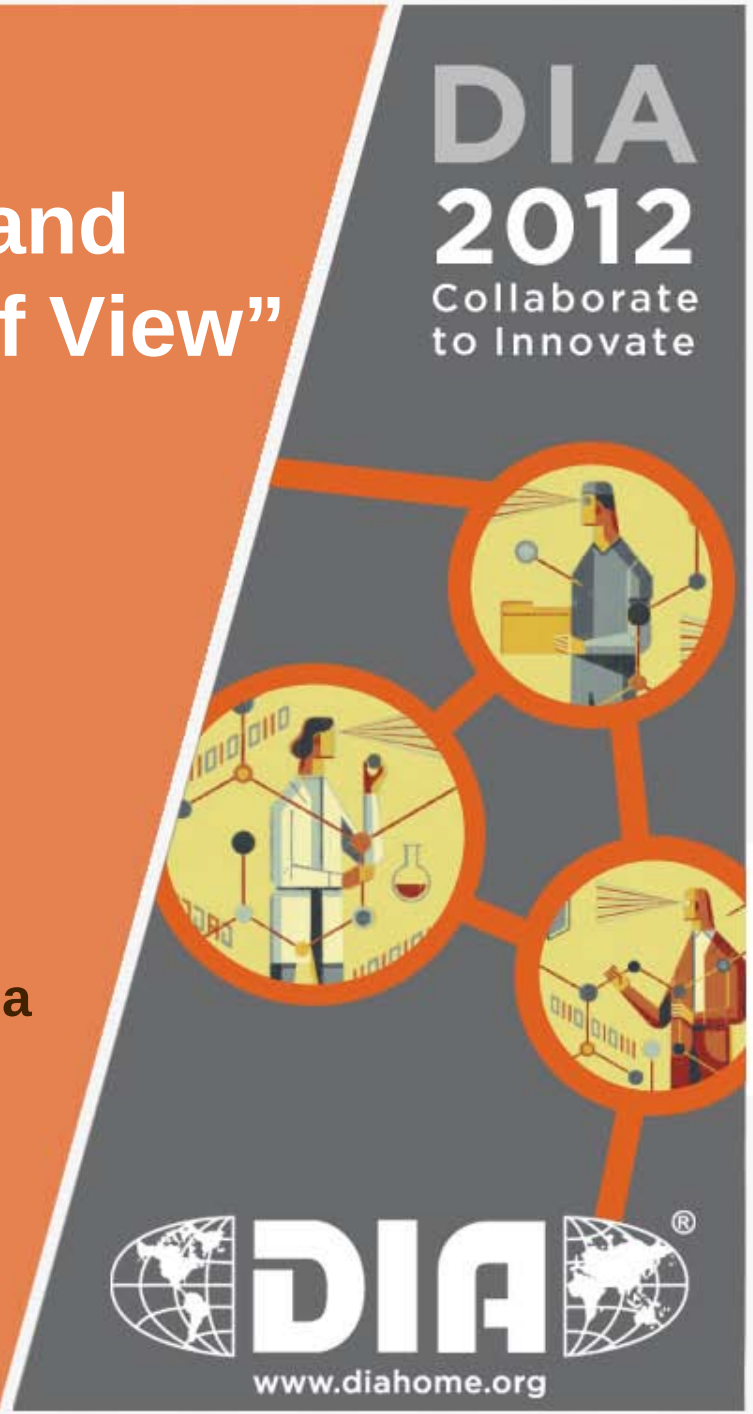
“Asian Ethnic Similarities and Differences: PMDA Point of View”

Yoshiaki Uyama, Ph.D.

Pharmaceuticals & Medical Devices Agency (PMDA)

Visiting Professor, Graduate School of Medical and Pharmaceutical Sciences, Chiba University

Visiting Professor, Graduate School of Medicine, Nagoya University



pmda
Pharmaceuticals and Medical Devices Agency

Disclaimer

- The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.
-

China, Korea, Japan Tripartite Cooperation

China, Korea, Japan Tripartite Cooperation

- Joint Statement of 3 Ministers Meeting (Apr. 2007)
  - Clinical Researches
    - Recognizing that East Asia has been rapidly gaining importance as a venue of today's worldwide drug development, three Ministers affirmed the significance of cooperation among three countries on clinical researches, including clinical trials, especially in clarifying the ethnic factors on the clinical data, in order to facilitate drug development.

Current Projects
-Working Group-

- Research on ethnic factors (Project coordinated by Japan)
  - Evaluate ethnic factors in drug clinical trial data to examine the possibility of sharing drug clinical trial data from three countries
- Information sharing (Project coordinated by Korea)
  - Mutual understanding of the regulatory frameworks for clinical trials in the three countries.
- Guideline on regional clinical trials (Project proposed by China)
  - Make guidelines on regional clinical trials with close cooperation with Korea and Japan.

Research on ethnic factors

PK comparison among East Asian and Caucasian populations

1st Stage:
Literature-based PK comparison among populations (Tohkin Study Group, MHLW Research Grant)

- In the study, a part of ethnic variability was explained by the frequency differences in functional genetic polymorphisms of the drug metabolizing enzymes and transporters.

- However, involvement of other factors in PK differences among populations has been suggested in some drugs, such as Moxifloxacin, Simvastatin, and Meloxicam.

