

Asian anti-angiogenic experience in mRCC

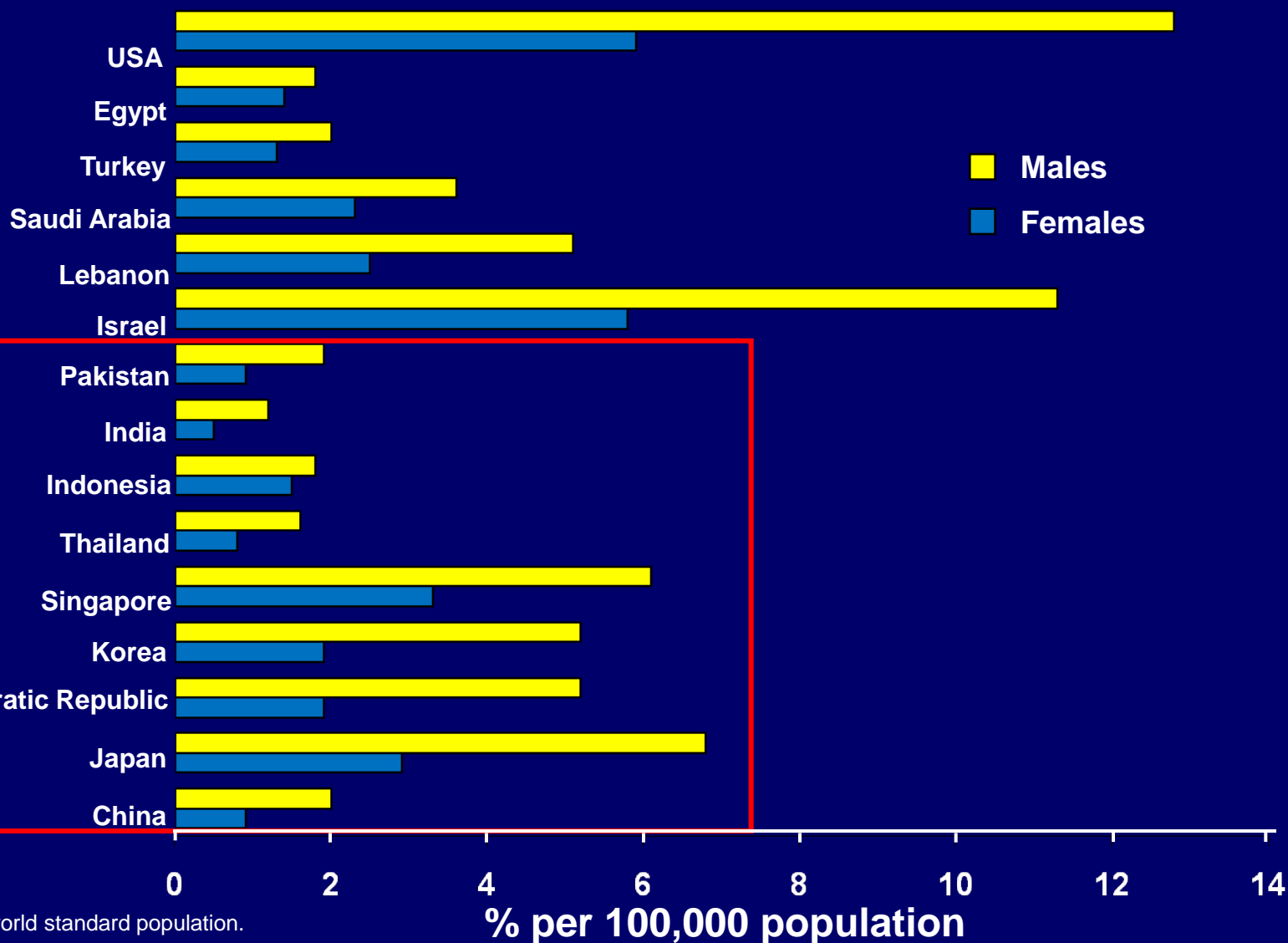
Sun Young Rha (羅善英), M.D., Ph.D.

Medical Oncology, Internal Medicine

Yonsei Cancer Center, Cancer Metastasis Research Center

Yonsei University Health System, Seoul, Korea

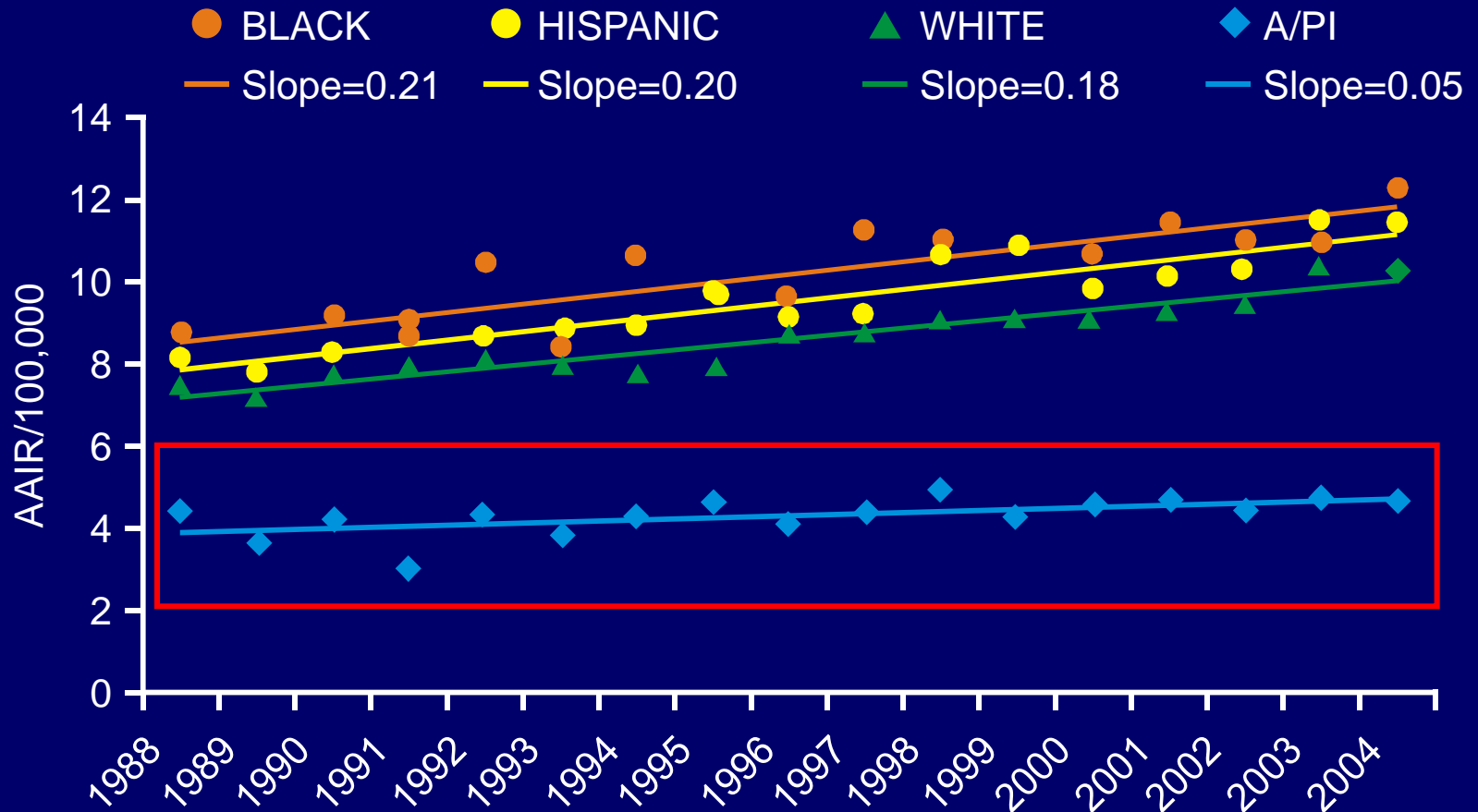
Kidney Cancer: Age-standardized* Incidence Rates by Country: 2002 Estimates



* To world standard population.

