Global Clinical Trials in Asia: Challenges and Opportunities

Vijay R. Prabhakar MD Medical Director PharmaNet, Singapore







Contents

- Complexity of oncology clinical trials
- Opportunities in Asia
- ✓ Epidemiology of cancer in Asia
- ✓ Rapidly evolving infrastructure
- Effect on timelines and quality
- ✓ Potential market access
- Challenges in Asia
- Differences in medical practice culture between Western countries and Asia
- ✓ Lesser awareness among potential subjects
- ✓ Talent retention and turn over
- ✓ Inconsistent quality of sites within countries
- ✓ Longer approval timelines in some Asian countries
- ✓ Concerns about IP and data protection





3

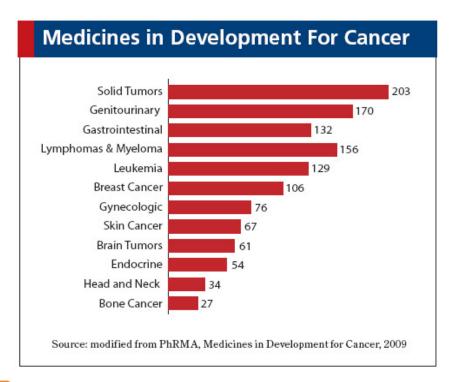
Relative complexity of oncology trials

- High amount of patient participation is required:
- Survival data and QOL is required by almost all protocols. Patients motivation to follow-up even after progression is essential.
- ✓ Most anti-cancer agents have narrow therapeutic index. Patients should have high level of confidence in investigator and understanding of protocol to continue long-term follow-up in the study.
- ✓ If standard of care is not provided by sponsor, subject retention is difficult. Many Asian countries do not have compulsory health insurance.
- ✓ Personalized medicine and increasing role of biomarkers
- ✓ Saturated sites. Poor site response to feasibilities: lack of response or overestimation
- ✓ Stringent eligibility criteria not considering the wide variability in actual clinical management of cancer



Why are we talking about this here?

- The global market in sales for oncology drugs is anticipated to expand from around \$48 billion in 2008 to more than \$85 billion in 2013.
- Currently, more than 4,700 clinical trials are in progress for oncology drugs.
- About 20% of clinical trials are in oncology and about 46% of them are global trials.
- Major pharma companies continue to have an active pipeline in oncology.
- Increasing shift of R&D activity to China





J&J Opens R&D Center in Shanghai Drug Discovery & Development - June 12, 2009



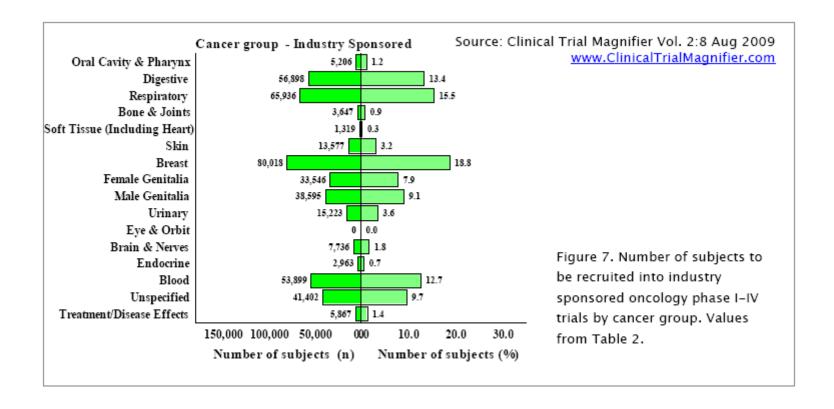
AstraZeneca's R&D investment in China 'the largest yet'



Merck Serono opens Beijing R&D centre



Trial Activity in Oncology





Opportunities for oncology clinical development in Asia



Global Cancer Trials: Current scenario

- Epidemiology of cancer in Asia is different from US in many indications but even in cancers that are more frequent in Asia (HCC, HNC) the global trials that involve Asia are proportionately low.
- According to the Biopharm Insight database globally 1416 industrysponsored cancer studies were initiated from Jan 2009 to Dec 2009.
- ✓ About 1018 (72%) of them involved at least one site in USA.
- ✓ In contrast, only 170 (12%) of them involved at least one site in Asia Pacific: 63 (4%) in Korea, 35 (2.5%) in Taiwan, 28 (2%) in China, 22 (1.5%) in Singapore and 20 (1.5%) in India.
- The disparity between the potential in Asia and the actual number of global trials being conducted in Asia is large and should be addressed.