2nd Stage: prospective PK study (Kawai Study Group, MHLW Research Grant)

- To examine factors involved in PK differences of 3 drugs (Moxifloxacin, Simvastatin, and Meloxicam) among populations, prospective global PK studies under same protocol with strictly adjusted trial conditions were conducted in 4 countries (Japan, China, Korea, USA)

Japan:
- Toho University
- Kitasato University Research Center for Clinical Pharmacology
- National Institute of Health Science

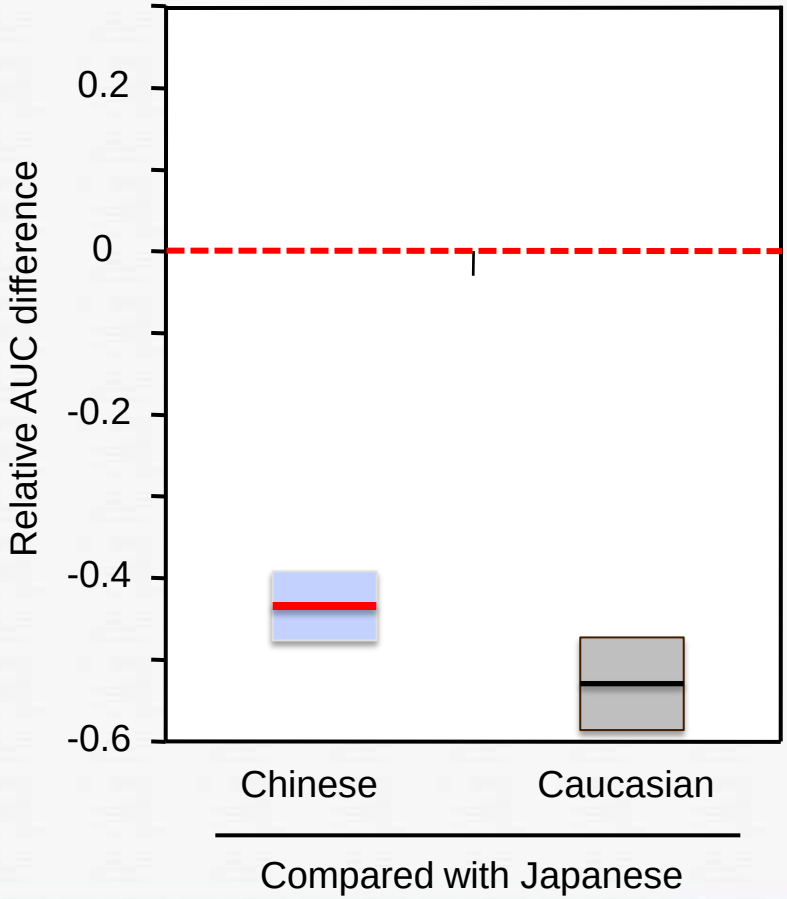
China:
Peking University First Hospital

Korea
Seoul National University Hospital

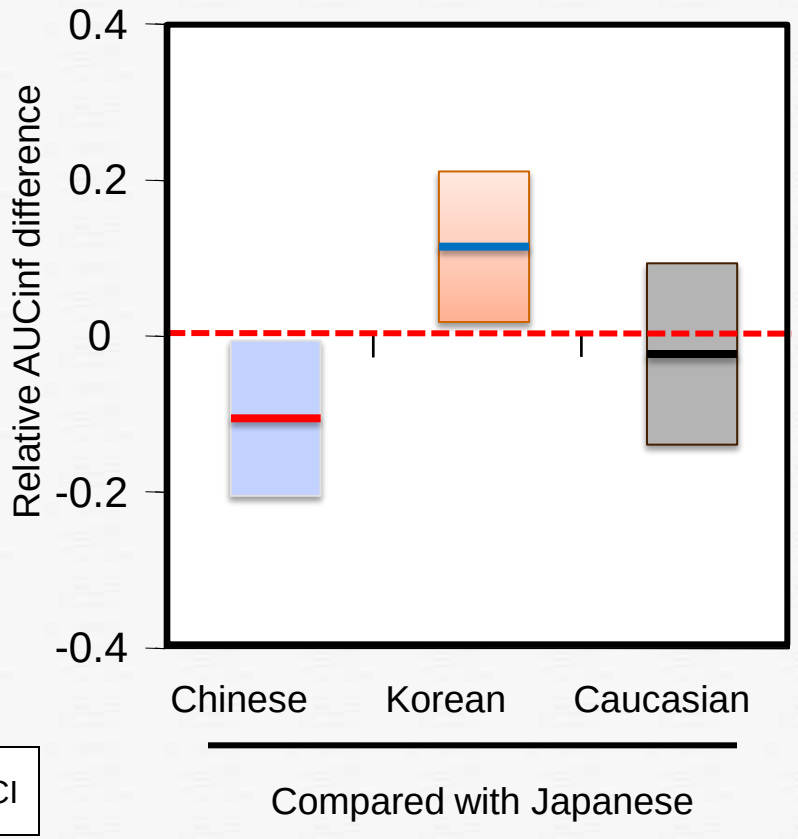
USA:
SNBL Clinical Pharmacology Center

Example: Comparison of AUCinf of Moxifloxacin

Literature-based comparison (Tohkin Study group)



Prospective PK Study (Kawai Study Group)