% per 100,000 population

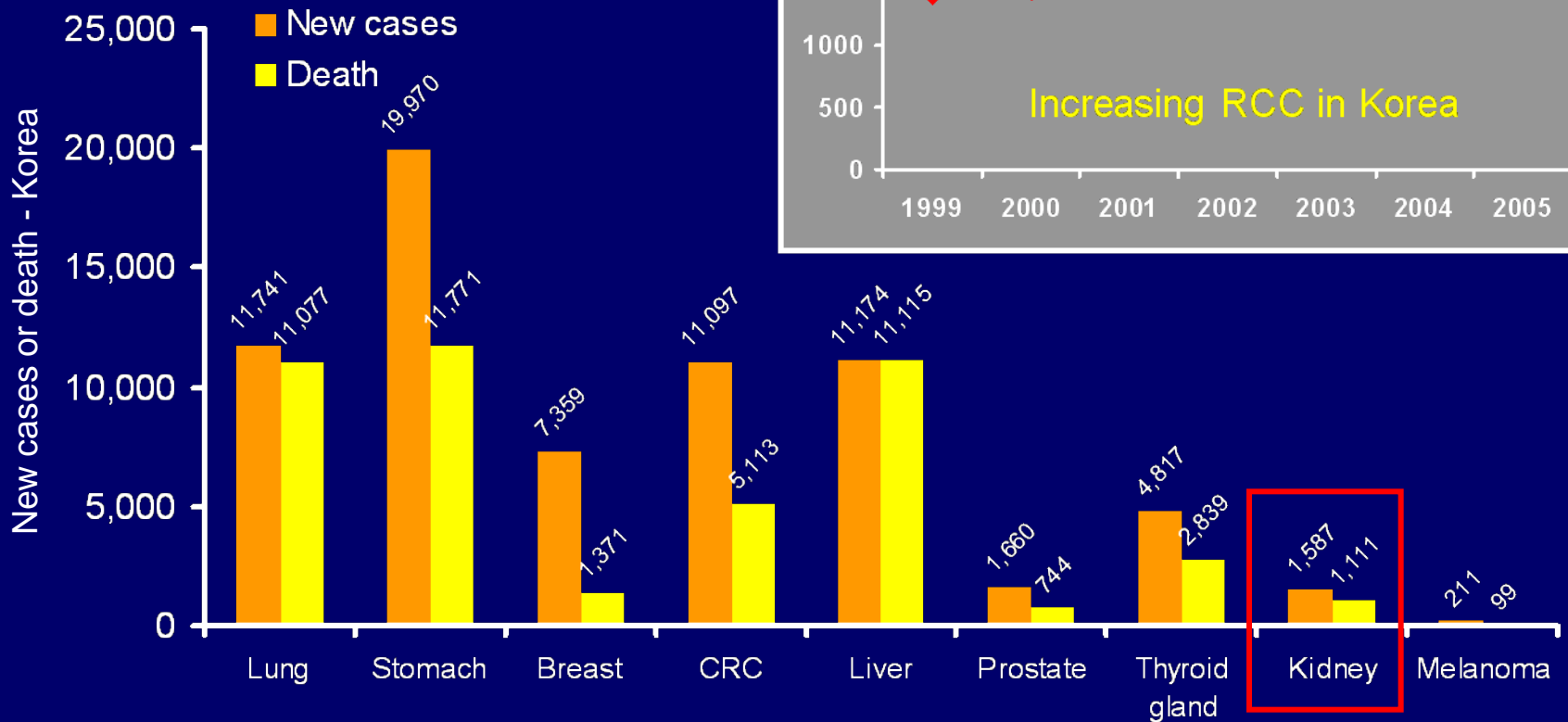
Age Adjusted Incidence Rate by Race/Ethnicity



A/PI = Asian/Pacific Islander

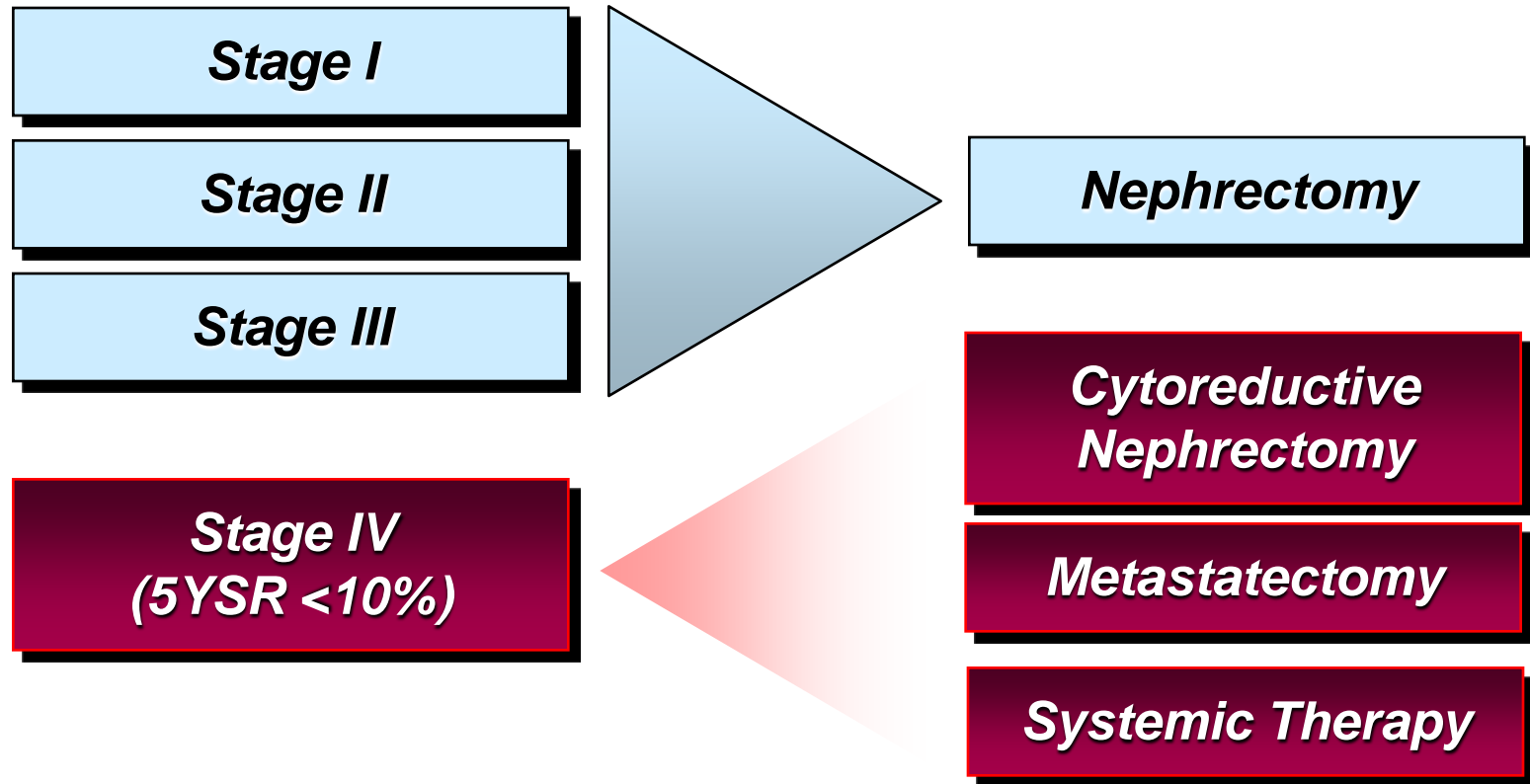
Cancer Incidence & Mortality in Korea

- Most common cancers: stomach, lung, liver, and colorectal
- Kidney cancer: 1.9%



Treatment of Renal Cell Carcinoma

According to Stage at Presentation

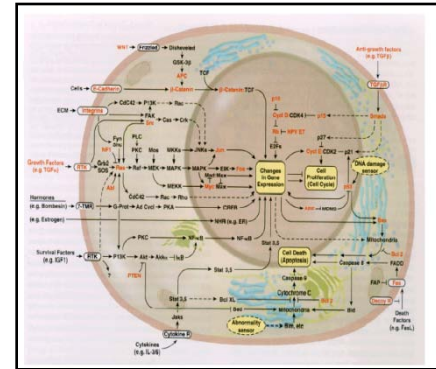


- Cytokines
- Chemotherapy
- **Molecular Targeted Agents**

Molecular targeted agents; cancer-specific, novel targets

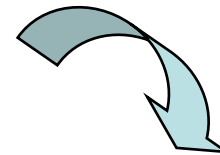
1. Cancer cell specific molecules

- 1) signal transduction pathway
- 2) cell cycle regulation
- 3) tumor suppressor genes

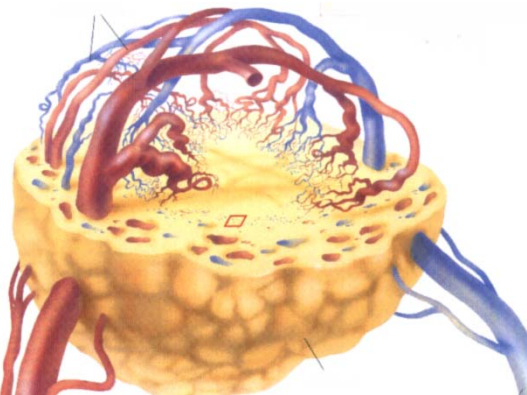


2. Targeting microenvironment: crosstalk between cancer cell and normal host cell

- 1) Invasion
- 2) Metastasis
- 3) Angiogenesis



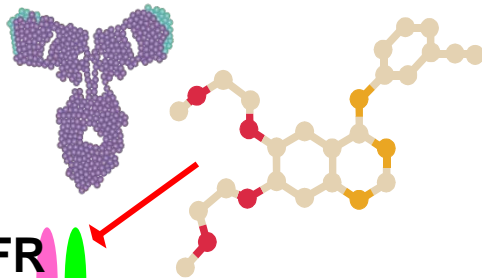
- MMPIs
- Angiogenesis inhibitors



Combination of 2 selective inhibitor:

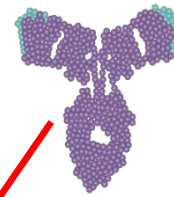
Combined blockade of cancer and endothelial cell pathway

Erlotinib
Cetuximab,
etc



EGFR

Bevacizumab



Pazopanib
Axitinib etc.