Burden of cancer: world compared to Asia Pacific

Worldwide premature death and disability by conditions compared to the Asia Pacific Region, 2002								
Cause		World			Asia Pacific			
Cause	YLL	YLD	DALYs	YLL	YLD	DAIYs		
All causes	100%	100%	100%	100%	100%	100%		
A. Malignant ne oplasms	7.76	0.69	5.07	9.19	0.44	5.58		

•YLL: Years of Life Lost due to premature mortality in the population

YLD: Years Lost due to DisabilityDALY: Disability-adjusted life year

WHO Report. Downloaded on 26 Mar 2010



Age-Standardized Incidence Rate (ASR per 100,000) of leading cancers in Asia (male)

	China	Korea	India	Singapore	USA
Lung	51 - 71	50	11	45	52.8
Prostate	2 to 15	8.5	3 to 7	17	113.7
Colorectal	17 to 30	29	4 to 5	40	38
Gastric	9 to 34	66	4 to 12	18	7
Liver	26 to 42	45	2 to 4	19	6.2
HNC	3 to 32	6	16 to 22	17	11
Renal	2 to 5	5	2	5	11
NHL	4 to 8	6	3 to 5	8	15
Myeloma	1 to 2	1.3	2	1.4	4

IARC data 2002



Age-Standardized Incidence Rate (ASR per 100,000) of leading cancers in Asia (female)

	China	Korea	India	Singapore	USA
Lung	13 to 35	12.5	2 to 3	16	34
Breast	14 to 35	23	24 to 31	54	91
Colorectal	12 to 23	17	3 to 4	29	27
Gastric	4 to 17	26	2 to 3	10	3
Liver	5 to 12	12	1 to 2	5	2
HNC	3 to 12	2	8 to 10	6	4
Renal	1 to 2	2	1	2	5
Cervical	2 to 9	15	10 to 28	10	7
Myeloma	1 to 2	1	1 to 2	1	3

IARC data 2002



Global Oncology Trials in Asia: Current Status and Trend



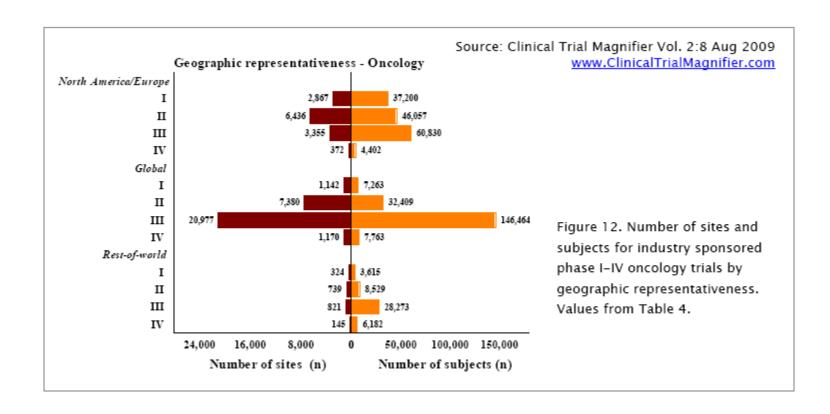
Comparative Industry-Sponsored Global Trial Activity for Cancers more Common in Asia: limit study start date from Jan 2009 to Dec 2009

	Total	USA	China	India	Korea	Taiwan	Singapore
Lung	136	76	12	3	13	10	4
Liver	41	24	9	3	9	11	6
Cervical	7	3	0	1	1	3	0
Gastric	29	15	3	0	7	2	2
HNC	32	17	2	1	1	0	1

