Early Developments of New Agents in Asia

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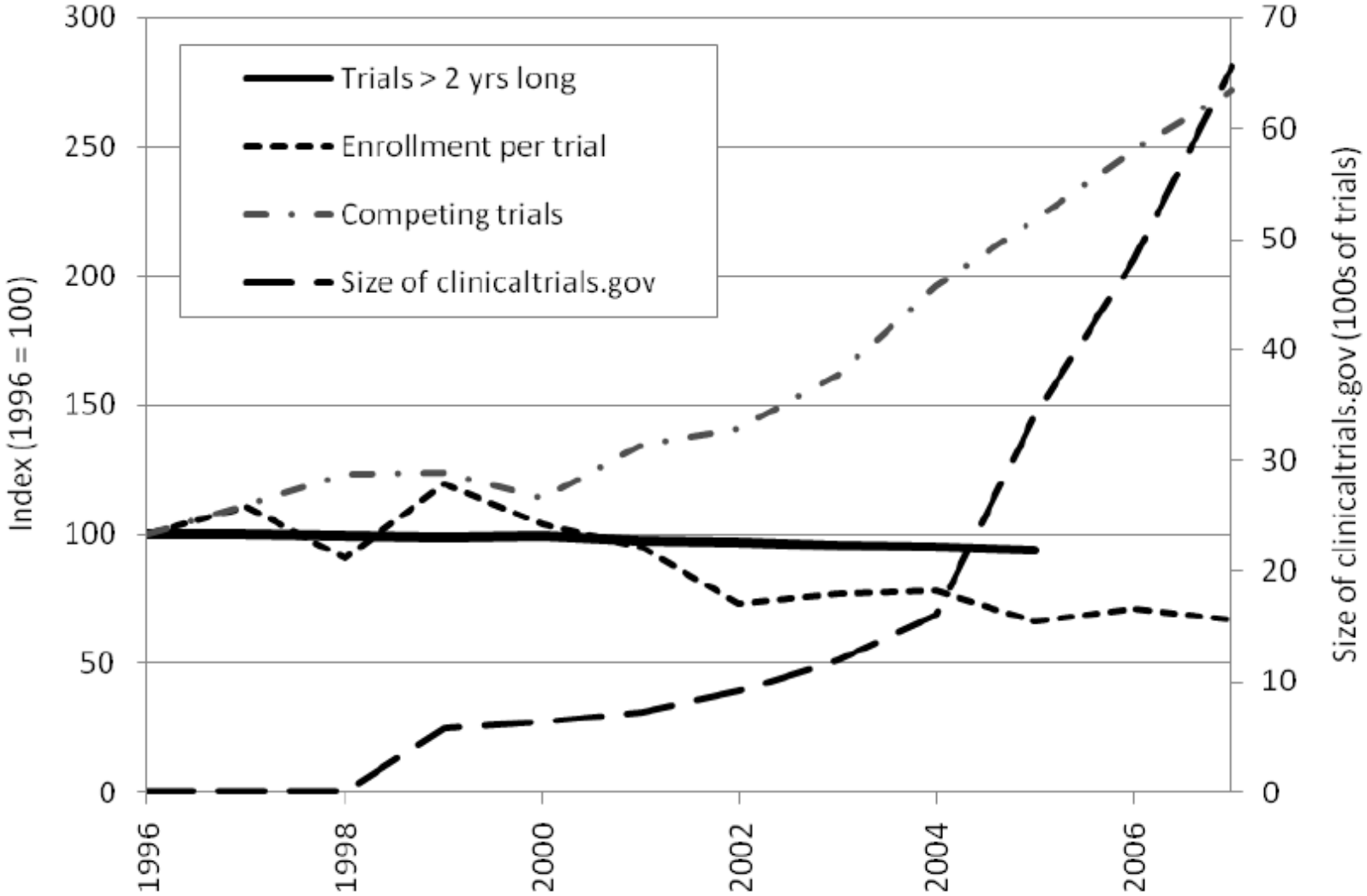
Why Asia?