Endothelial cells

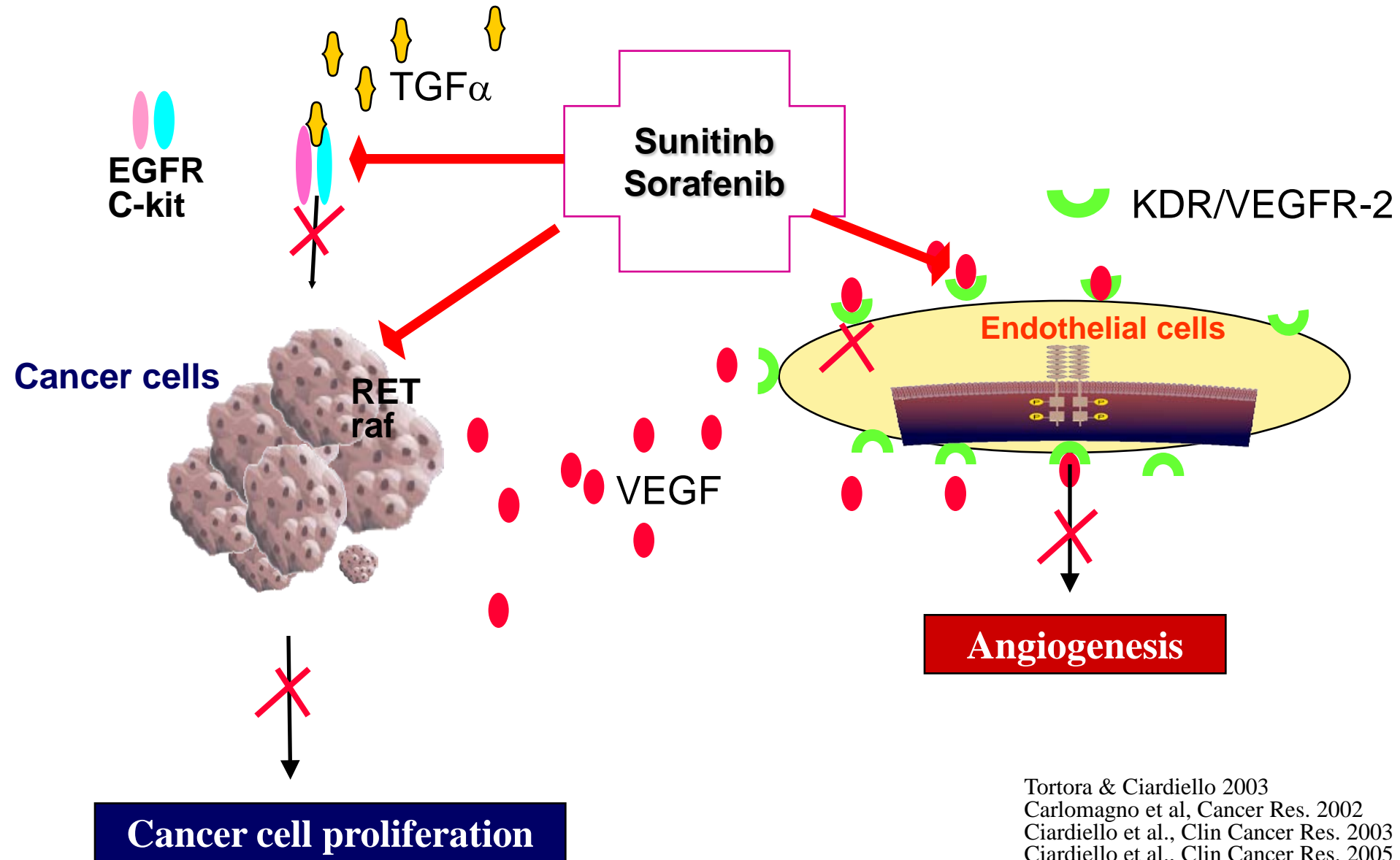
VEGF

Angiogenesis

Cancer cells

Cancer cell proliferation

Multi-targeted agents inhibiting VEGFR/EGFR axis

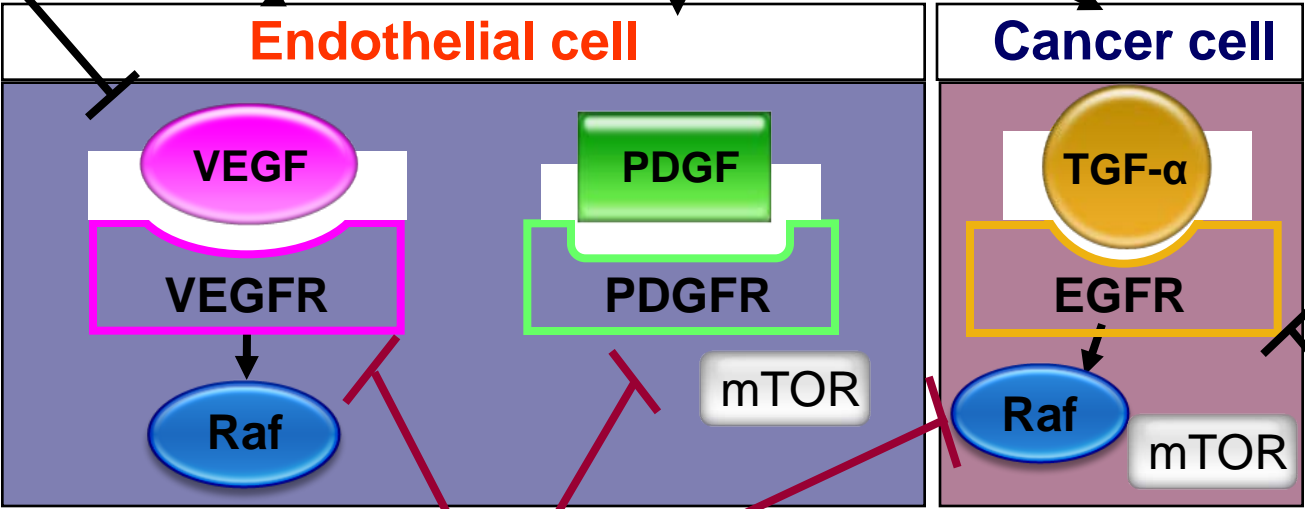


Tortora & Ciardiello 2003
Carlomagno et al, Cancer Res. 2002
Ciardiello et al., Clin Cancer Res. 2003
Ciardiello et al., Clin Cancer Res. 2005
Damiano et al., Clin Cancer Res 2005