Data from biopharm insight 25 Mar 2010



Global Oncology Studies: more room for growth in Asia





Current Proportion of Global Oncology Studies in Asia

	Global	North America	Western Europe	Asia	Eastern Europe	Australia	South America	Latin America	Middle East	Africa	New Zealand
Total	6107	2999 (49%)	1338 (22%)	474 (8%)	383 (6%)	302 (5%)	209 (3%)	125 (2%)	115 (2%)	105 (2%)	57 (1%)
Phase											
-1	1192	856 (72%)	212 (18%)	68 (6%)	11 (1%)	29 (2%)	4 (0%)	0 (0%)	6 (1%)	1 (0%)	5 (0%)
1/11	666	435 (65%)	139 (21%)	36 (5%)	19 (3%)	20 (3%)	9 (1%)	2 (0%)	3 (0%)	2 (0%)	1 (0%)
II	2529	1348 (53%)	584 (23%)	185 (7%)	150 (6%)	101 (4%)	62 (2%)	29 (1%)	33 (1%)	29 (1%)	8 (0%)
11/111	137	34 (25%)	40 (29%)	14 (10%)	18 (13%)	10 (7%)	4 (3%)	4 (3%)	8 (6%)	3 (2%)	2 (1%)
III	1407	289 (21%)	318 (23%)	153 (11%)	168 (12%)	129 (9%)	118 (8%)	77 (5%)	57 (4%)	62 (4%)	36 (3%)
III/IV	3	0 (%)	1 (33%)	0 (0%)	0 (0%)	1 (33%)	0 (0%)	0 (0%)	1 (33%)	0 (0%)	0 (0%)
IV	169	35 (21%)	42 (25%)	18 (11%)	17 (10%)	12 (7%)	12 (7%)	13 (8%)	7 (4%)	8 (5%)	5 (3%)

Number of oncology trials initiated during the period 2004–2007. Source: TrialTrove (accessed May 2008)

- •Sites in North America and Europe dominate global oncology trials
- Most oncology studies in Asia are late phase clinical trials

GCPj Aug 2008



Changing Trial Landscape

PAST/CURRENT SCENARIO

US data for US market

- Lack of capability/resources in Asia
- Lack of confidence in Asian sites/data

CHANGING TREND

- Share of market value increasing for China, Korea and India
- Increasing presence of CROs in Asia and R&D from Asian units of MNCs. Growing number of clinical research units within hospitals.
- Increasing visibility and integration of Asia: regional NCCN panels and cancer trial groups. FDA acceptance of Asian data and cost/time benefits.

The coming years will see a trend towards increasing number of global cancer studies in Asia



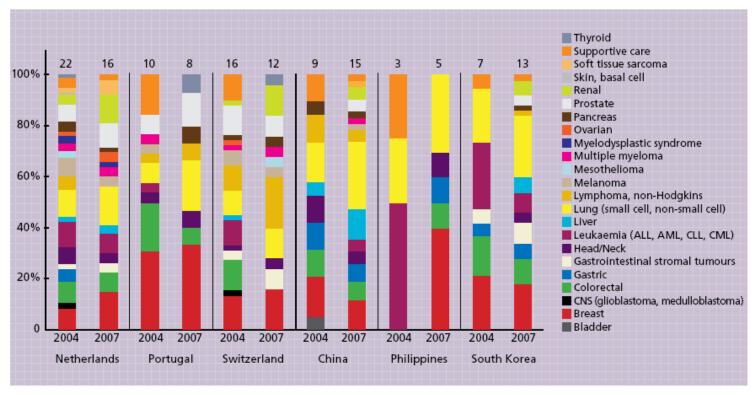
Estimated Time to Enroll All Open Phase III Cancer Studies in U.S.-only versus Globally