90%CI

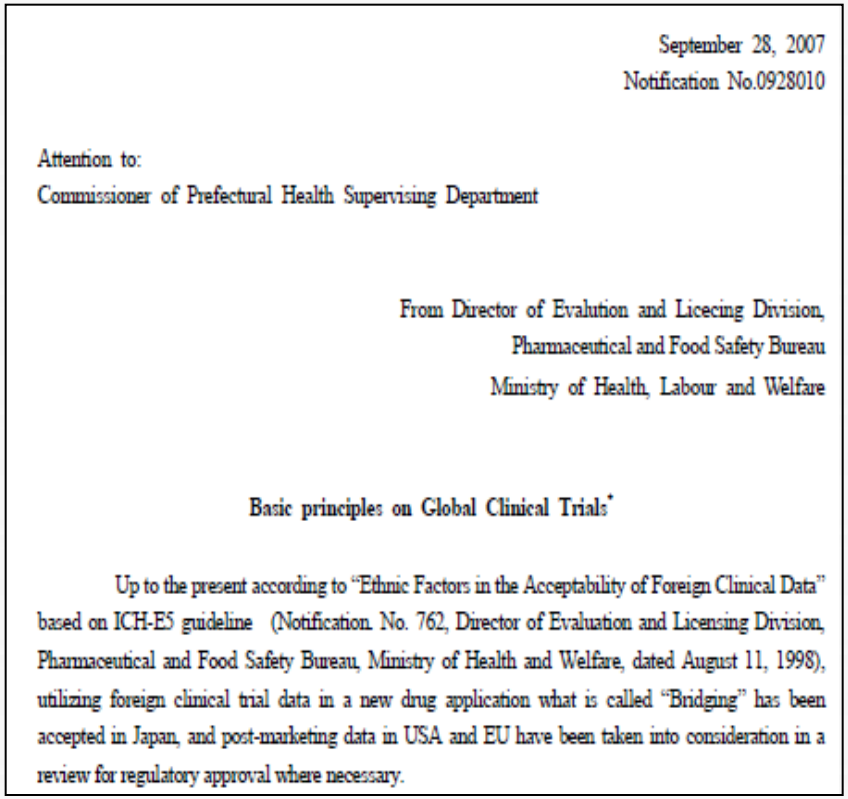
Suggestions from the study results

- In order to assess ethnic differences in PK, a single protocol that controls extrinsic factors should be employed and uniformly applied to the study populations.

- Because polymorphisms of the relevant genes affects PK of a drug, it is recommended to know genotypes of study subjects and take them into consideration before evaluating the clinical data.

Japanese experiences
to review data from Global Clinical Trials

Guidance:
Basic Principles on Global Clinical Trials (GCTs)
(September 28, 2007)



September 28, 2007
Notification No.0928010

Attention to:
Commissioner of Prefectural Health Supervising Department

From Director of Evalution and Licecing Division,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

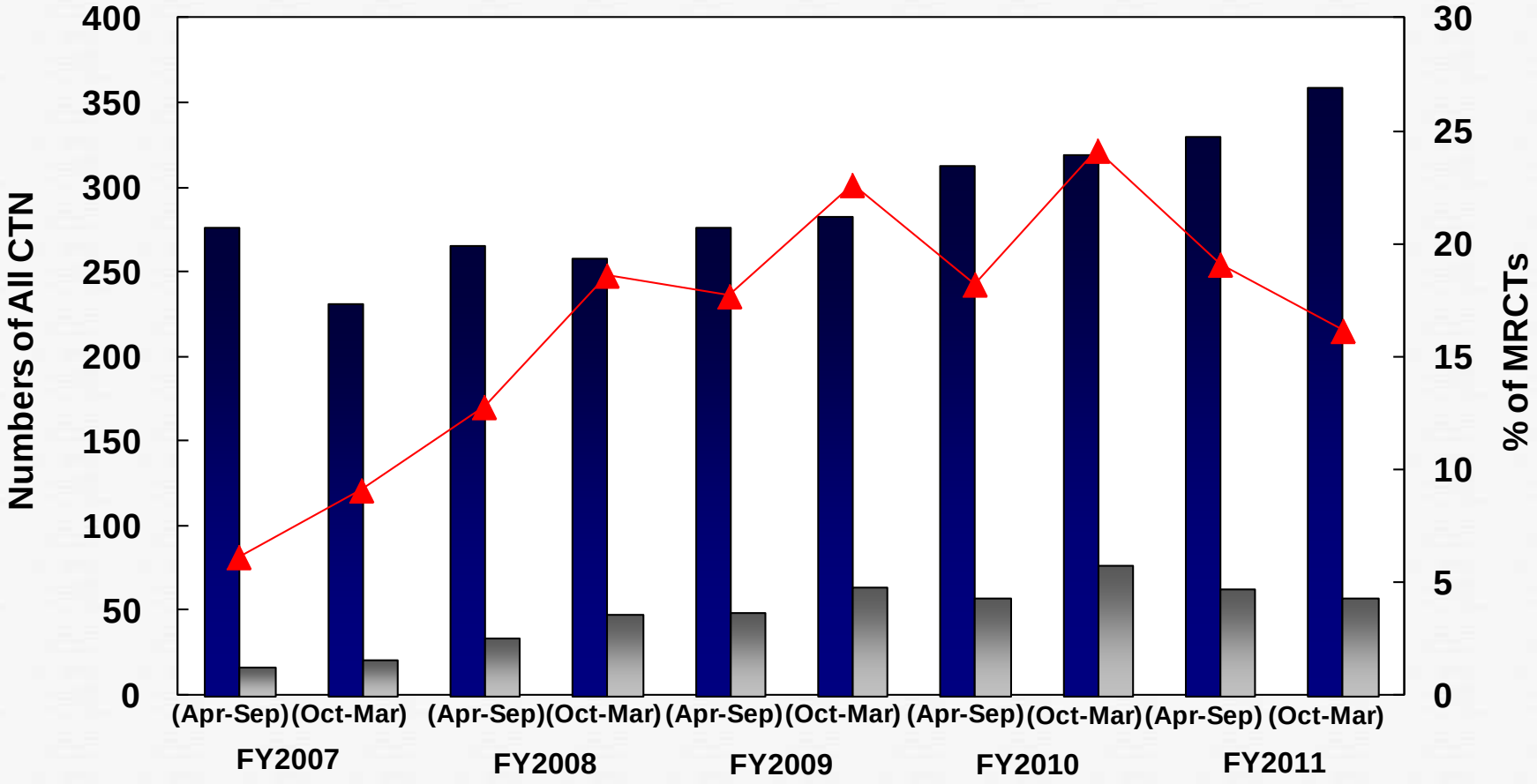
Basic principles on Global Clinical Trials*