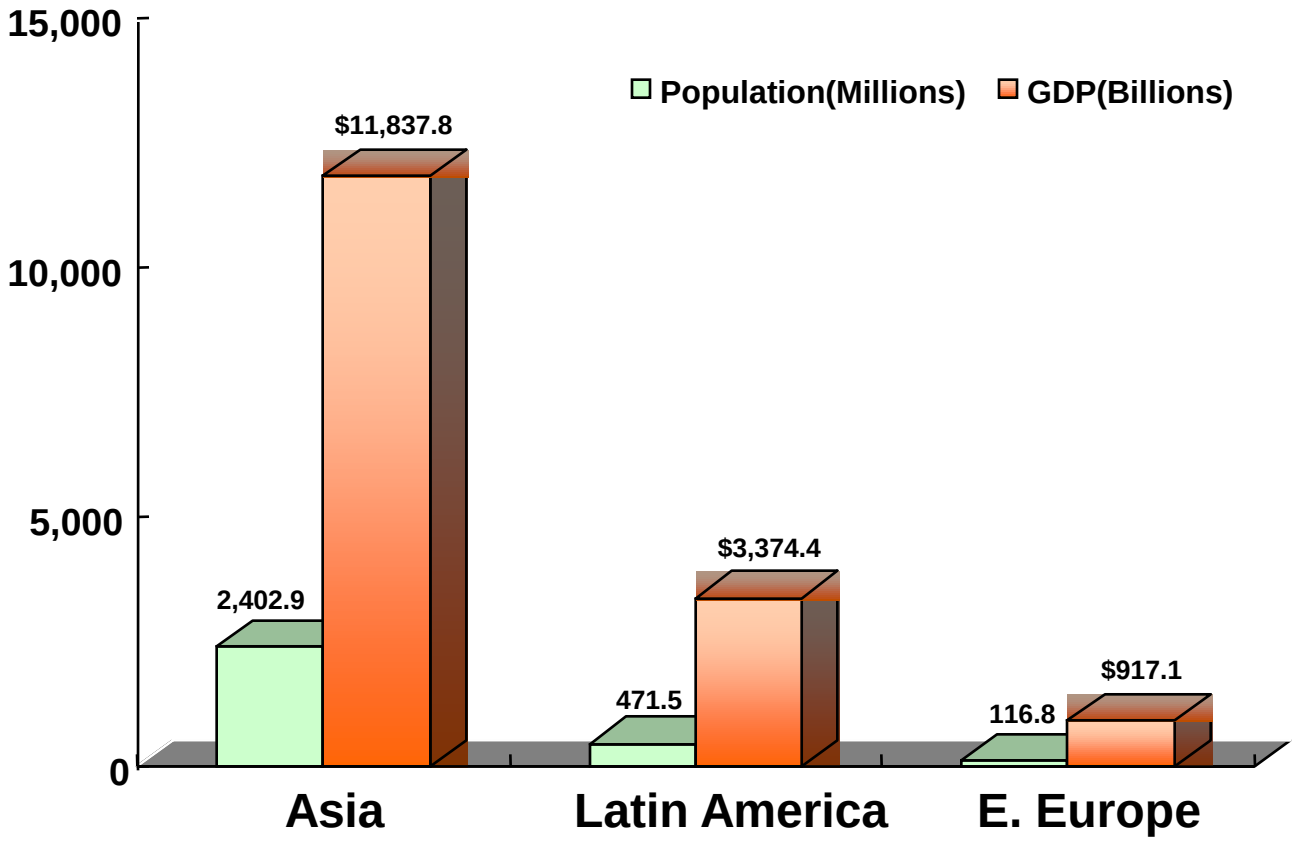
- Resources

Trends in oncology trials during 1996 - 2007



Malani A & PhilipsonT. 2008

Population and output in Ascending regions



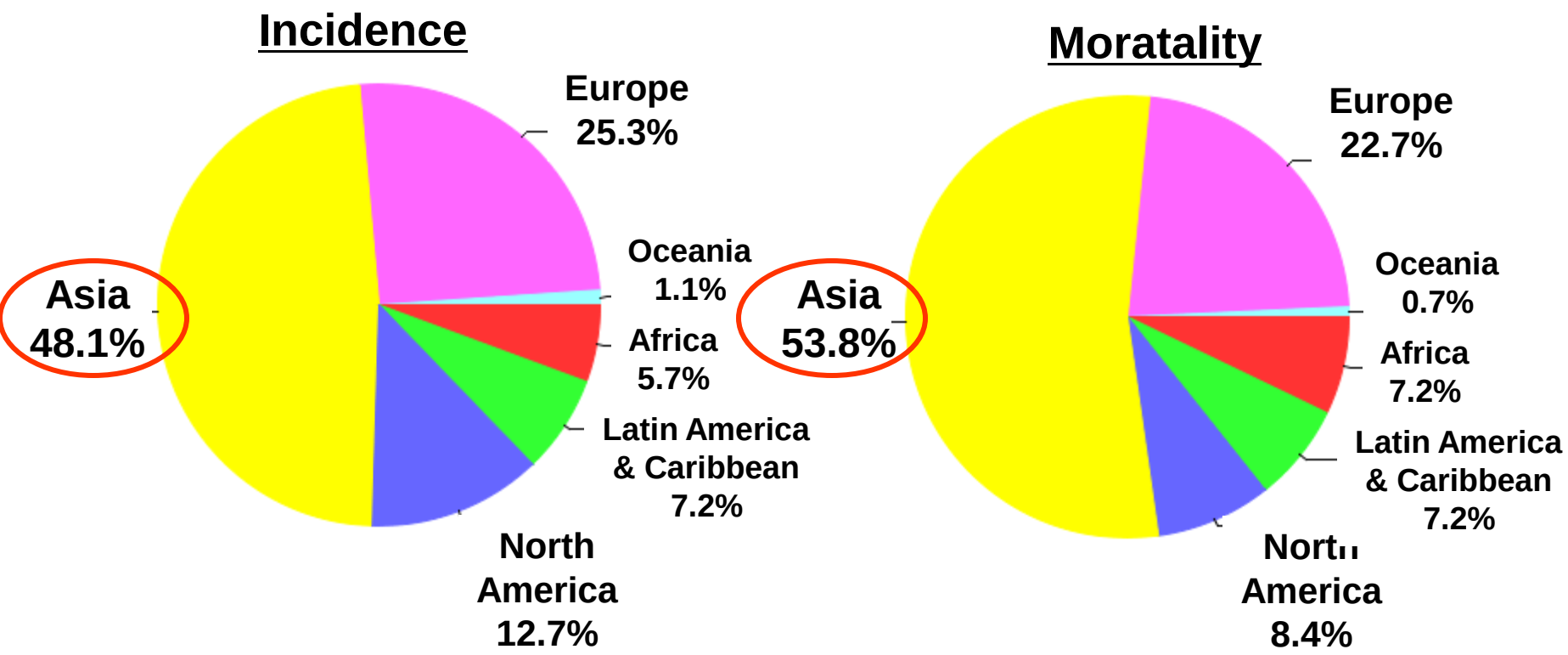
Source: Central Intelligence Agency and Center watch

Why Asia?

- Resources

- Market

Global cancer statistics, 2008

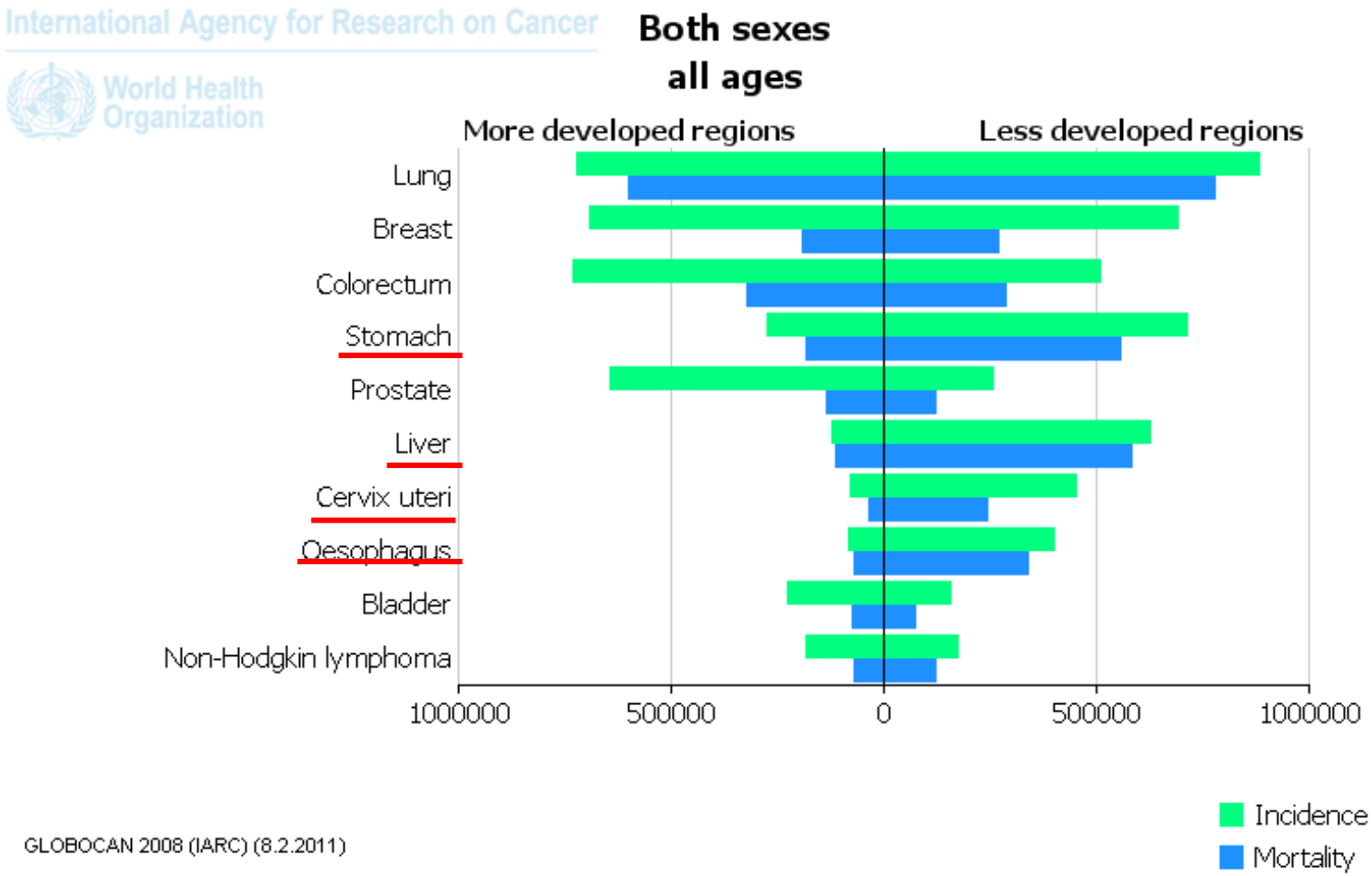


Data source: Globocan 2008 (IARC) 8 2 2011

Why Asia?