Geography	Line	Statistic	Figure	Source or Calculation
US Only	A	Total Cancer Incidence in US	1,437,180	American Cancer Society 2008
	В	Participation Rate	5%	Industry Statistics
	C	Total Annual Patients Willing to Enroll	71,859	A×B
	D	Number Phase III Cancer Studies in US	481	Clinicaltrials.gov (open Phase III cancer studies)
	E	Patients Willing to Enroll Per Study	149	C/D
	F	Percent Excluded due to Screening Factors	20%	Industry Statistics
	G	Patients Willing and Able to Enroll Per Study	120	Ex(1-F)
	н	Average Patients in a Phase III Cancer Drug Trial	691	VOI Consulting: Label analysis of cancer drugs approved 2006-09
	1	Years Necessary to Fully Enroll all Phase III Cancer Trials with US Patients	5.8	H/G
Geography	Line	Statistic	Figure	Source or Calculation
Global	J	Total Cancer Incidence Worldwide / Male	5,801,839	Globocan 2002
	K	Total Cancer Incidence Worldwide / Female	5,060,657	Globocan 2002
	L	Total Worldwide Cancer Incidence	10,862,496	J + K
	M	Participation Rate	5.0%	Assumes same as US. Conservative estimate.
	N	Total Annual Patients Willing to Enroll	543,125	L×M
	О	Number Phase III Cancer Studies Globally	1,218	Clinicaltrials.gov (open Phase III cancer studies worldwide)
	P	Patients Willing to Enroll Per Study	446	N/O
	Q	Percent Excluded due to Screening Factors	2016	Industry Statistics
	R	Patients Willing and Able to Enroll Per Study	357	P x (1 - Q)
	s	Average Patients in a Phase III Cancer Drug Trial	691	VOI Consulting: Label analysis of cancer drugs approved 2006-09
	т	Years Necessary to Fully Enroll all Phase III Cancer Trials with Global Patients	1.9	S/R
		Difference between US-only and Global Trials (Years)	(3.8)	T-I

Value of Insight Consulting, Inc. www.voiconsulting.com July 21, 2009



Geographical Drift in Oncology Trial Activity: 2004 to 2007

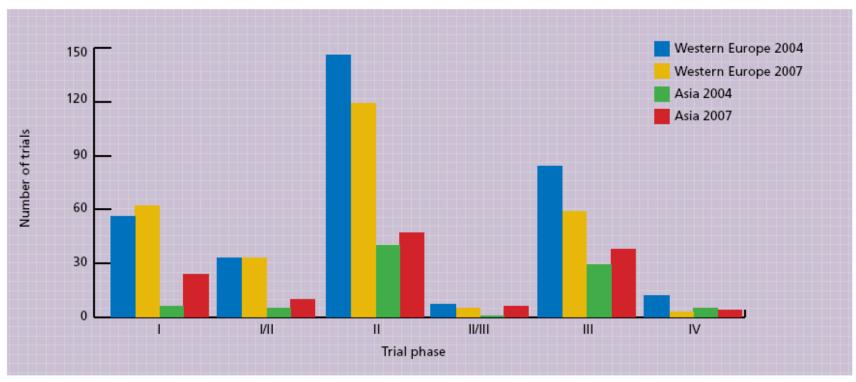


Number of oncology disease types in clinical trials in selected Western European and Asian countries. Source: TrialTrove (accessed May 2008)

GCPj Aug 2008



Increasing Trend For Conducting Early Phase Trials in Asia



Western European and Asian oncology trials by study phase. Source: TrialTrove (accessed May 2008)

GCPj Aug 2008



Results of FDA Clinical Investigator Inspections 2000-08

		Voluntary		
	No Action	Action	Official Action	
	Required	Indicated	Indicated	Total
Africa	41%	59%	0%	29
Asia/Pacific, other	63%	38%	0%	16
Australia/New Zealand	50%	50%	0%	4
Canada	33%	67%	0%	94
Central, Eastern Europe	42%	57%	1%	183
China	6%	94%	0%	17
India	40%	60%	0%	10
Japan	100%	0%	0%	1
Korea	0%	100%	0%	2
Latin America	31%	67%	3%	117
Middle East	18%	73%	9%	11
US	25%	65%	10%	4,014
Western Europe	25%	74%	1%	314
Total	1,248	3,157	407	4,812



Interim Conclusion

- Potential to conduct oncology clinical trials in Asia is large and currently under-utilized
- Growing trend towards involving Asia in global oncology clinical trials