Druggable therapeutic targets in RCC



Bevacizumab



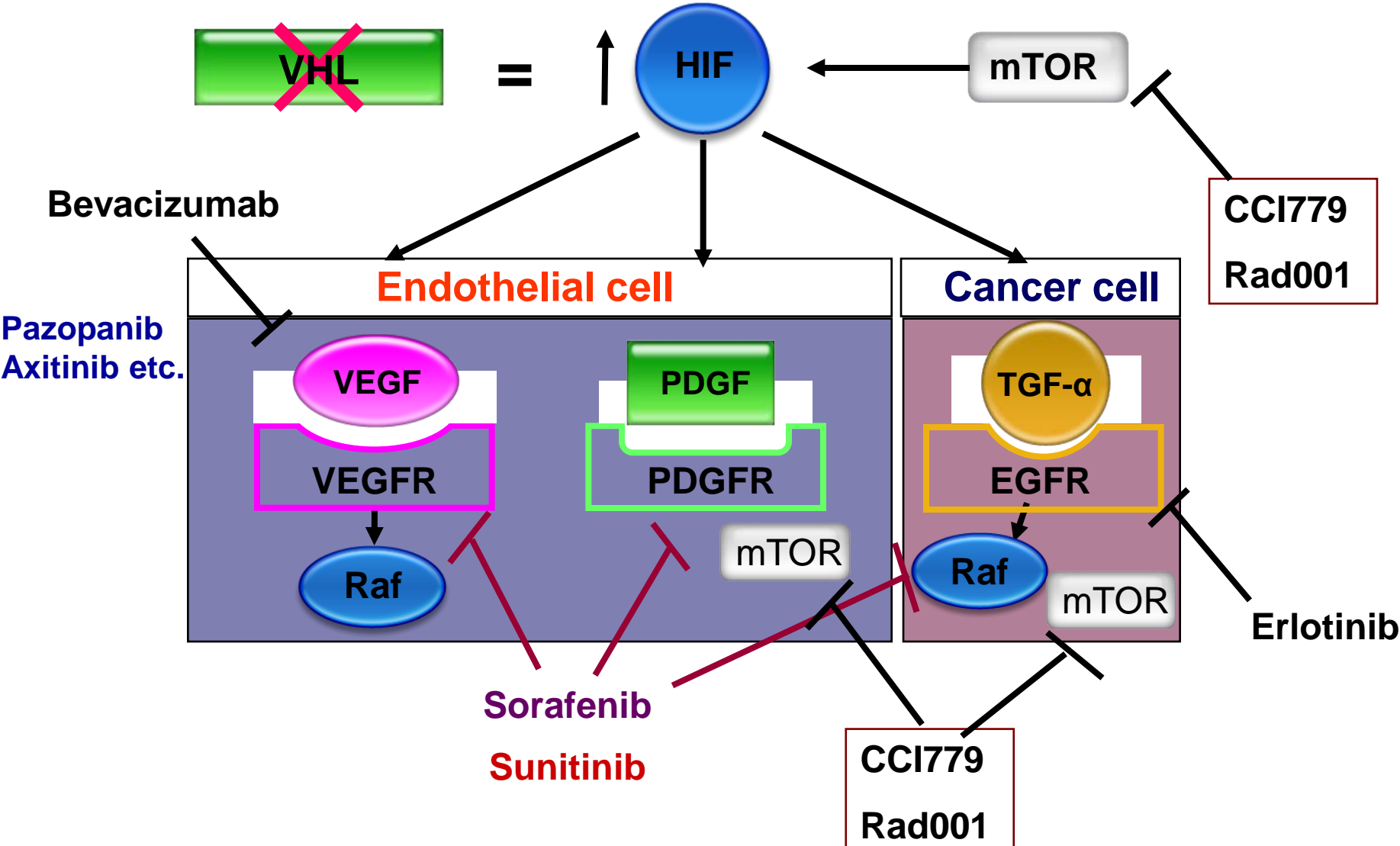
Pazopanib
Axitinib etc.

Sorafenib
Sunitinib

Erlotinib

mTOR = mammalian target of rapamycin

Druggable therapeutic targets in RCC

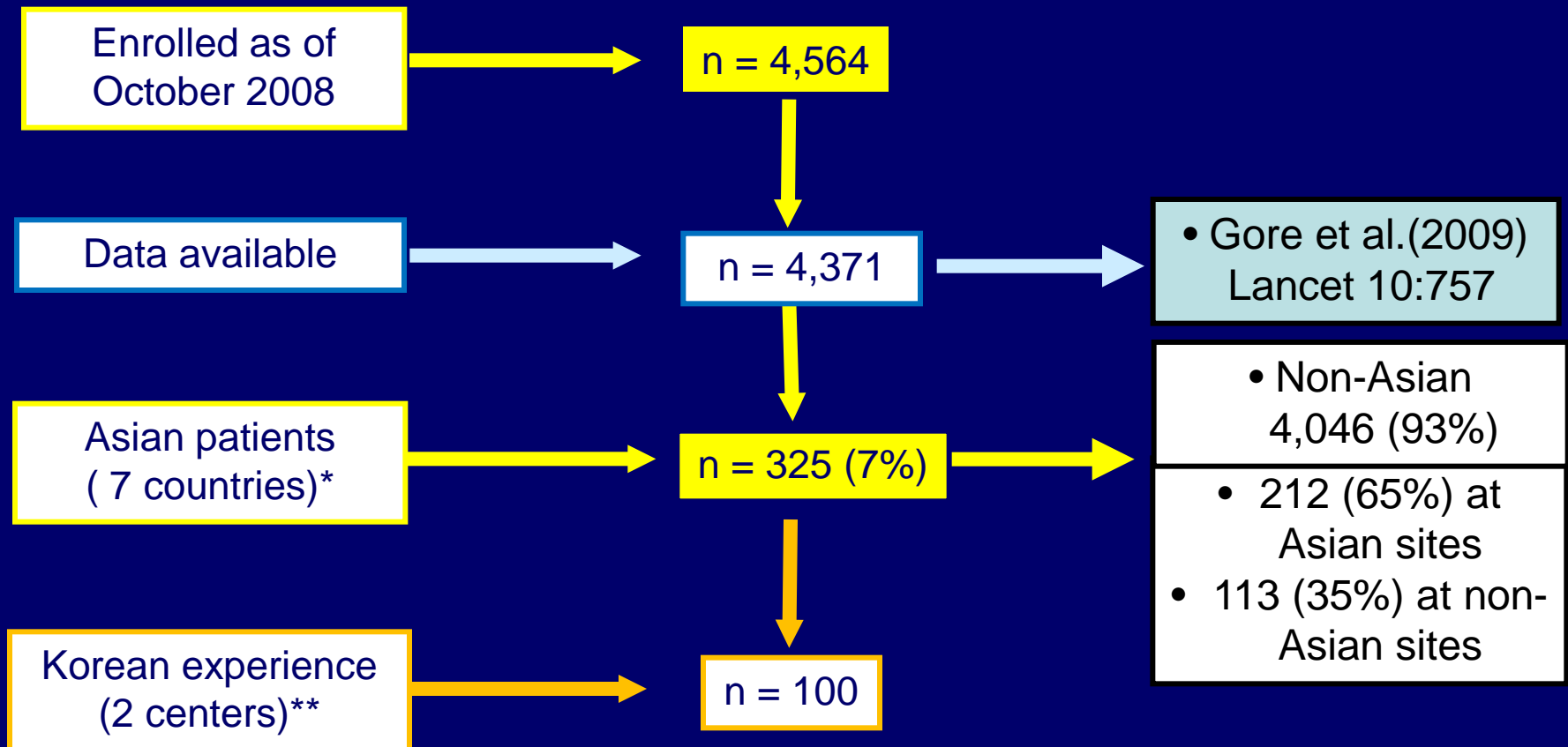


mTOR = mammalian target of rapamycin

RCC Treatment Algorithm: 2010

Setting	Patients	Therapy (level 1)	Other options (level 2)
Advanced/ 1 st line	Good or Intermediate risk	Sunitinib Bevacizumab + IFN Pazopanib(?)	HD IL-2 Sorafenib Temsirolimus Clinical trial
	Poor risk	Temsirolimus	Sunitinib
Advanced/ Refractory	Cytokine failed	Sorafenib	Sunitinib Bevacizumab
	VEGF-TKI failed	Everolimus	
Adjuvant	High risk	Observation	Clinical trial

Asian Experience with Sunitinib in mRCC Among EAP, as of March 2009



* Hong Kong, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand

** Yonsei Cancer Center, Seoul National University Hospital

Patients Characteristics

- Baseline characteristics were similar among patient groups and for Asian patients treated in Asian and non-Asian sites

	Asian	Non-Asian
Nephrectomy	85%	89%
Prior Cytokine Tx	58%	69%

Safety

Grade 3-4 AEs occurring in >5% of patients

	Asian (Asian sites; n=212)	Asian (non-Asian sites; n=113)	Non-Asian (n=4046)
Diarrhea	8 (4, 12)	4 (0, 7)	4 (4, 5)
Fatigue	8 (4, 12)	9 (4, 14)	8 (7, 9)
Stomatitis	5 (2, 8)	<1 (0, 3)	2 (2, 3)
Hand-foot syndrome	17 (12, 22)	7 (2, 11)	6 (5, 6)
Vomiting	4 (2, 7)	<1 (0, 3)	3 (2, 3)
Nausea	2 (0, 4)	0 (0, 0)	2 (2, 3)
Skin discoloration	<1 (0, 1)	0 (0, 0)	<1 (0, 0)
Rash	2 (0, 4)	3 (0, 6)	<1 (0, 1)
Mucosal inflammation	1 (0, 3)	<1 (0, 3)	3 (2, 3)
Thrombocytopenia	26 (20, 32)	13 (7, 20)	7 (6, 7)
Neutropenia	19 (14, 24)	2 (0, 4)	6 (5, 6)
Leukopenia	4 (2, 7)	<1 (0, 3)	2 (1, 2)