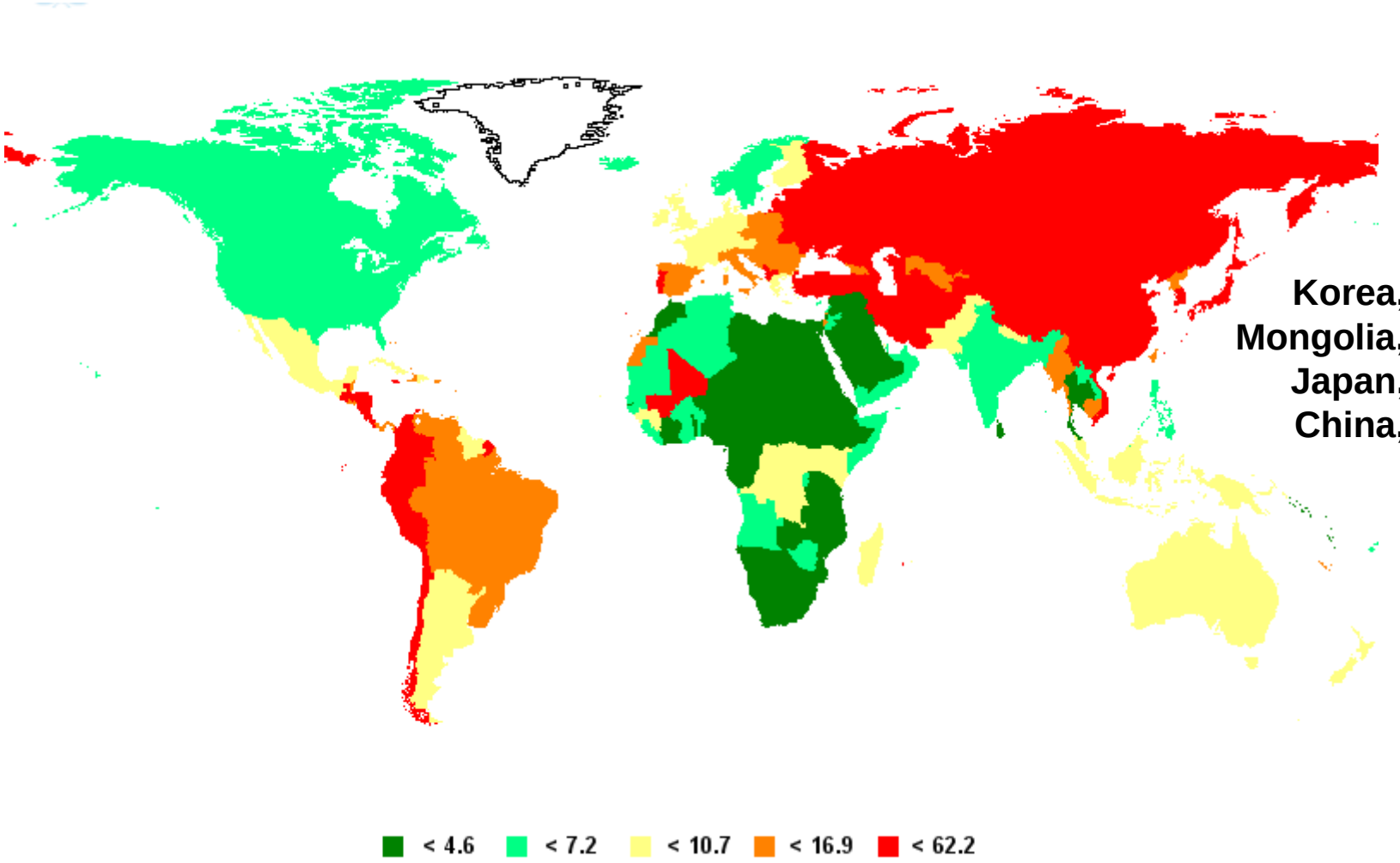
- Resources
- Market
- Epidemiologic difference

Estimated numbers of new cancer cases and deaths, 2008



Data source: Globocan 2008 (IARC) 8 2 2011

Estimated ASR of Stomach cancer in Male

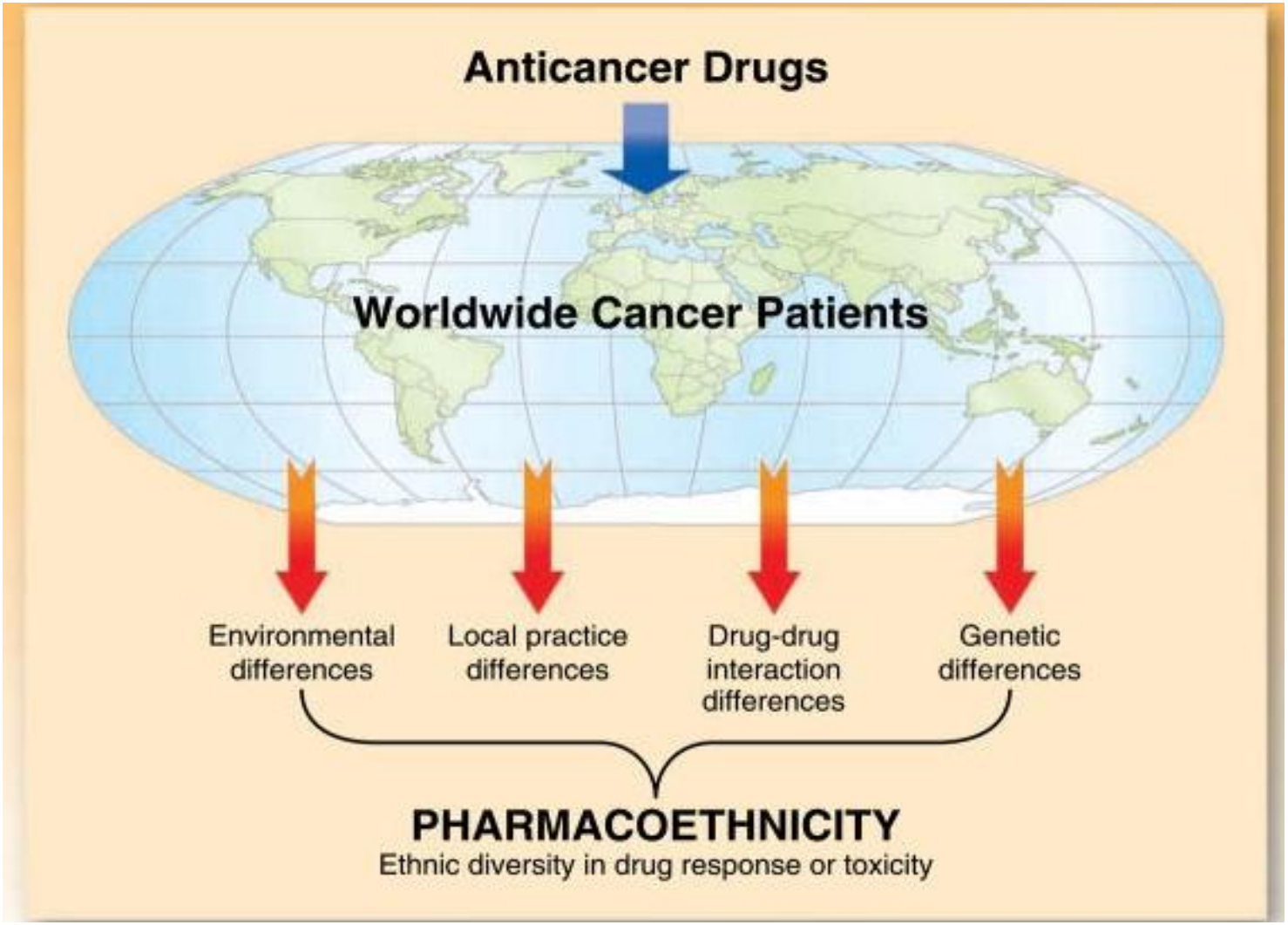


Data source: Globocan 2008 (IARC) 8 2 2011

Why Asia?

- Resources
- Market
- Epidemiologic difference
- Ethnic difference

Cancer Pharmacoethnicity



O'Donnel PH & Dolan ME. Clin Cancer Res 2009

UFT/LV for advanced colorectal cancer

	No.	Response	Gr ¾ Diarrhea
Japanese	44	36.4%	9%
American	44	34.1%	22%

Shirao K. et al. JCO, 2004

Phase I trials of TS-1*

	MTD	DLT
Japan[1]	40 mg/m^2 bid	Leucopenia
Dutch[2]	40 mg/m^2 bid	Diarrhea
U.S.[3]	30 mg/m^2 bid	Diarrhea etc.