But not without challenges



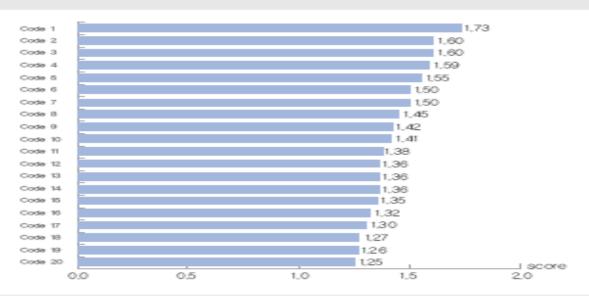
Major Challenges in Asia

- Lack of awareness about clinical trials among patients
- Lack of harmonization of regulatory requirement for clinical trials within Asia
- Inconsistent quality of sites within country
- Demand for experienced clinical research staff is higher than supply
- Differences in disease presentation, medical practice, language, ethnicity and culture
- Lack of regular audits by regulatory agencies and concerns about ethics and IP protection



Challenge: subject awareness and motivation: Understanding patients with cancer

Needs of Cancer Patients [2008]

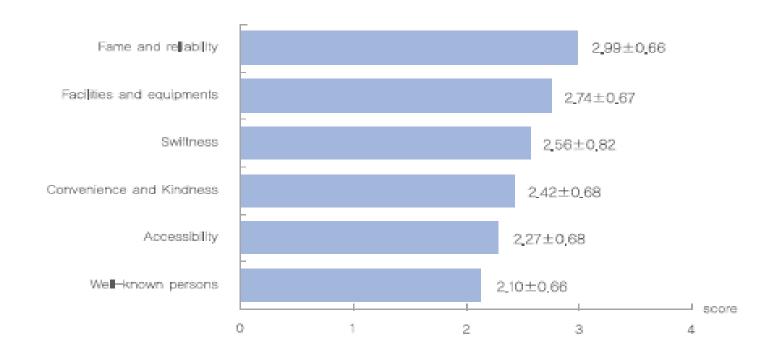


Source) Development of Cancer Care Quality Assurance and Cancer Patients' Welfare System 2008 Note] Code 1: Information on governmental or private financial support Code 2: Help for medical costs and income loss related to cancer Code 3: A short waiting time from reservation to consultation with a doctor Code 4: A fast and easy contact with a doctor if necessary Code 5: Information on a current status and a prognosis of disease Code 6: An easy and detailed explanation by a doctor Code 7: Information on examinations and treatments Code 8: Information on diet (recommended and avoided foods) Code 9: Information on symptoms needing a visit to a hospital Code 10: A comfortable environment for treatment Code 11: Help to cope with weakness and fatigue Code 12: Consultation and guide for necessary all services after diagnosis of cancer Code 13: Fast nursing care when discomfortable or painful Code 14: Information and education on health management at home Code 15: Help for dealing with fear of recurrence Code 16:An active cooperation and communication between medical staffs Code 17: Explanation on nursing care related to cancer Code 18: A sincere concern and empathy of nurses Code 19: Help to cope with side effects following treatments Code 20: Participating on decision process about examinations or treatments



Challenge: subject awareness and motivation: Understanding factors affecting choice of institution

Priority among Factors Affecting Cancer Patients' Choice of Medical Institutions [2008]



Source) Development of Cancer Care Quality Assurance and Cancer Patients' Welfare System 2008



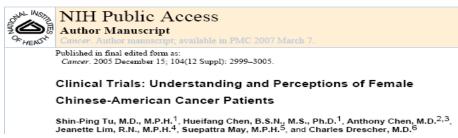
Challenge: subject awareness and motivation: Lessons learned from NCC Korea survey

- Patients like to participate in decision-making process but rely heavily on their physician for advice

 do physician spend sufficient time with their patients? A trial participant is more likely to receive extra attention and information through ICF process.
- Patients expect longer in-room consultation period and less waiting time trials requiring complex assessments and repetitive visits will deter patients from enrolling in study. An efficient study coordinator can facilitate this for a trial subject.
- Concerns on treatment cost and loss of income could be a motivating factor for patients to enrol
 in a trial. How will this information reach potential subjects? Creating study awareness is
 important.
- Advice from fellow patients and relatives very important in Asian context. Patient forums/internet
 will be useful. Patients may be suspicious of experimental treatment and advertisements may not
 always be useful.