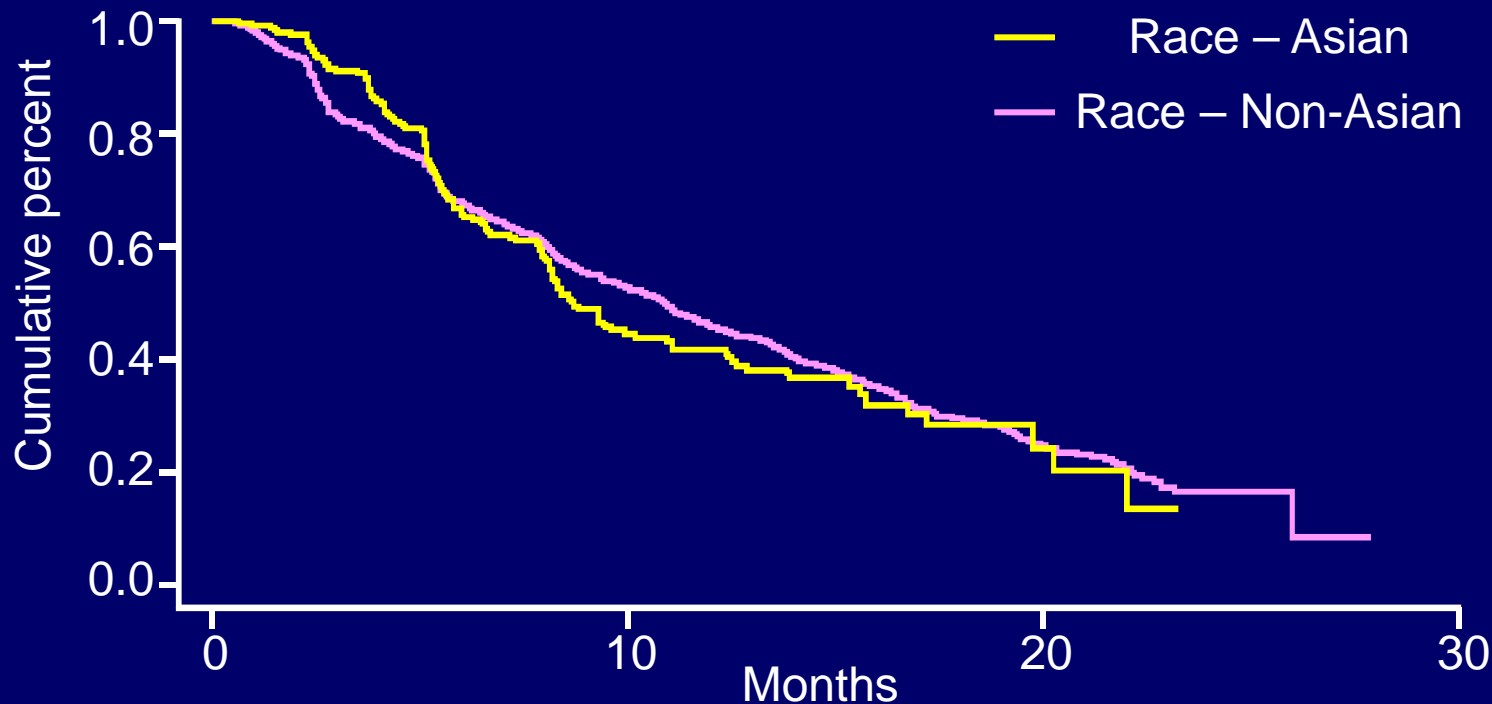
Sunitinib Dose Reductions and Discontinuations Due to AE

	All patients		
	Asian (Asian sites; n=212)	Asian (non-Asian sites; n=113)	Non-Asian (n=4,046)
Level of dose reduction, n (%)			
37.5 mg	76 (36)	28 (25)	1,340 (33)
25.0 mg	38 (18)	18 (16)	529 (13)
12.5 mg	2 (<1)	1 (<1)	15 (<1)
Discontinuation due to AEs	8 (4)	3 (3)	351 (9)

Tumor Response by RECIST

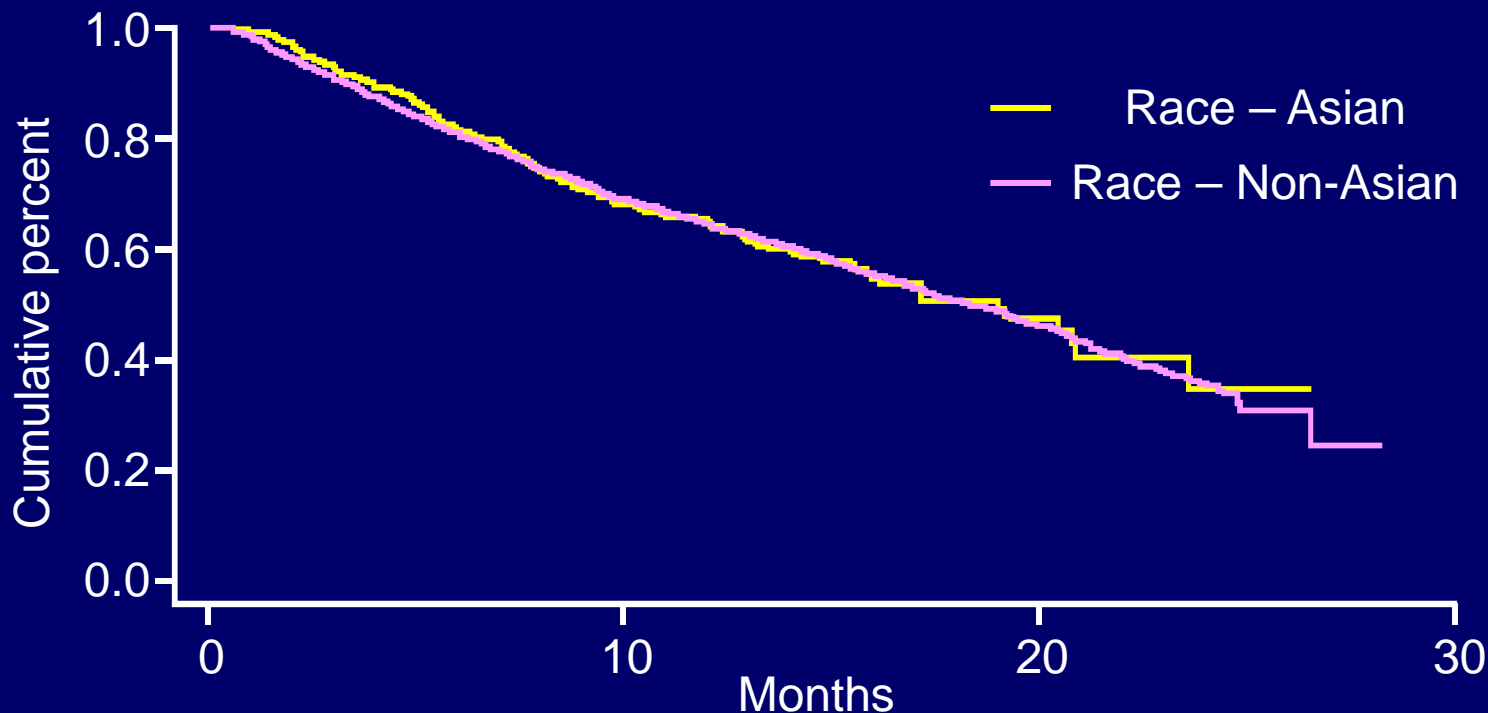
	Asian (Asian sites; n=176)	Asian Total (n=266)	Non-Asian (n=3198)
Objective response rate (%)	51 (29)	58 (22)	545 (17)
Complete response	2 (1)	2 (<1)	32 (1)
Partial response	49 (28)	56 (21)	513 (16)
Stable disease ≥ 3 mo	90 (51)	141 (53)	59 (47)
Progressive disease or stable disease <3 mo,	35 (20)	67 (25)	24 (19)

Kaplan-Meier Estimates of PFS Asian and Non-Asian Patients



	Asian (n=325)	Non-Asian (n=4024)	Total (n=4349)
Median PFS, months	8.7	10.9	10.9
(95% CI)	(8.1–11.1)	(10.5–11.3)	(10.3–11.2)

Kaplan-Meier Estimates of OS Asian and Non-Asian Patients



	Asian (n=325)	Non-Asian (n=4024)	Total (n=4349)
Alive, n (%)	202 (62%)	2250 (56%)	2452 (56%)
Median OS, months	18.9	18.4	18.4
(95% CI)	(15.5–23.5)	(17.4–19.2)	(17.4–19.2)

Conclusions

- **Sunitinib is similarly effective and well-tolerated for the first- and second-line treatment of mRCC in Asian and non-Asian patients**
- **The safety profile of sunitinib was similar for Asian and non-Asian patients for most AEs,**
 - **except for a higher incidence of hematologic AEs, especially thrombocytopenia**

Possible explanations for the difference!

- ❑ Polymorphisms in metabolizing genes

Various genotypes in CYP1A, FLT, ABCB1 genes*

- ❑ Environmental: diet, herbal medication use, smoking, or air pollution
- ❑ Body weight/ body surface area
- ❑ Etc...