Up to the present according to "Ethnic Factors in the Acceptability of Foreign Clinical Data" based on ICH-E5 guideline (Notification. No. 762, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated August 11, 1998), utilizing foreign clinical trial data in a new drug application what is called "Bridging" has been accepted in Japan, and post-marketing data in USA and EU have been taken into consideration in a review for regulatory approval where necessary.

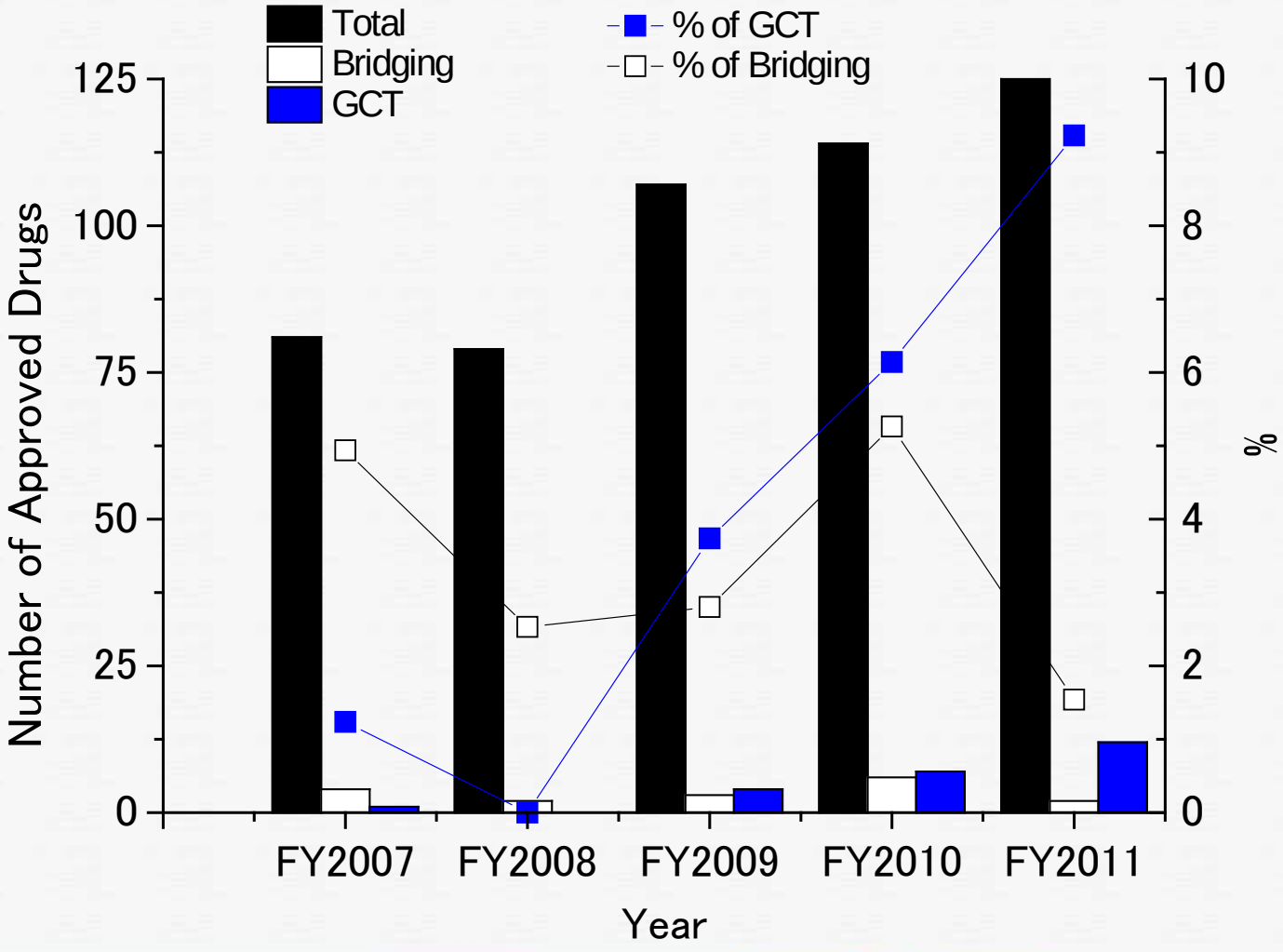
- Encourage Japan's participation to GCTs from an early stage of drug developments
- Clear points to be considered in GCTs
- Promote conducting global clinical trials more appropriately in consideration of ethnic factors

Japanese : http://www.pmda.go.jp/operations/notice/2007/file/0928010.pdf
English : http://www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf

Trends of GCTs including Japan



GCTs or Bridging-based Drug Approval



GCT-based Drug Approval (1)