Challenge: subject awareness and motivation: lack of knowledge about clinical trial designs can deter subjects



- Subject: I'm not familiar with the English [term of randomization]. What is that in Chinese?
- Interviewer: That word in Chinese means... it means that, even though it is a "clinical trial," not everybody will receive it. Not everyone will receive the [research] treatment method that was suggested. Half of the patients will receive treatment, half of them won't. But who is going to—to receive it or not to receive it, they have to, um, use—they have to draw straws to decide. I don't know whether you're familiar with this or not.
- Subject: What do you mean, how [do] they decide?
- Interviewer: They have to follow... maybe they will design [it] a different way, but basically [to randomize] is—for example—the first patient comes in, maybe he will receive the treatment, and the second patient that comes in, he— he will not receive the treatment. And then the next patient comes in, then she will receive the treatment, and then the next patient comes in and there's no treatment. Something like this.
- Subject: So, this is decided by the doctors? Or is it [the] patients, [who] arrange it?



Challenge: subject awareness and motivation: negative attitude to clinical trials

- All except one participant expressed negative perceptions of clinical trials. The majority (65%) of these participants associated clinical trials as the last resort
- When you have a disease that is very serious, you would go to that program. A dying horse could be used as a guinea pig to be treated.... I felt when other methods have failed, then you go to the clinical trials.
- So, my feeling is that, when doctors mention a clinical trial, it seems like [they are] going to give up on you.
- If I have no way to save [treat] it, then I won't even do it [clinical trial].... Because I don't want to continue to suffer any more. I don't want to be like mice, to be tested on.
- For example, the reason I participated in your study [is] because I think it will contribute some benefits to this community and nursing care. That's why I came. But if there's anything that might be dangerous or threaten lives, then I won't participate [in] it.
- The patient's life is in their [doctors'] hands. So, for today's case, then you can do it on some other patient. Don't do it on my parent, because that's how everybody thinks. Otherwise, who will take care of their parents and take care of their kids? Right? Please don't take my Mom or Dad for a joke [guinea pig].
- Why they are like this? Is this doctor capable or not? Suspicious!...





Overcoming Negative Perception of Clinical Trials

- Survey conducted by the Korean Centers of Disease Control and Prevention has found a large proportion of South Koreans unlikely to volunteer for clinical trials, despite realising their importance.
- The government body polled 1,023 adults, of whom 87% said trials were essential for the development of medicines, 82% thought that their participation would help in the development of new drugs for patients yet only 33% were willing to personally take part in clinical trials.
- It also reported that 82% of those polled feared being administered a fake drug, and 70% worried about the side effects.
- Encouraging transparency and not just awareness appear to be an important determinate for improving patient participation in clinical trials

Scrip CR 23 Apr 2010



Challenge: subject awareness and motivation: Facilitators to trial participation



- Lack of standard treatment options
- Recommendation by trusted relative
- Advice by well known physician
- Previous safety data on other patients



Challenge: Regulatory Barriers

- CMC requirement for CTA (Korea, India, China, Malaysia, Thailand)
- Long duration taken for CTA approval in China
- In China, export of blood samples is restricted



Challenge: Inconsistency in quality of sites

- Increased trial activity is not matched by increase in number of investigative sites. Many trials now compete for few sites
- Invariably sites in tier-II cities are moving in to fill the gap. Lack of experience and infrastructure has resulted in risk of low quality data
- Physicians primarily focussed on patient care with little time for clinical trials. Most routine trial-related work is done by study coordinator. Turn-over of site staff and lack of experience will significantly affect quality of data