* JCO 2009 Va Erp N et al. Pharmacogenomics in 219 Danish patients. 7 PK and 5 PD genes

Detailed analysis of 132 Korean mRCC patients treated with Sunitinib

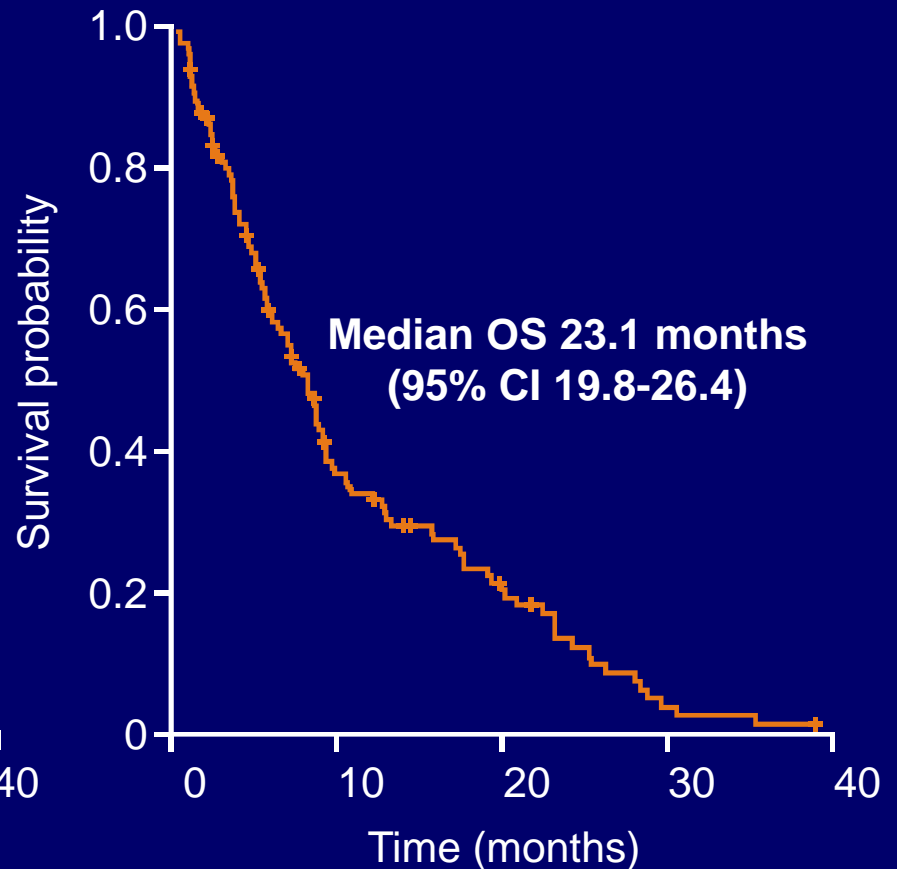
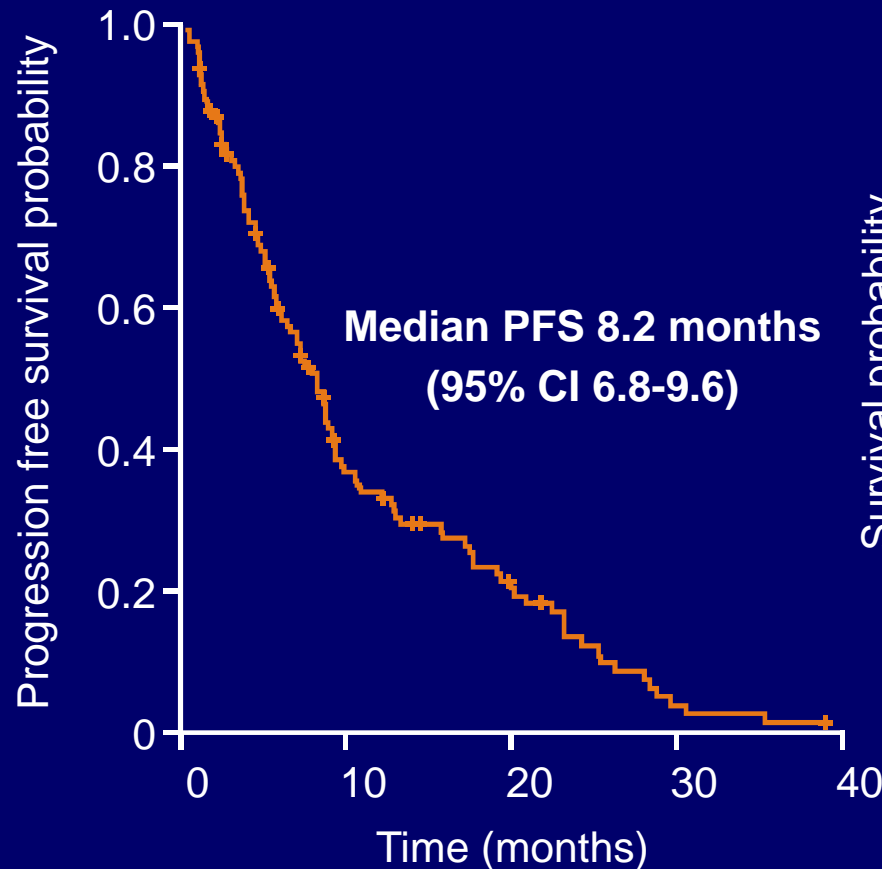
- Same eligibility, treatment, follow-up (F/U) as EAP

Patient demographics		Previous treatment	
Male/Female (n, %)	106 (80.3)/26 (19.7)	Nephrectomy	119 (90.2%)
Age – year (range)	57.0 (29.0-80)	Radiotherapy	38 (28.8%)
Weight (median, range)	63 (42-92)	Systemic Tx	94 (72.2%)
BSA (median, range)	1.69 (1.33-2.14)	Immunotherapy only	42 (31.8%)
Histology		Immunotherapy + Chemotherapy only	43 (32.6%)
Clear	109 (82.6%)	Chemotherapy	9 (6.8%)
Non-clear cell type	18 (17.7%)		
ECOG PS		Number of previous systemic treatment	
0	41 (31.1%)	0	38 (28.8%)
1	75 (56.8%)	1	30 (22.7%)
2	11 (8.3%)	2	33 (25.0%)
3	5 (3.8%)	≥3	31 (23.5%)
MSKCC risk groups (Total 111)		Number of disease sites	
0 (favorable)	8 (7.2%)	1	35 (26.5%)
1,2 (intermediate)	70 (63.0%)	2	52 (39.4%)
≥3 (poor)	33 (29.7%)	≥3	45 (34.1%)

Comparison of Korean data with Western results

Trial (Phase)	Korea EAP ¹	Global EAP ²	RCT ³
Number of patients	100	3,997	750 (375 in Sunitinib arm)
Histology	RCC (Clear 81%)	RCC (Clear 86.1%)	Clear-cell only
Age, median (range)	57 (29–79)	59 (19–85)	62 (27–87)
ECOG PS			
0	31	0–1 (84.8%)	61
1	54	-	39
>2	15	2–4 (11.3%)	-
MSKCC risk factor		(n = 1840)	
0	21%	28.9%	38%
≥1	79%	42.7%	62%

Survival curves of Korean mRCC patients



Similar to western patients!

Different toxicity profiles compared to Western data

	Korea	Global EAP ²	RCT ³
Grade 3/4 toxicity			
Neutropenia	34%	4.1	12%
Anemia	19%	2.6	4%
Thrombocytopenia	37%	6.4	8%
Elevated creatinine	0%		1%
Elevated AST	7%		2%
Elevated ALT	2%		3%
Hyperbilirubinemia	2%		1%
Fatigue	13%	7.1	7%
Stomatitis	11%	2.1	3%
HFS	13%	4.5	5%

Tx summary

- **97% developed any grade toxicity with 45% of G $\frac{3}{4}$ Toxicities**
- **48% needed Dose modification**
- **Discontinuation from Tx due to AEs: 7.7%**
- **DI: 85%, maintained after 3-4 cycles**
- **Recommend q 2weeks F/U for 1st cycle**