* schedule; daily for 28 days

[1]Taguchi T et al. Jpn J Cancer Chemother 1997, Hirata K et al. Clin Cancer Res 1999; [2]van Groeningen CJ et al. JCO 2000; [3]Hoff PM et al. Clin Cancer Res 2003

≥ Grade III diarrhea in phase II trials*

	No. of pts	≥ Gr. III Diarrhea
European[1]	7	2 (28.6%)
Japanese[2]	62	1 (1.6%)
Korean[3]	31	2 (6.5%)

*schedule; 80 mg/m^2/day for 28 days

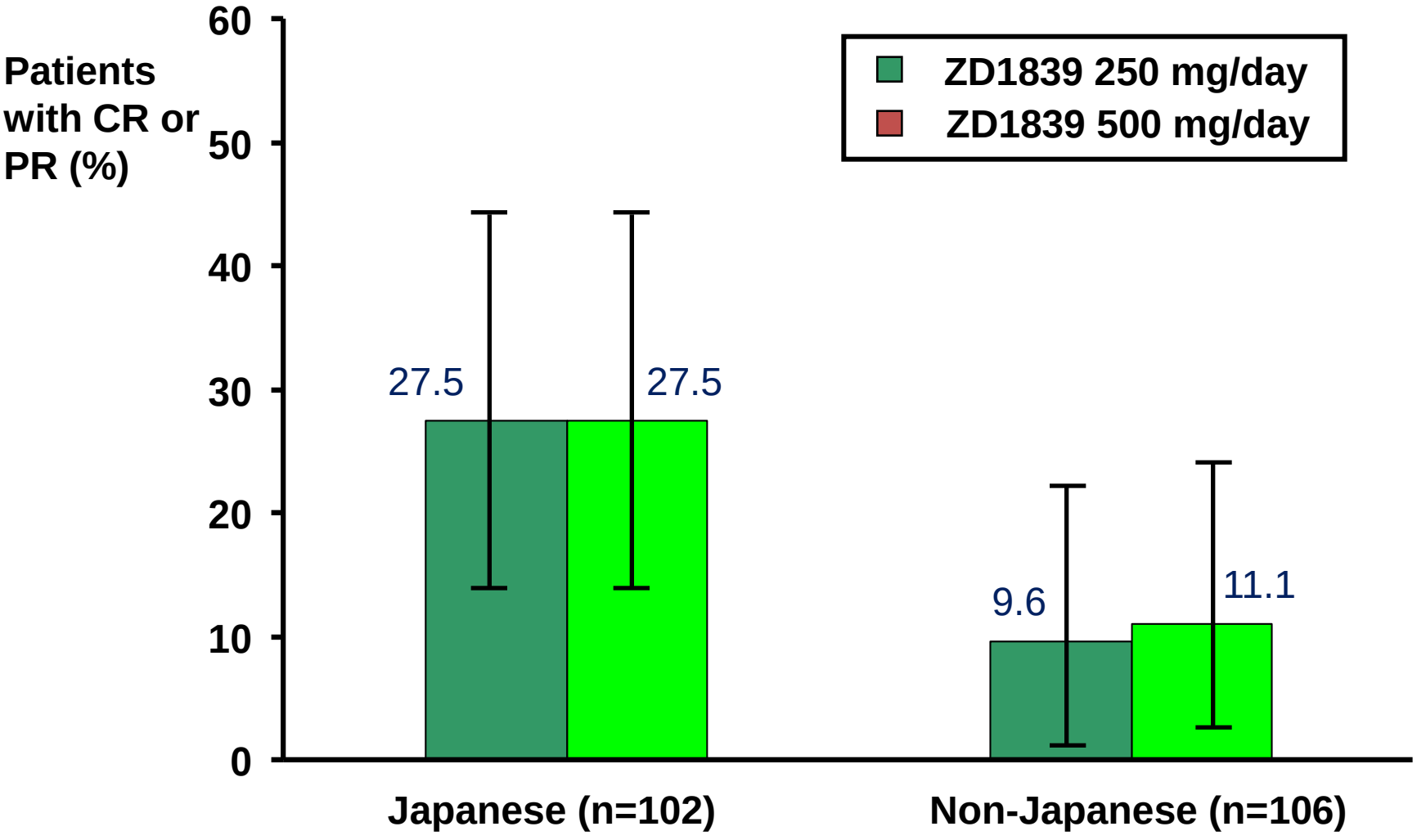
[1]Chollet P et al. Eur J Cancer 2003; [2]Ohtsu et al. Br J cancer 2000; [3]Jeung HC et al. Oncologist 2007

Pharmacokinetics of TS-1

	5-FU C_{max} (mmol/L)	5-FU AUC (mmol/L • min)
Japanese[1]	0.98 - 0.32	331.6 - 124.9
Dutch[2]	1.38 - 0.23	522.6 - 152.8
U.S.[3]	1.34 - 0.17	460.6 - 26.1

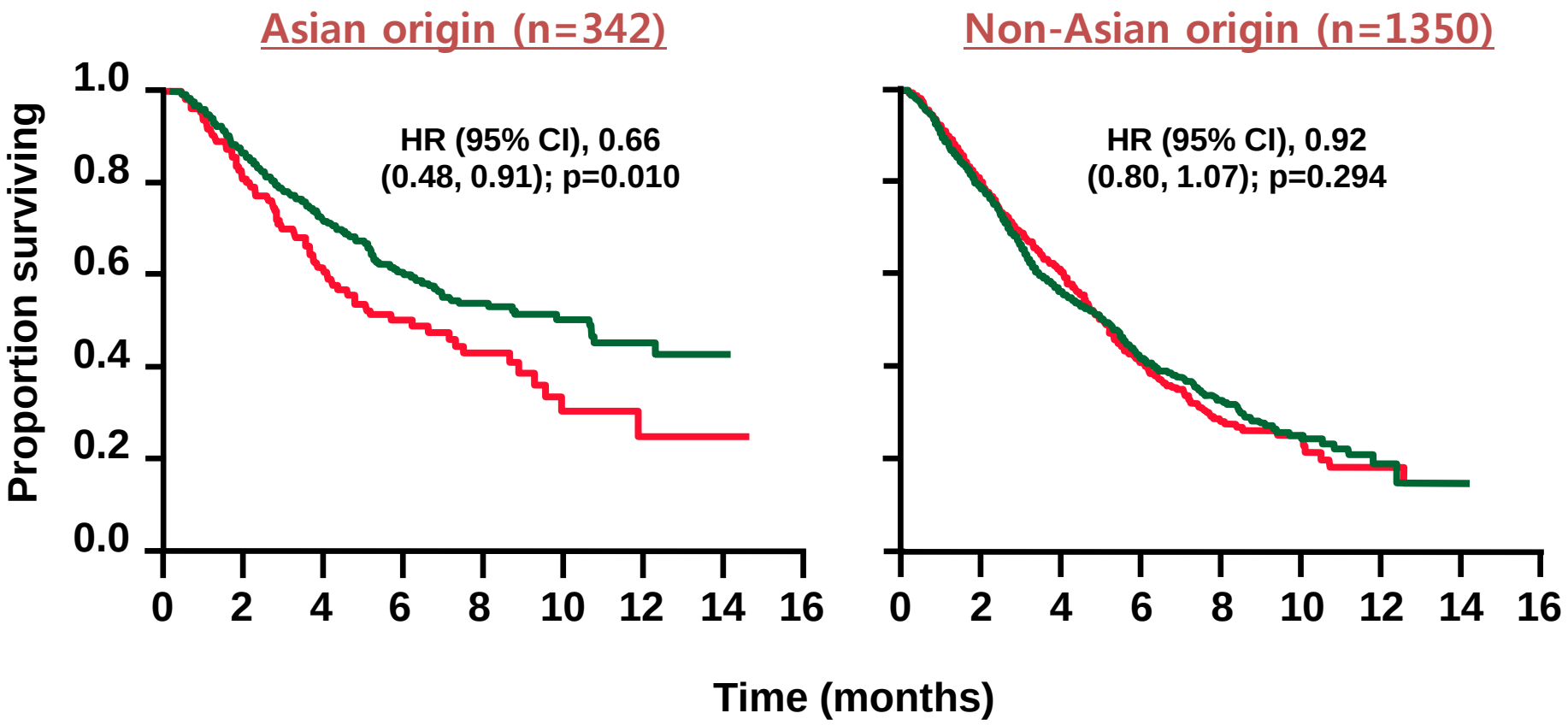
[1]Hirata K et al. Clin Cancer Res 1999; [2]van Groeningen CJ et al. JCO 2000; [3]Hoff PM et al. Clin Cancer Res 2003