Name of Drug	Indication	Approval
Tolterodine	Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	Apr. 2006
Losartan	Diabetic nephropathy with proteinuria and hypertension in patients with type 2 diabetes	Apr. 2006
Trastuzumab	Adjuvant therapy for metastatic HER2-overexpressing breast cancer	Feb. 2008
Insulin glulisine	Diabetes mellitus	Apr. 2009
Tadalafil	Pulmonary arterial hypertension	Oct. 2009
Peramivir *	Type A and Type B Influenza virus infection	Jan. 2010
Everolimus	Metastatic renal cell carcinoma	Jan. 2010
Panitumumab	Metastatic colorectal carcinoma with wild-type KRAS tumors	Apr. 2010
Travoprost/Timolol*	Glaucoma	Apr.2010
Temsirolimus	Advanced renal cell carcinoma	Jul. 2010

Red: Asian Global Clinical Trial *: First Approval in the world

GCT-based Drug Approval (2)

Name of Drug	Indication	Approval
Laninamivir *	Type A and Type B Influenza virus infection	Sep. 2010
Nilotinib	Newly diagnosed chronic myeloid leukemia in chronic phase	Nov. 2010
Dabigatran	Stroke and systemic embolism in patients with non-valvular atrial fibrillation	Jan. 2011
Trastuzumab	Metastatic HER2-overexpressing gastric cancer	Mar. 2011
Pramipexole	Parkinson's disease	Apr. 2011
Edoxaban*	Prevention of venous thromboembolism after major orthopedic surgery	Apr. 2011
Dasatinib	Chronic myeloid leukemia (CML)	Jun. 2011
Indacaterol	Chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.	Jul. 2011
Linagliptin	Type 2 diabetes mellitus (adjunctive to diet and exercise)	Jul. 2011

Red: Asian Global Clinical Trial *: First Approval in the world

GCT-based Drug Approval (3)

Name of Drug	Indication	Approval
Gefitinib	EGFR-Positive unresectable or metastatic non-small cell lung cancer (NSCLC)	Nov. 2011
Everolimus	Progressive neuroendocrine tumors of pancreatic origin (PNET)	Dec. 2011
Denosumab	Bone complications in patients with multiple myeloma or solid tumour that has spread to the bone.	Jan. 2012
Aripiprazole	Manic episodes associated with bipolar disorder	Jan. 2012
Olanzapine	Depression episodes associated with bipolar disorder	Feb. 2012
Exenatide	Type II diabetes mellitus (adjunctive to diet, exercise and treatment with SU)	Mar. 2012
Crizotinib	Anaplastic lymphoma kinase (ALK)-positive, advanced or metastatic non-small cell lung cancer (NSCLC)	Mar. 2012

Red: Asian Global Clinical Trial *: First Approval in the world

- Rapidly accumulating experiences of GCT data review
- Recognize an importance of East-Asian contribution

Example of East Asian GCT-based Drug Approval in Japan

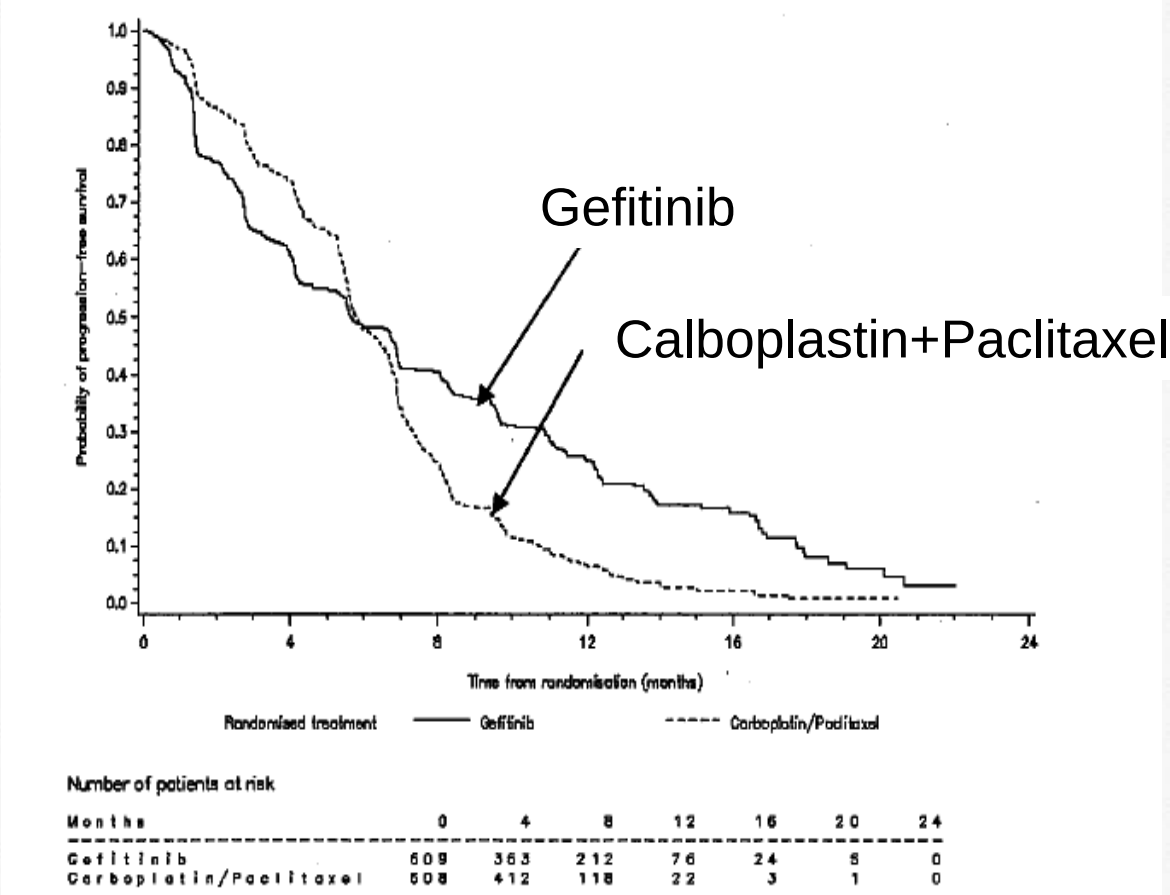
Example 1:

Gefitinib for EGFR-Positive unresectable or metastatic non-small cell lung cancer (NSCLC)

Gefitinib: IPASS study

PFS(Progression Free Survival: Overall population)

Enrolled population	
Total (randomized)	1217
Chinese	618
Japanese	233
Other Asian	363
Others	3

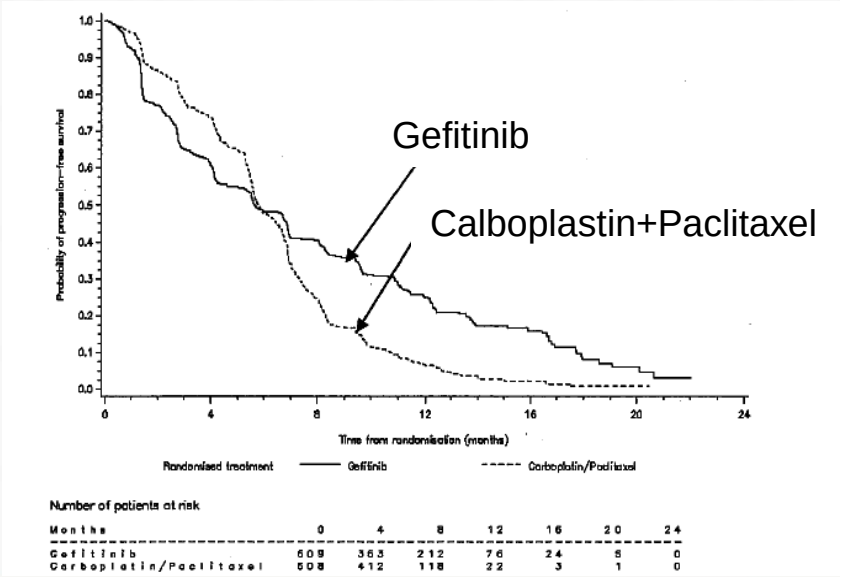


- Confirmed the non-inferiority of gefitinib to calbplastin+paclitaxel

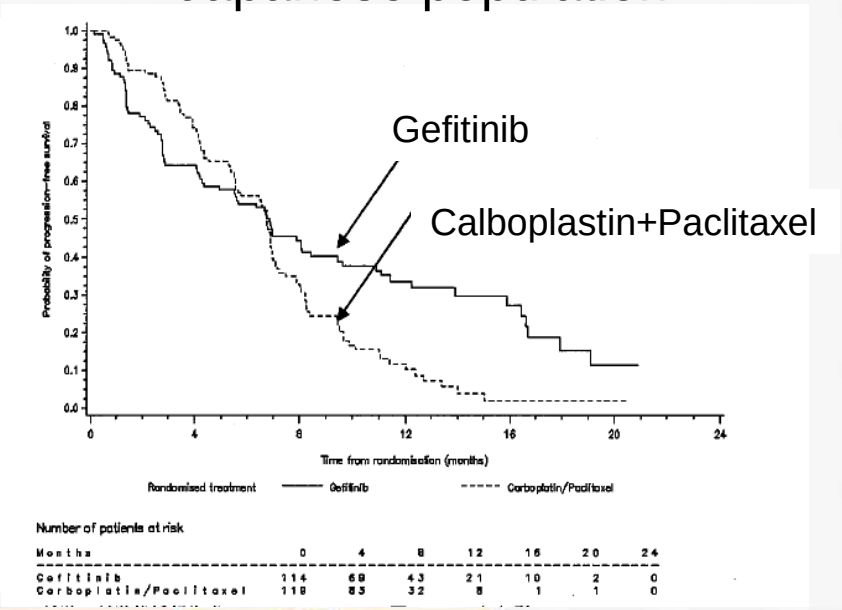
IPASS: PFS (ITT)

	Gefitinib	Calboplastin+ Paclitaxel	HR
Overall	5.7 [5.4, 6.8] (n=609)	5.8 [5.6, 6.4] (n=608)	0.741 [0.651, 0.845]
Japanese	6.9 [4.4, 8.4] (n=114)	6.8 [5.6. 7.0] (n=119)	0.693 [0.510, 0.942]