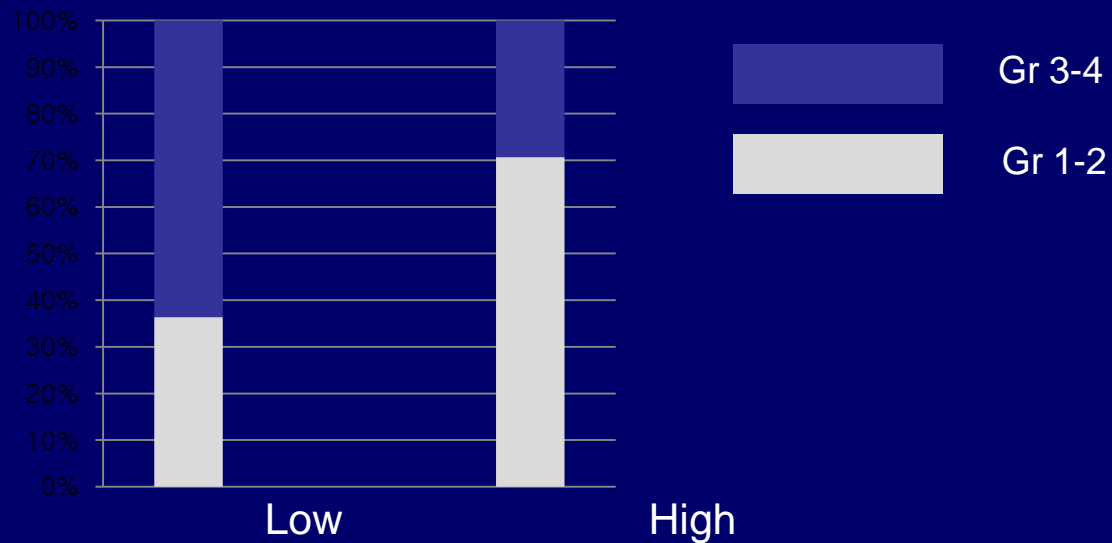
Body Weight Difference Between Eastern and Western Patients

	Western ¹	Korean ²	Japanese ³
N	73 volunteers, 517 patients	132 RCCs	36 GIST
Race	Caucasian 505, Asian-Pacific 58	Korean	Japanese
Body Weight (Kg), median (range)	76.9 (34-168)	63 (42-92)	52 (40-79)

Toxicity based on BSA (< 1.6 vs ≥1.6)

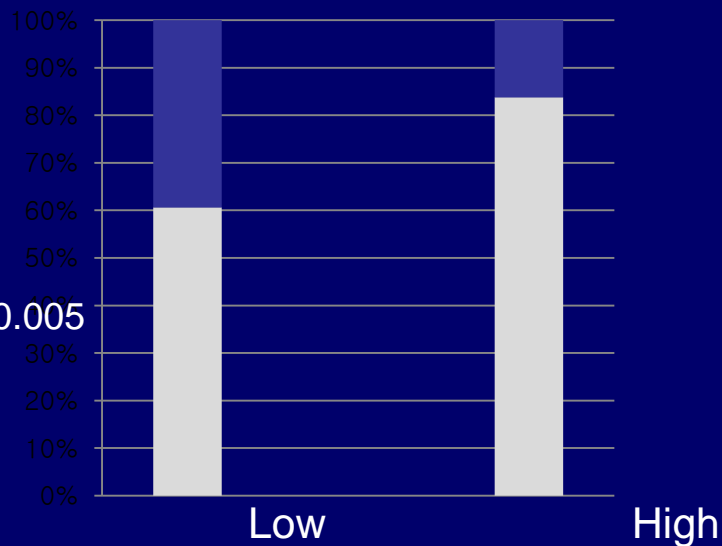
Thrombocytopenia

P < 0.001



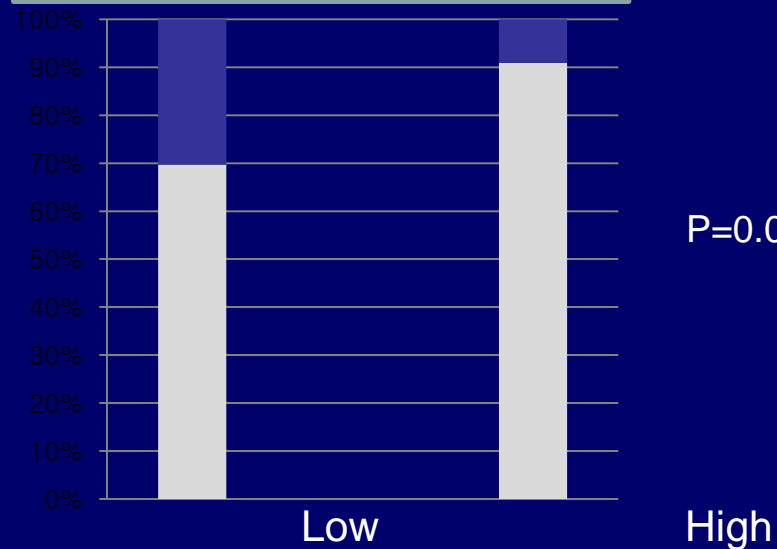
Anemia

P=0.005



Leukopenia

P=0.003



Dose Intensity

- **Dose Intensity:** unit dose of drug administered per unit time (mg/day)
- **Relative dose intensity:** Actual dose intensity / planned dose intensity

50mg 4 weeks treatment-> total 1,400mg

1) **Planned DI:** 33.3mg/ day for 4/2 standard schedule (6 weeks, 42 days)

2) If 2 weeks delay as 4 weeks on 4 weeks off (8 weeks, 56 days)

-> **Actual DI:** 25mg/day

-> **RDI:** 25 / 33.3 = 75 (%)



BW 55Kg

≠



~75kg



BNR (BSA adjusted RDI)

$$\text{BNR} = \frac{\text{RDI}}{\text{BSA}}$$

Tumor Response

	CR	PR	SD	PD	ORR (%)	DCR
All evaluable patients (N = 130)	2 (1.5%)	43(33.1%)	59(45.4%)	26(20%)	34.6	104 (80%)
Histology (N = 127)	ORR 34.6%					
Clear (N = 107)	2 (1.9%)	39 (36.4%)	43 (40.2%)	23 (21.5%)	38.3	84 (78.5%)
Non-clear (N = 18)	0 (0)	3 (16.7%)	13 (72.2%)	2 (11.1%)	16.7	16 (88.9%)
BNR (N = 122)						
Low (<0.49, N = 61)	1 (1.6%)	28 (45.9%)	29 (47.5%)	3 (4.9%)	47.5	58 (95%)
High(\geq 0.49, N = 61)	1 (1.6%)	15 (24.6%)	30 (50.8%)	15 (24.6%)	26.2	46 (77%)

BNR: BSA adjusted RDI, Low BNR suggests higher BSA.

Survival Outcome

Median (95% CI)	PFS		OS	
All evaluable patients (N = 130)	8.2 (6.8–9.6)		23.1 (19.8–26.4)	
Histology (N = 127)				
Clear (N = 107)	8.2 (6.7–9.7)	P = 0.20	23.7 (19.7–27.7)	P = 0.44
Non-clear (N = 18)	5.8 (4.0–7.6)		15.4 (13.2–17.6)	
BNR (N = 122)				
Low (< 0.49, N = 61)	9.2 (8.1–10.3)	P = 0.02	25.3 (21.4–29.2)	P = 0.10
High (≥ 0.49, N = 61)	6.6 (4.7–8.5)		21.8 (16.3–27.3)	

BNR: BSA adjusted RDI, Low BNR suggests higher BSA.