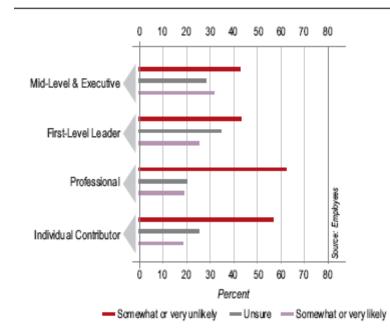
Challenge: Talent retention in industry

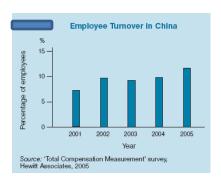
Younger employees with university credentials often don't have the practical experiences or leadership skills required in the business world

As demand for talent outstrips supply, the employee turnover rate also has escalated

Western managers should be able to understand 'Guanxi', 'Mianzi' of their Chinese colleagues

Likelihood of Leaving Within the Next Year







AstraZeneca-Shanghai Holds Down Turnover

With an average growth rate of 30 percent over the last five years, AstraZeneca's Shanghai initiative. Internal surveys : important factors for retai



Challenge: Differences in disease presentation

- There is now data that shows that some cancers could present differently in Asian populations.
- For example in breast cancer: East Asian women when compared to Caucasians, present with a younger age of onset (40 to 50 vs. 55 to 75), diagnosed before menopause, proportionally higher incidence of ER negative tumours and are in advanced stage at time of diagnosis. ¹
- Disparity in socioeconomic indicators with Asian countries is likely to affect prognosis. Prognosis could be worse in countries with low GDP. Five-year survival for breast cancer was only 12% in Gambia compared to 80% in Korea.²
- A study reported that for gastric cancer, median survival for Asians was 13.1 months compared to 11.1 months for non-Asians. Asians were less likely to have proximal tumour location and had more favourable outcome after curative surgery even after adjusting for age and location.³
- These differences in disease presentation should be taken into consideration while estimating recruitment rate and enrolling sufficient number of Asian patients that will enable data to be generalized.
- Co-existence of TB and NSCLC is frequent in Asia
- Nationwide mammogram screening and use of MRI is less frequent in Asia compared to western countries. USG is preferred in some Asian countries.
- 1. Perry et al. Asia Pacific Journal Clin Oncol 2009
- 2. Sankaranarayanan et al. Lancet Oncol 2009
- 3. Gill et al. JCO 2003



Challenge: Differences in medical practice and culture

- Treatment available for cancer is not different between western countries and Asia. Methods for diagnosis and treatment in Asia are mostly similar to US or European guidelines. However, in some countries like India, China and Thailand cost is a barrier for access to best available standard of care.
- The doctor-patient relationship in Asia is slightly different from west.
- In an article, Ishikawa and Yamazaki cited four social factors in Japanese physician-patient relationship that differs from west. Some of them could be applicable to other countries in North Asia. ¹

•

- 1. Individualism vs. collectivism: In Western countries the patient decision-making is often autonomous. Whereas, in Asia patients tend to discuss with relatives and friends before taking major decisions such as participating in a clinical trial. The informed consent process should be appropriately detailed in Asian countries and allow sufficient time for patients to discuss with relatives and friends.
- 2. Low context vs. high context: very often in western countries physicians and direct in informing patients about diagnosis and prognosis. Whereas, in Asia physicians could try to indirectly imply bad prognosis and delay directly mentioning to patients diagnosis of near-fatal diseases. In countries like Japan, a brief period of silence could convey a powerful message compared to a period of talking directly.
- 3. Femininity vs. masculinity: A society with high masculinity is one which differentiate gender roles and society with high femininity tend to have more fluid gender roles. Some countries in Asia tend to have masculine culture and decision-making is usually done by male head of family. However, this is changing with increasing acceptance of western culture in Asia but could be persistent in some middle-east countries.
- **4. Family tradition Eastern vs. Western**: East Asian tradition values social harmony and respect for elders. Western traditions places more value on friendliness and egalitarian relationship. Asian patients are likely to accept clinical trials only if it is also acceptable to family elders and does not burden other family members.
- 1. Ishikawa and Yamazaki, IJJS 2005