IDEAL 1: Tumor response to gefitinib



Fukuoka M et al. JCO 2003:21:2237-46

ISEL Study; Survival by race



Thatcher N, et al. Lancet 2005:366:1527-37

Response prediction to gefitinib

VOLUME 23 · NUMBER 11 · APRIL 10 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Predictive and Prognostic Impact of Epidermal Growth Factor Receptor Mutation in Non–Small-Cell Lung Cancer Patients Treated With Gefitinib

Sae-Won Han, Tae-You Kim, Pil Gyu Hwang, Soohyun Jeong, Jeongmi Kim, In Sil Choi, Do-Youn Oh, Jee Hyun Kim, Dong-Wan Kim, Doo Hyun Chung, Seock-Ah Im, Young Tae Kim, Jong Seok Lee, Dae Seog Heo, Yung-Jue Bang, and Noe Kyeong Kim

From the Department of Internal Medicine, Department of Pathology, and Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital; Department of Internal Medicine, Seoul Municipal Boramae Hospital; Department of Internal Medicine, Seoul National University Bundang Hospital; Cancer Research Institute, Seoul National University College of Medicine; Petagen Inc, Seoul, Korea.

Submitted September 21, 2004; accepted December 21, 2004.

Supported in part by a grant from the Korean Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (03-PJ10-PG13-GD01-0002); and by AstraZeneca Pharmaceuticals, Seoul, Korea.

Terms in blue are defined in the glossary, found at the end of this issue and online at www.jco.org.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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A B S T R A C T

Purpose
This study was undertaken to investigate the effects of epidermal growth factor receptor (EGFR) mutation and its downstream signaling on response and survival in non-small-cell lung cancer (NSCLC) patients treated with gefitinib.

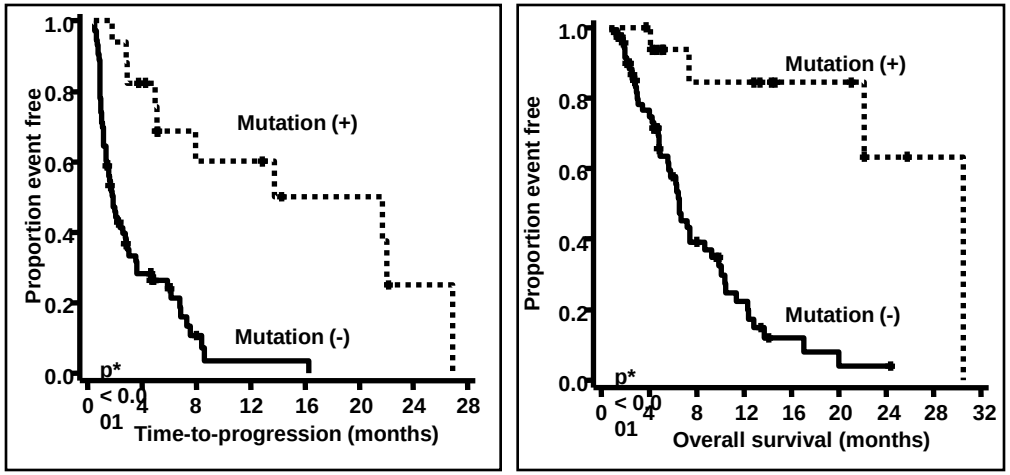
Patients and Methods
For 90 consecutive NSCLC patients who had received gefitinib, EGFR mutation was analyzed by DNA sequencing of exons 18, 19, 21, and 23 in the EGFR tyrosine kinase domain. Expressions of phosphorylated (p) -Akt and p-Erk were determined via immunohistochemistry. Response rate, time to progression (TTP), and overall survival were compared between each group according to EGFR mutation, as well as p-Akt and p-Erk expression.

Results
Seventeen patients (18.9%; 95% CI, 10.8 to 27.0) harbored EGFR mutations. These mutations include deletions in exon 19 in seven patients, L858R in six patients, G719A in three patients, and a novel A859T in one patient. Response rate in patients with EGFR mutation was 64.7% (11 of 17 patients; 95% CI, 42.0 to 87.4), in contrast to 13.7% (10 of 73 patients; 95% CI, 5.8 to 21.6) in patients without mutation ($P < .001$). Moreover, these 17 patients with EGFR mutation had significantly prolonged TTP (21.7 v 1.8 months; $P < .001$) and overall survival (30.5 v 6.6 months; $P < .001$) compared with the remaining 73 patients without mutation. Although no significant correlation was detected between EGFR mutation and expressions of p-Akt or p-Erk, p-Akt overexpression was associated with prolonged TTP in patients with EGFR mutation.

Conclusion
Our data further support the importance of EGFR mutation with regard to gefitinib sensitivity. In addition to its predictive role, EGFR mutation confers significant survival benefits on NSCLC patients treated with gefitinib.

J Clin Oncol 23:2493-2501. © 2005 by American Society of Clinical Oncology

- 90 NSCLC pts treated with gefitinib
- 17 (18.9%) had EGFR mutation
- 15/17 (88.2%) benefited from gefitinib including 11 PR
- RR 64.7% *vs*. 13.7% (p<0.001)



Han SW et al. JCO 2005;23;2593

CLINICAL TRIALS (ISTs only) ❖ *Source: www.clinicaltrials.gov, 2010. 12. 31*

	2005			2006			2007			2008			2009			2010		
1	US	4103	47.85%	US	3710	43.54%	US	3557	40.69%	US	4664	39.48%	US	3488	36.91%	US	2602	33.48%
2	Germany	4791	5.59%	Germany	5679	6.66%	Germany	11841	13.55%	France	13057	11.05%	Germany	8107	8.58%	Germany	8423	10.84%
3	Canada	4503	5.25%	France	4434	5.20%	France	3420	3.91%	Germany	8477	7.17%	France	7744	8.19%	France	7968	10.25%
4	France	3950	4.61%	Canada	3942	4.63%	Canada	2856	3.27%	Japan	4023	3.40%	Canada	2894	3.06%	**Japan**	**4610**	**5.93%**
5	Italy	2575	3.00%	UK	2607	3.06%	Spain	2348	2.69%	Canada	3862	3.27%	Spain	2771	2.93%	Canada	2718	3.50%
6	UK	2530	2.95%	Spain	2375	2.79%	Italy	2154	2.46%	Spain	3146	2.66%	Belgium	2676	2.83%	Spain	1805	2.32%
7	Spain	2177	2.54%	Italy	2000	2.35%	UK	2146	2.45%	Italy	2774	2.35%	Japan	2674	2.83%	Italy	1772	2.28%
8	Netherlands	1758	2.05%	Japan	1715	2.01%	Japan	2022	2.31%	UK	2709	2.29%	Italy	2463	2.61%	Czech republic	1654	2.13%
9	Japan	1683	1.96%	Poland	1646	1.93%	Russia	1793	2.05%	Russia	2152	1.82%	UK	2386	2.52%	UK	1544	1.99%
10	Australia	1599	1.86%	Russia	1559	1.83%	Poland	1741	1.99%	Poland	1995	1.69%	Poland	2177	2.30%	Russia	1534	1.97%
11	Belgium	1422	1.66%	Netherlands	1391	1.63%	Belgium	1670	1.91%	Belgium	1815	1.54%	Russia	2138	2.26%	Belgium	1392	1.79%
12	Poland	1318	1.54%	Australia	1360	1.60%	Australia	1337	1.53%	India	1560	1.32%	Australia	1340	1.42%	Poland	1276	1.64%
13	Sweden	1227	1.43%	Belgium	1350	1.58%	Netherlands	1084	1.24%	Czech republic	1509	1.28%	India	1323	1.40%	**Korea**	**1145**	**1.47%**
14	Denmark	934	1.09%	Brazil	1071	1.26%	India	1029	1.18%	Australia	1483	1.26%	**Korea**	**1222**	**1.29%**	**China**	**1078**	**1.39%**
15	Russia	911	1.06%	Argentina	1036	1.22%	Hungary	983	1.12%	Netherlands	1419	1.20%	Hungary	1122	1.19%	**India**	**961**	**1.24%**
16	Czech republic	900	1.05%	Czech republic	1022	1.20%	Czech republic	947	1.08%	**Korea**	**1400**	**1.18%**	China	1091	1.15%	Australia	866	1.11%
17	South africa	804	0.94%	India	996	1.17%	Brazil	849	0.97%	Brazil	1236	1.05%	Netherlands	1040	1.10%	Romania	831	1.07%
18	Norway	756	0.88%	Hungary	834	0.98%	Argentina	751	0.86%	Hungary	1146	0.97%	Romania	983	1.04%	Hungary	819	1.05%
19	Hungary	750	0.87%	Austria	812	0.95%	**Korea**	**748**	**0.86%**	China	1125	0.95%	Czech republic	971	1.03%	Brazil	678	0.87%
20	Brazil	690	0.80%	Sweden	803	0.94%	Ukraine	748	0.86%	Romania	1063	0.90%	Brazil	866	0.92%	Ukraine	666	0.86%
21	Finland	649	0.76%	Mexico	790	0.93%	China	745	0.85%	Sweden	1060	0.90%	Sweden	837	0.89%	Sweden	645	0.83%
22	Mexico	591	0.69%	**Korea**	**753**	**0.88%**	Sweden	729	0.83%	Austria	937	0.79%	Austria	801	0.85%	Slovakia	619	0.80%
23	Argentina	587	0.68%	South africa	744	0.87%	Austria	683	0.78%	Argentina	924	0.78%	Mexico	769	0.81%	Austria	615	0.79%
24	**India**	**550**	**0.64%**	Ukraine	703	0.82%	Mexico	650	0.74%	Mexico	841	0.71%	Slovakia	716	0.76%	Netherlands	601	0.77%
25	Switzerland	481	0.56%	Israel	686	0.80%	Israel	605	0.69%	South africa	799	0.68%	South africa	695	0.74%	Mexico	567	0.73%
26	Austria	478	0.56%	China	666	0.78%	South africa	589	0.67%	Ukraine	783	0.66%	Ukraine	670	0.71%	Greece	539	0.69%
27	Israel	411	0.48%	Denmark	549	0.64%	Romania	536	0.61%	Israel	783	0.66%	Israel	669	0.71%	Israel	482	0.62%
28	Greece	390	0.45%	Romania	467	0.55%	Denmark	506	0.58%	Denmark	744	0.63%	Argentina	625	0.66%	Turkey	438	0.56%
29	**China**	**370**	**0.43%**	Finland	420	0.49%	Taiwan	502	0.57%	Slovakia	674	0.57%	Switzerland	620	0.66%	Argentina	422	0.54%