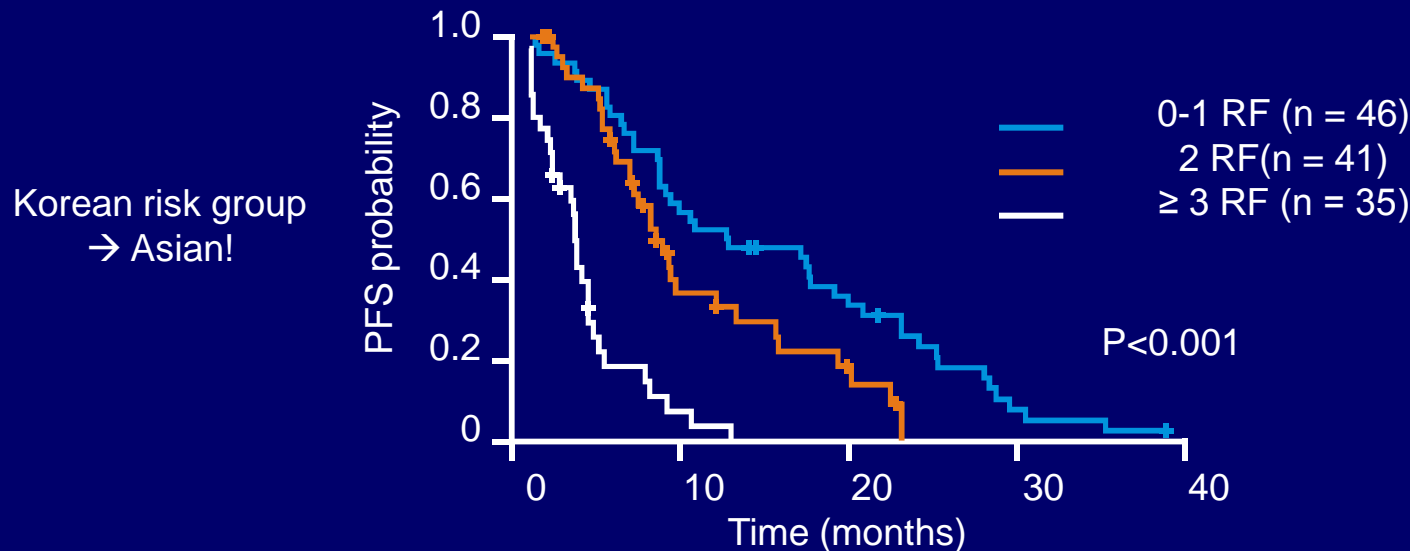
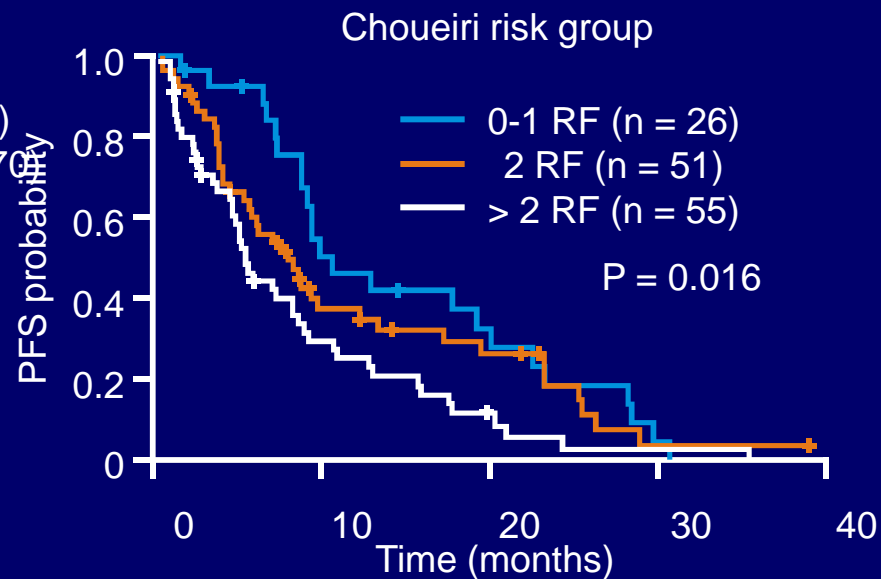
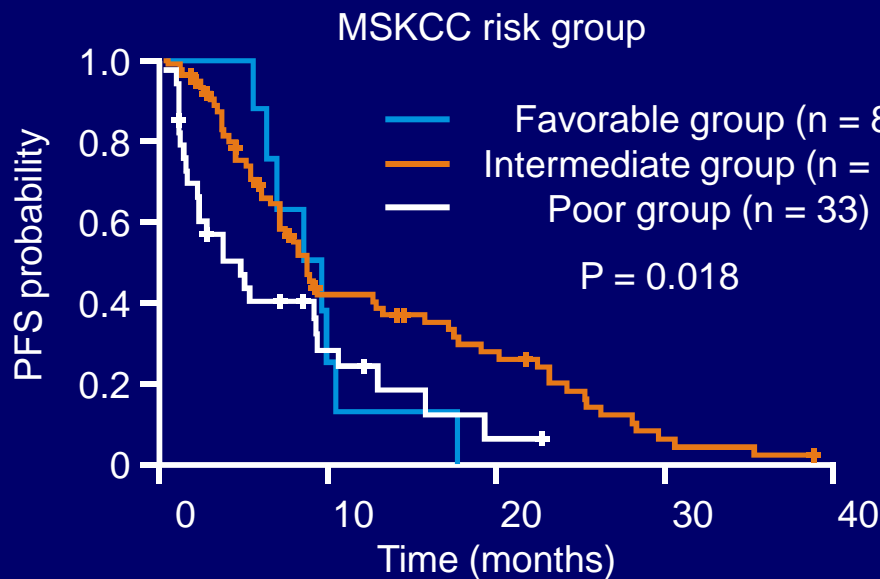
Potential Novel Prognostic Factor

- Liver metastases
- Abnormal corrected calcium
- ECOG PS
- Abnormal hemoglobin
- **BNR (BSA adjusted RDI)**



3 risk groups

Comparison of PFS based on Risk Groups





National
Comprehensive
Cancer
Network®



Scientific
Communication

NCCN Official Representative in Asia

NCCN Asia Consensus Statement **Kidney Cancer** V.1.2009

- Understanding the current situation and problems of each country
- Understanding the current available local evidences
- Put the realistic treatment guideline
- Plan for future evidence generation

Panel Members: 6 Countries, 9 Members

- Hideyuki Akaza, University of Tsukuba, Tsukuba, **Japan**
- Narmada Gupta, All India Institute of Medical Sciences, New Delhi, **India**
- Shiro Hinotsu, Kyoto University, Kyoto, Japan
- Philip Kwong, Queen Mary Hospital, **Hong Kong**
- Ming Kuen Lai, National Taiwan University, Taipei, **Taiwan**
- Seiichiro Ozono, Hamamatsu University School of Medicine, Japan
- Sun Young Rha, Yonsei University College of Medicine, Seoul, **Korea**
- Jae Mann Song, Yonsei University Wonju College of Medicine, Korea
- Rainy Umbas, University of Indonesia, Jakarta, **Indonesia**

Differences in practices between Asia and the West

- Compared to Western countries, **cytokines are more widely used** in Asian countries
 - Optimal dose of cytokines differ from those of Western countries, as discovered in a dose-finding study for Japanese patients
- Ultrasonography and retrograde pyelography are practical options for initial workup
- For first- and second-line therapy for mRCC:
 - Cytoreductive nephrectomy + cytokine therapy remains an option for first-line therapy where TKIs are not available
 - However, treatment with **TKI is preferred first-line therapy where available & affordable**
 - In view of **higher incidences of toxicity among Asian patients**, relative risks/benefits of sunitinib and sorafenib as first-line therapy should be considered before initiating treatment
- Everolimus is recommended as second-line treatment for relapse or stage 4 and medically or surgically unresectable disease, if available
- In surgery:
 - Laparoscopic radical nephrectomy may be considered a standard procedure for patients with T1 tumors, in centers where facilities and expertise are available
 - Routine extended lymphadenectomy is not considered as a standard procedure
 - Lymphadenectomy should be restricted to the perihilar tissue

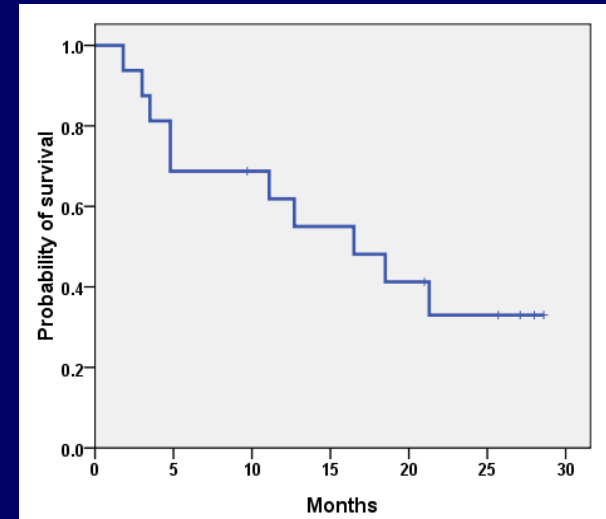
Preliminary Korean experience with Temsirolimus

- Enroll period : 2007.1.1~2009.6.30 (Data cut-off : 2010.3.1)
- **16 evaluable patients** (12 male, 4 female) with 2 on-going patients
- Cell type: 11 clear cell, 5 non clear cell
- Nephrectomy 100%
- 14 (87.5%) with previous anti-VEGFR TKIs

- Trial off : 14
 - PD : 9
 - Toxicity : 3 (ILD G2, pneumonia G4)
 - Others : 2

- Median Treatment cycle : 3.5 (range : 1-13)
- Median PFS: 7.3 months
- Median OS: 16.5months

Overall Survival



Non-infectious pneumonitis

After 10 weeks of temsirolimus



- Radiologic changes 10/16 patients (62.5%)
- Median time to pneumonitis: 2.4months(1.7-8.1)
- Respiratory Sxs with radiologic changes: 5/10
- No dose modification 2
- Dose modification 3 -> Study off 2 due to ILD and superimposed pneumonia

Summary

- **Significant activity** of currently available targeted agents in advanced RCC patients in Asia, and comparable to Western studies
- **Significant toxicities** different from cytotoxic agents
- Similar toxicity profile with **different severity** from Western patients
 - More thrombocytopenia and skin toxicity with sunitinib
 - More non-infectious pneumonitis with mTOR inhibitor
 - Unknown mechanism: diet, dosing, ethnic difference
- Need proactive assessment and management of toxicities to optimized treatment
- **Ethnic difference!** → Need **Asian data** with translational research
- **Individualization!**

2013 Yonsei University Health System with New Cancer Center