Overall population



Japanese population

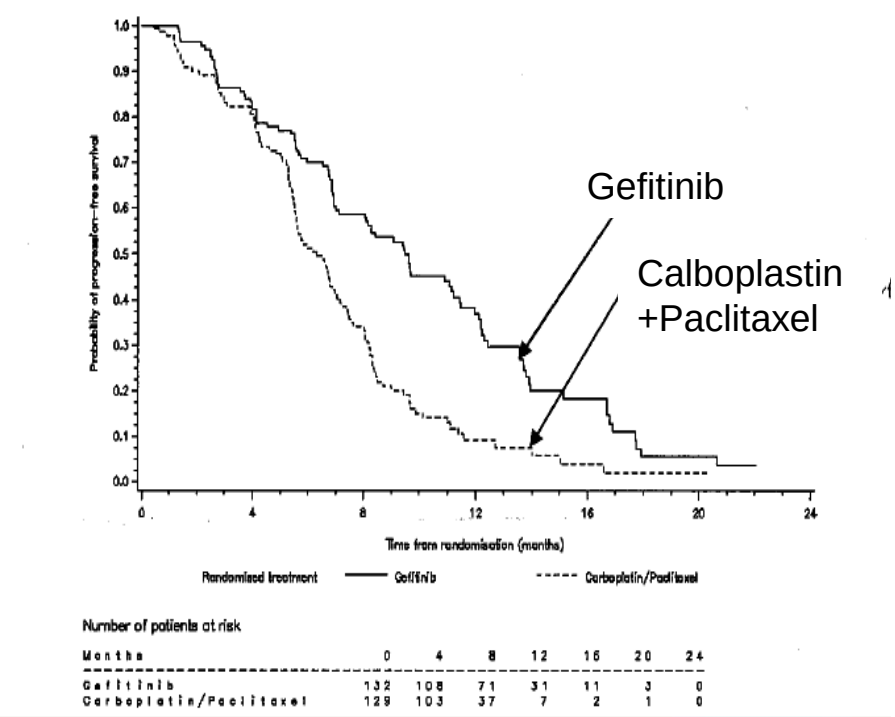


IPASS: Efficacy (EGFR Mutation)

- Genetic samples were collected from 653 patients (56 %)
- Samples from 437 patients (36 %) were available for genetic data review

PFS: Overall population

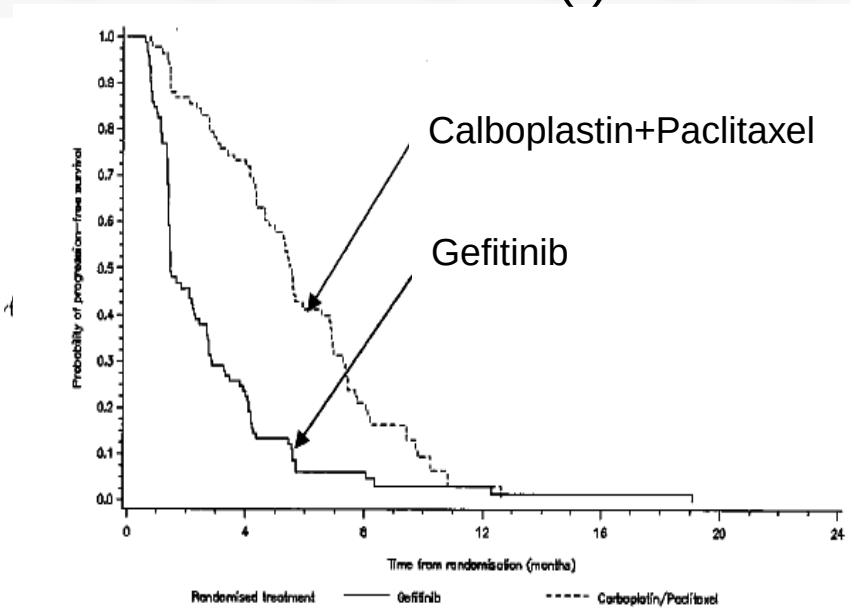
EGFR (+)



Number of patients at risk

Months	0	4	8	12	16	20	24
Gefitinib	132	108	71	31	11	3	0
Carboplatin/Paclitaxel	129	103	37	7	2	1	0

EGFR (-)



Number of patients at risk

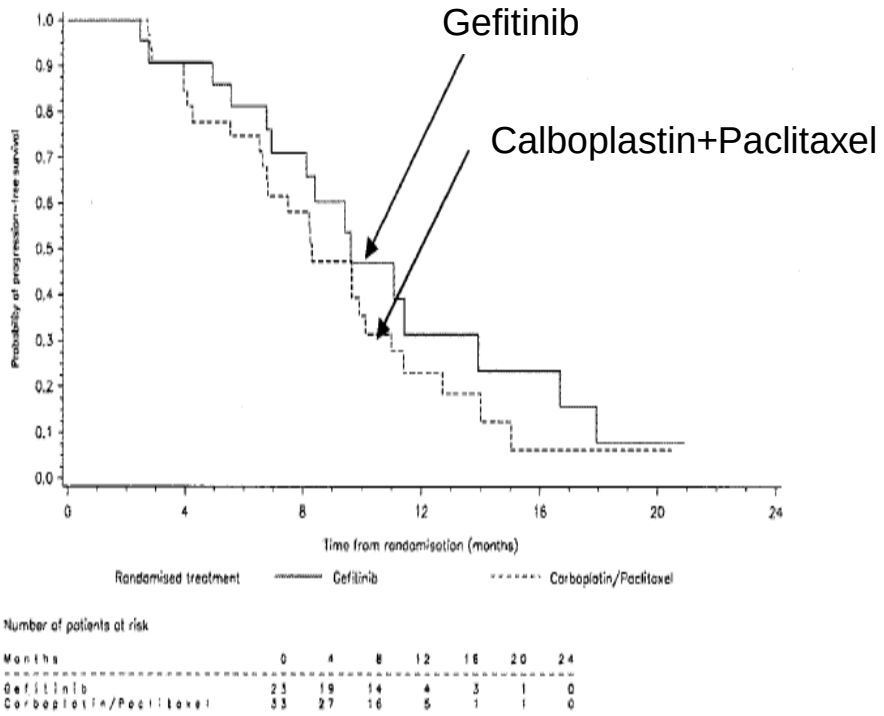
Months	0	4	8	12	16	20	24
Gefitinib	91	21	4	2	1	0	0
Carboplatin/Paclitaxel	85	58	14	1	0	0	0