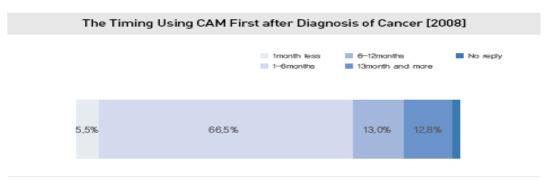


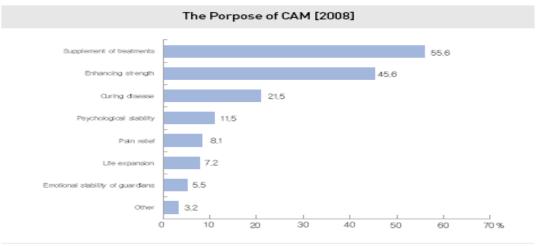
Challenge: Differences in medical practice and culture

- The standard of care for cancer is not different between western countries and Asia. Methods for diagnosis and treatment in Asia are similar to US or European guidelines but high cost of treatment is a limiting factor in Asia
- The significant difference is the use of traditional medicines by many patients.
- Excluding use of such medications could have significant impact on recruitment. Many patients perceive herbal medications to improve their 'strength and vitality' even if it does not directly have effect on main disease.

Complementary and Alternative Medicine (CAM) of Cancer Patients

66.5% used complementary and alternative medicine at 1~6 months after diagnosis of cancer.





Source) Development of Cancer Care Quality Assurance and Cancer Patients' Welfare System 2008
Note) Duplicate repty



Challenge: Differences in medical practice and culture

Breast cancer

• Asians appear to be less tolerant to chemotherapy. For example a lower dose of docetaxel (75 mg/m² instead of 100 mg/m²) is commonly used in Asian patients. Some tests like 21-gene RT PCR assay done for ER+, node-negative tumours is not standardized in Asia. USG is more commonly used to stage breast cancer due to younger age of Asians subjects, smaller size of breasts and relative density.

CML

Expensive drugs like imatinib or TKIs may not be reimbursed in some Asian countries. Patients may not
be able to complete full course or be compliant with regimen. Molecular monitoring of response to imatinib
is not routinely done in some Asian countries either due to lack of availability or high costs. Lower median
age of onset in Asia may result in treatment and social dilemmas, especially for women of child-bearing
age.

Renal cancer

- In RCC, use of cytokines in more frequent in some Asian countries compared to Western countries. The dose of IFN and IL may differ from standard Western regimens. HFS and hematologic toxicities are observed more frequently in Asian patients receiving sorafenib when compared to Western patients.
- Availability of generic versions of patented drugs in some countries could deter sponsors from conducting research due to concerns on data protection and standardization of standard of care.

Lung cancer

• With IPASS study showing gefitinib to be superior to conventional cisplatin+paclitaxel, there could be tendency to use gefitinib off-label as first-line agent. This may not be the case in western countries and should be considered in designing global protocols in lung cancer that involve Asia.



Challenge: Differences in ethnicity

- There is now conclusive evidence to show that ethnic factors could affect prognosis.
- There is now a trend towards increasing use of targeted therapy and biomarkers. In future there
 could be less use of toxic chemotherapy as subjects increasingly prefer targeted therapy. Some
 of the targeted therapies in development have been found to have more relevance for Asian
 patients.
- Case in point is the recent example of clinical development of gefitinib. While gefitinib did not confer any OS advantage in phase III trials, a sub-group analysis in Asian patients revealed significant benefit on OS. A recent study has also demonstrated superiority of gefitinib over conventional chemotherapy when given as first-line agent in advanced NSCLC.
- EGFR mutation rate in Asians is approximately twice that of whites.
- Stratification and inclusion of adequate number of Asian patients will enable generalization of results.

www.diahome.org



Conclusions and Moving Forward

- There will be an increasing trend to involve Asia in oncology drug development
- Existing challenges are surmountable
- Goal is to increase awareness and involve subjects in clinical trial decision-making. Can be achieved by improving local web-based trial databases and content in local languages.
- Regulatory harmonization is not present in the region but is moving in a co-operative direction
- Steps should be taken to train new investigators/sites in GCP and improve participation in clinical trials
- Physician societies should be encouraged to share registry information and hospital statistics on public domain to minimize feasibility requirement
- Pharmaceutical companies should consider Asia as a partner in drug development in early phase.



Thank you

谢谢你