ToGA trial: Patient demographics

Characteristic	F+C n=290	F+C + T 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)
Central / South 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

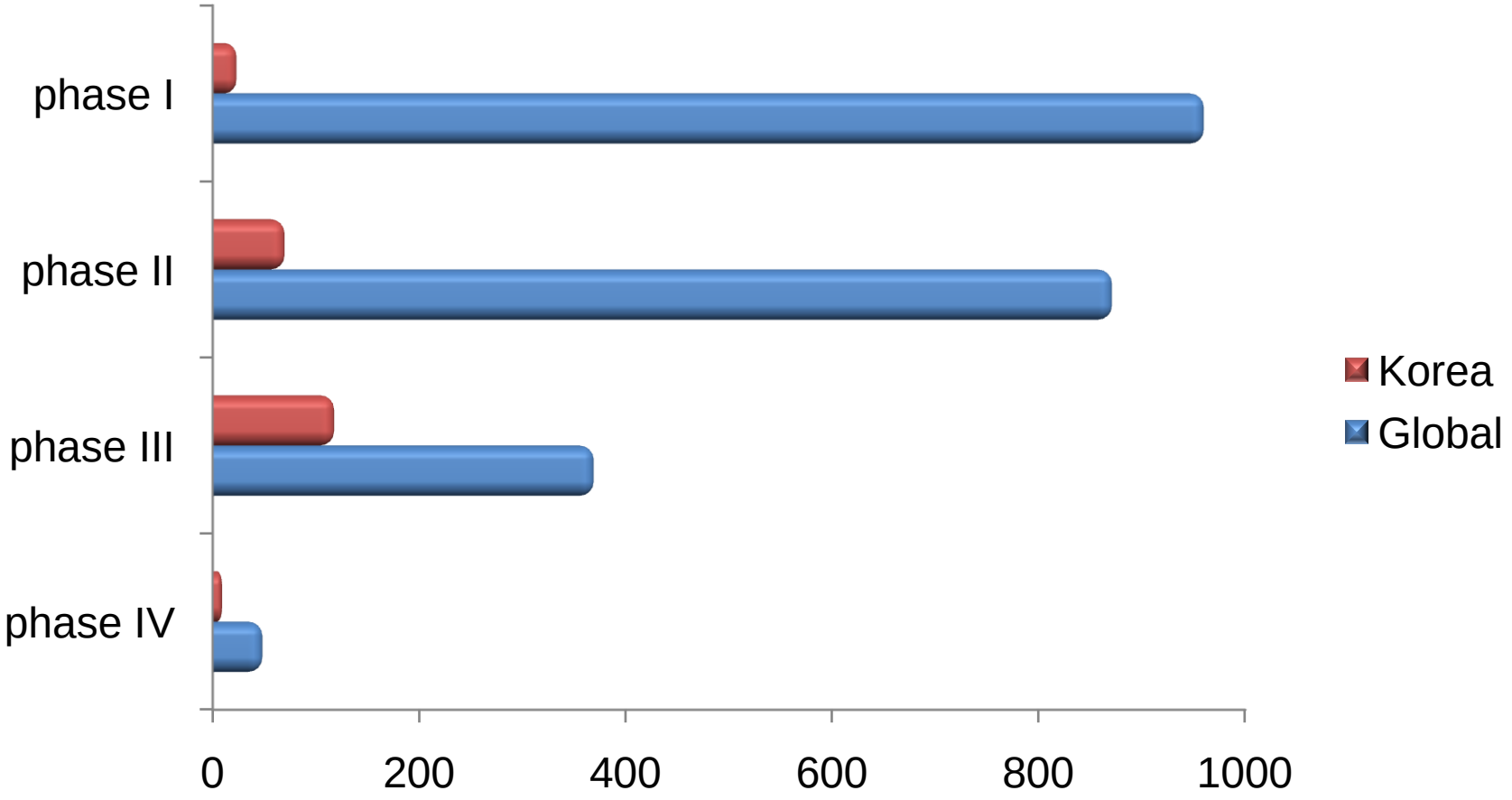
Bang YJ et al. Lancet 2010

AVAGAST trial: Patient characteristics

Number of patients N=774 (%)		XP + Placebo N=387	XP + Bev N=387
Gender	Male	258 (67)	257 (66)
Age, years	Median (range)	59 (22–82)	58 (22–81)
ECOG PS	0–1	367 (95)	365 (94)
	≥2	20 (5)	22* (6)
Region	Asia	188 (49)	188 (49)
	Europe	124 (32)	125 (32)
	Pan-America	75 (19)	74 (19)
Fluoropyrimidine	Capecitabine	365 (94)	364 (94)
	5-FU	22 (6)	23 (6)
Disease status	Locally advanced	9 (2)	20 (5)
	Metastatic	378 (98)	367 (95)

