian GCs

- Non-Asian GCs appear enriched in <u>T-cell pathways</u> (eg CTLA-4) and immune cell infiltrates

- Tumor immunity differences <u>do NOT seem</u> to be due to differences in MSI or EBV frequency

- Adjusting for immune differences (esp CD68/CD3) <u>impacts region-specific survival</u>

- Tumor immunity differences may influence GC <u>immunotherapy trials</u>

Lin et al (in press) *Gut*

Acknowledgements

SGCC
Singapore Gastric
Cancer Consortium