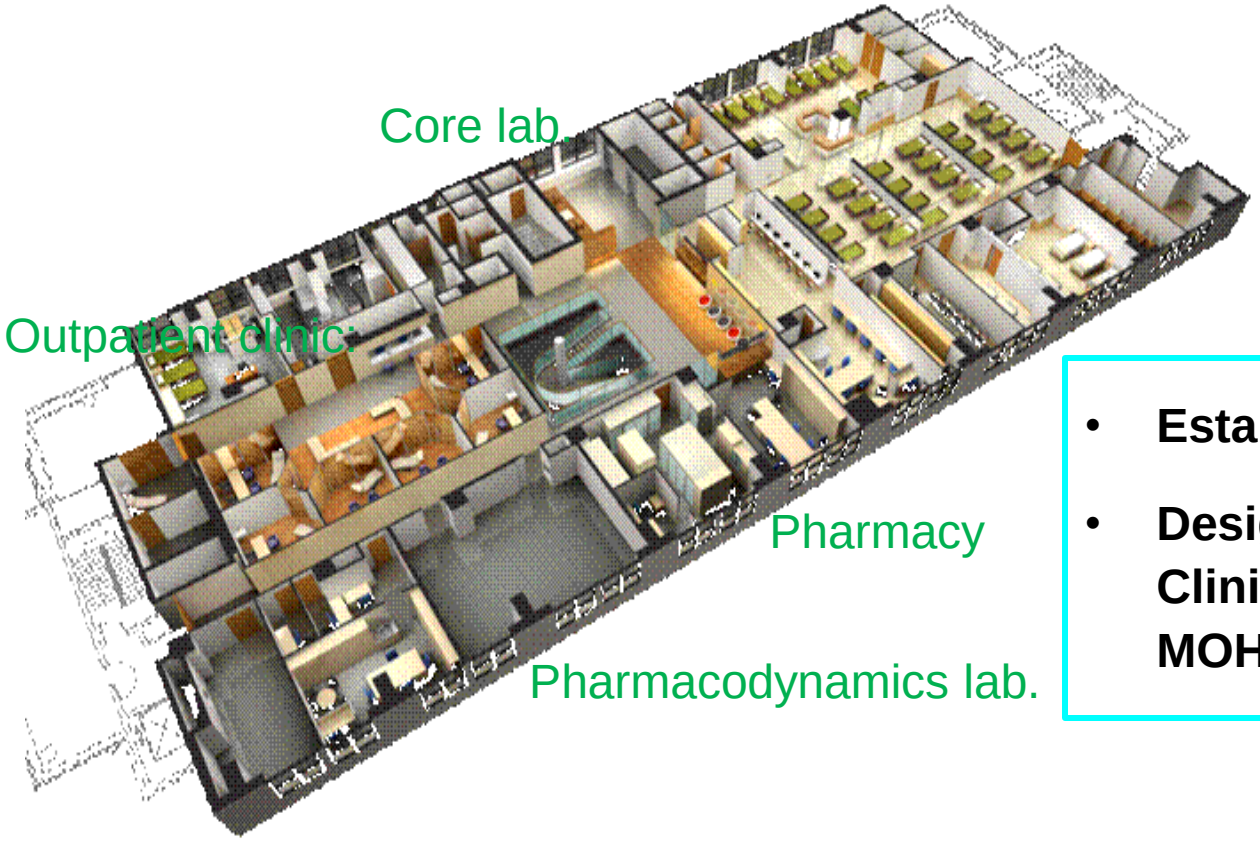
Kang YK et al. ASCO 2010

How about in early trials?



Clinical trial magnifier 2009
CiInicaltrials.gov(Oct 2005 – Jul 2009, interventional studies only)

SNUH CTC: History



- **Established on June 15, 1997**
- **Designated as the Regional Clinical Trials Center by the MOHW in Dec., 2004**

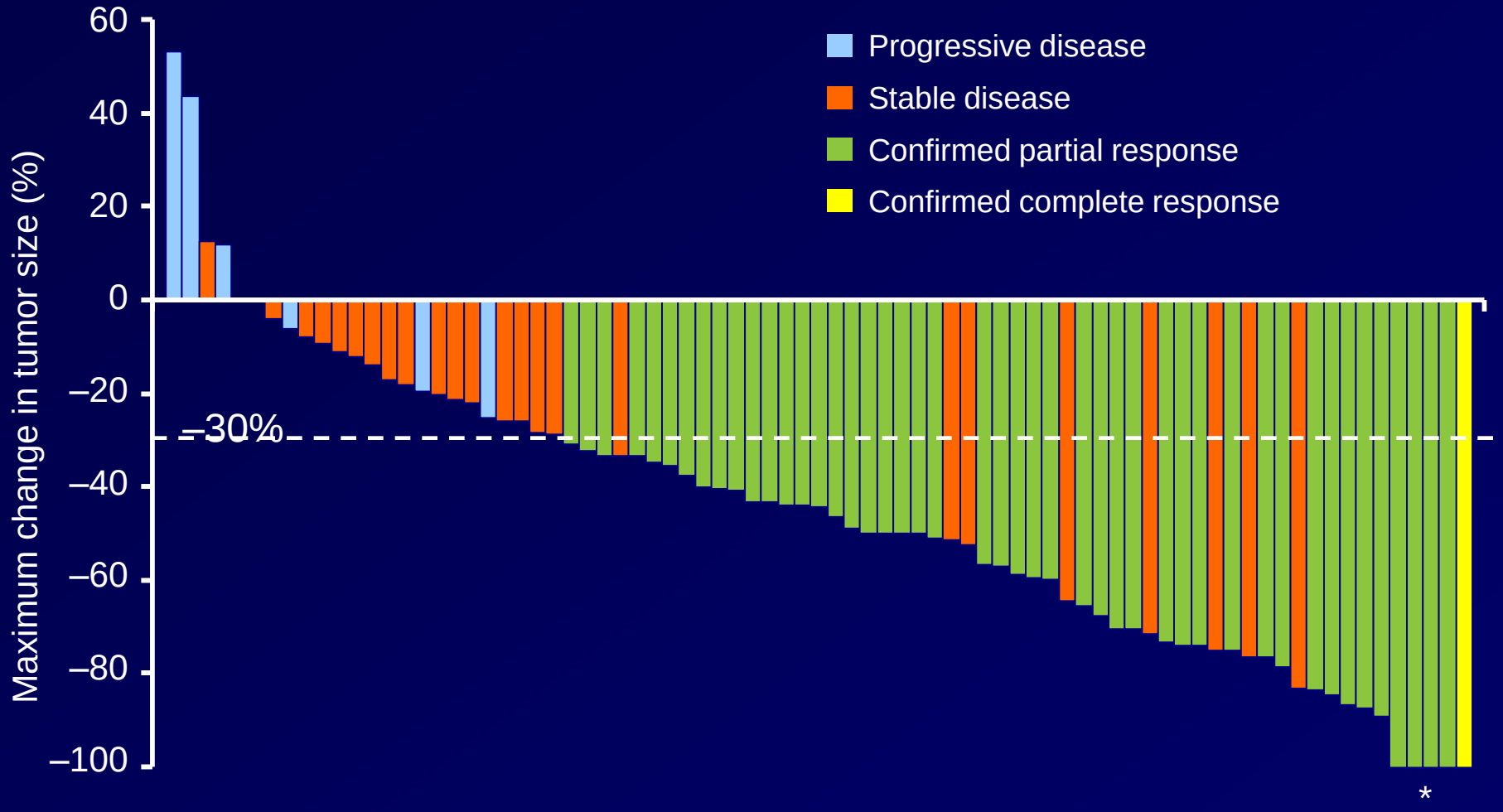
Clinical Activity of the Oral ALK Inhibitor, Crizotinib (PF-02341066), in Patients with *ALK*-positive Non-small Cell Lung Cancer

Bang Y,[1] Kwak EL,[2] Shaw A,[2] Camidge DR,[3] Iafrate AJ,[2] Maki RG,[4] Solomon B,[5] Ou SI,[6] Salgia R,[7] Clark J[2]

[1]Seoul National University, Seoul, Korea; [2]Massachusetts General Hospital, Boston, MA, USA; [3]University of Colorado Cancer Center, Aurora, CO, USA; [4]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [5]Peter MacCallum Cancer Centre, East Melbourne, Australia; [6]University of California at Irvine, Irvine, CA, USA; [7]University of Chicago Cancer Center, Chicago, IL, USA

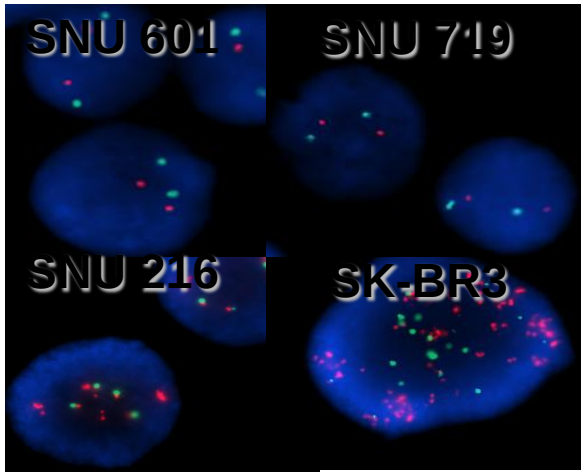
Abstract 3
ASCO Annual Meeting 2010

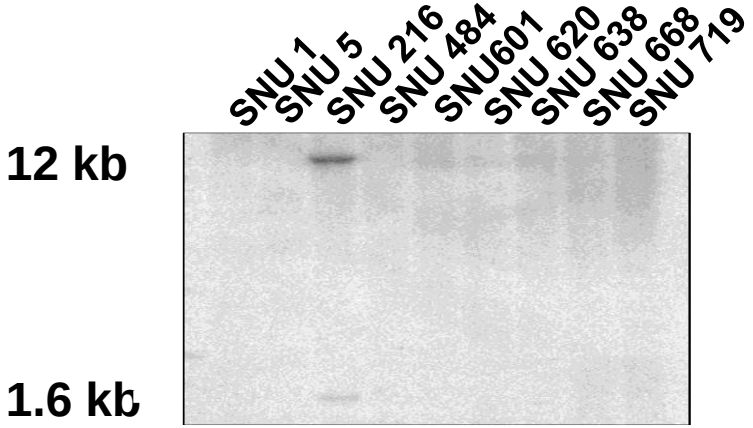
Tumor Responses to Crizotinib for Patients with *ALK*-positive NSCLC

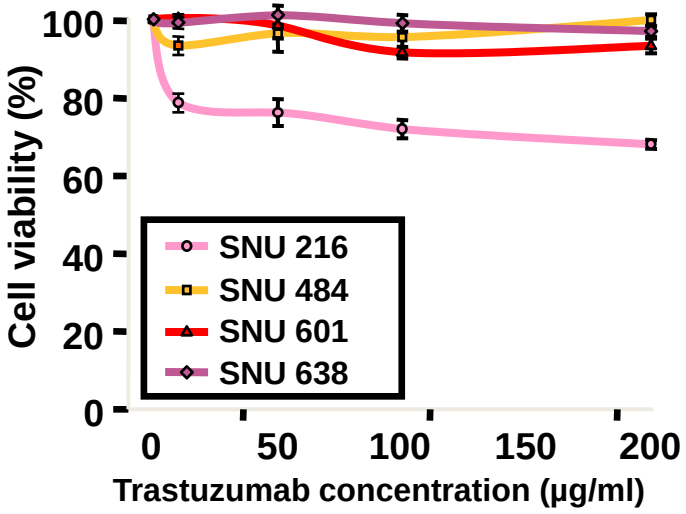


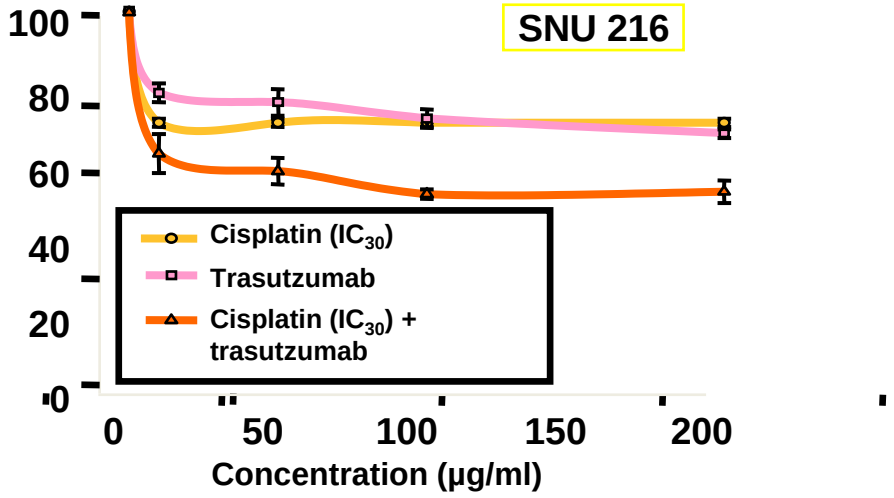
*Partial response patients with 100% change have non-target

In vitro efficacy of trastuzumab



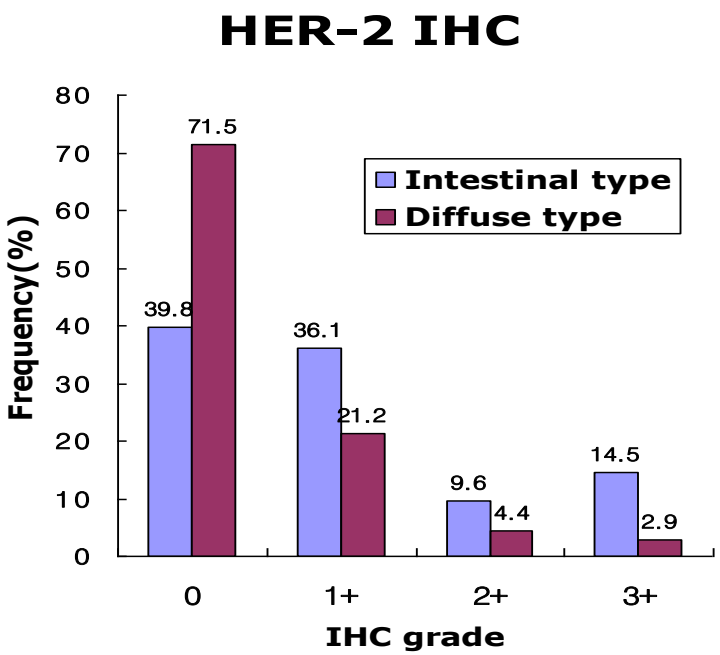


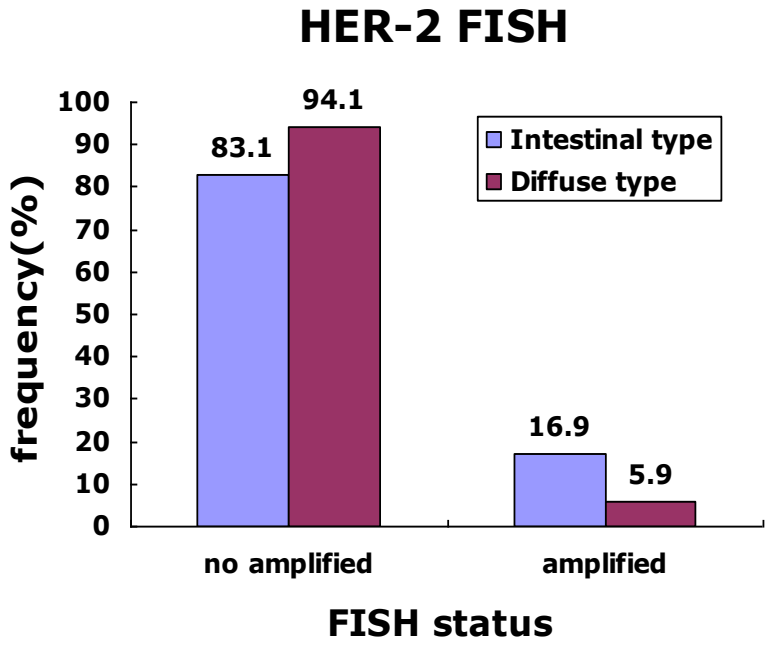




Kim SY, et al. Int J Oncol 2008;32:89-95

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. in press

Conclusion

- Participation of Asians in early oncology trials is essential considering potential ethnic differences.
- It could improve efficiency and effectiveness of clinical trials.
- We need to contribute more to translational and/or early clinical trials.
- Japan-Korea collaboration can further enhance the efficiency of early oncology trials.