IPASS: Efficacy (EGFR Mutation)

- EGFR mutation status was examined in only 91 Japanese patients (39 % of total Japanese patients)

PFS: Japanese population

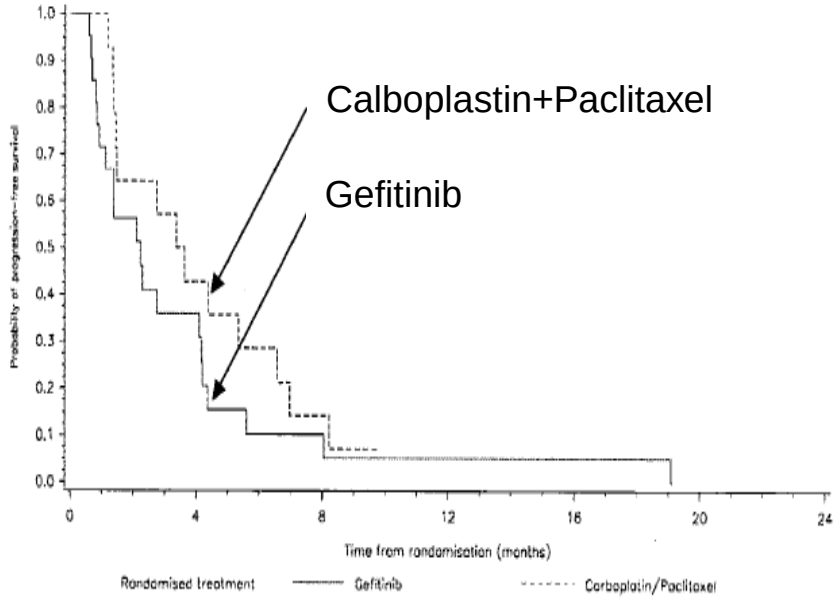
EGFR (+)



Number of patients at risk

Months	0	4	8	12	16	20	24
Gefitinib	23	19	14	4	3	1	0
Carboplatin/Paclitaxel	33	27	16	5	1	1	0

EGFR (-)



Number of patients at risk

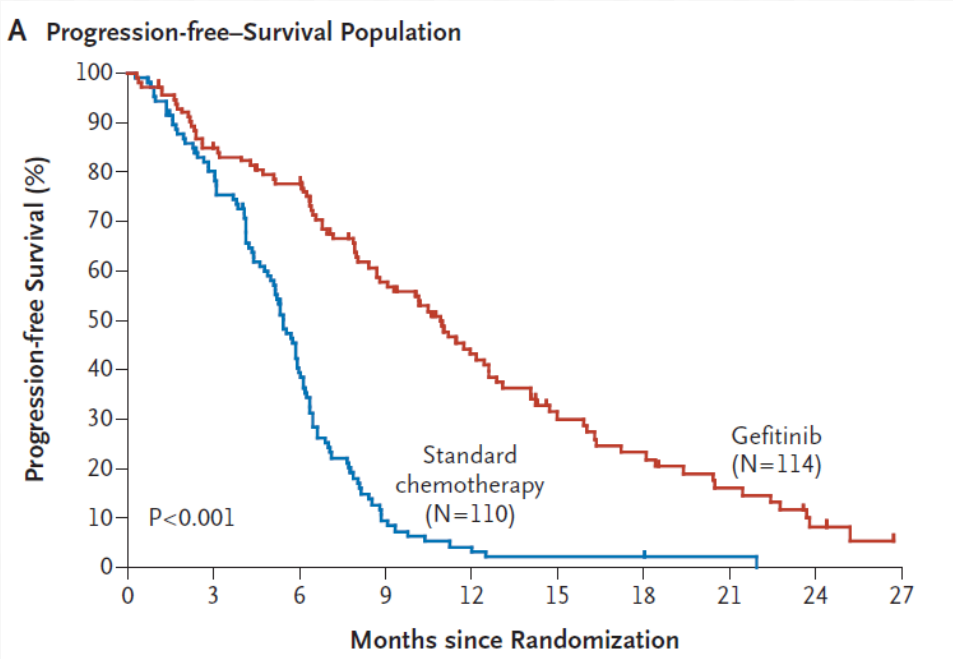
Months	0	4	8	12	16	20	24
Gefitinib	21	7	2	1	1	0	0
Carboplatin/Paclitaxel	14	6	2	0	0	0	0

Other studies available for review

- Independent prospective studies (Investigator-initiative trial) support the efficacy of gefitinib in EGFR(+) Japanese patients

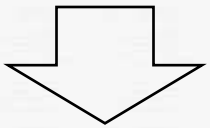
  (Maemond M et al., New Engl J Med., 362: 2380-8, 2010, Mitsudomi T et al, Lancet Oncol, 11: 121-8, 2010)

	Gefitinib (N = 114)	Carboplatin –Paclitaxel (N = 114)
Exon 19 deletion	58 (50.9)	59 (51.8)
L858R	49 (43.0)	48 (42.1)
Others	7 (6.1)	7 (6.1)



Summary

- Efficacy of gefitinib was confirmed in IPASS study (mainly including East-Asian patients)
- No major difference was shown between Japanese and overall population
- Favorable response were shown in EGFR(+) patients
- Independent prospective studies support efficacy of gefitinib in EGFR(+)-Japanese patients

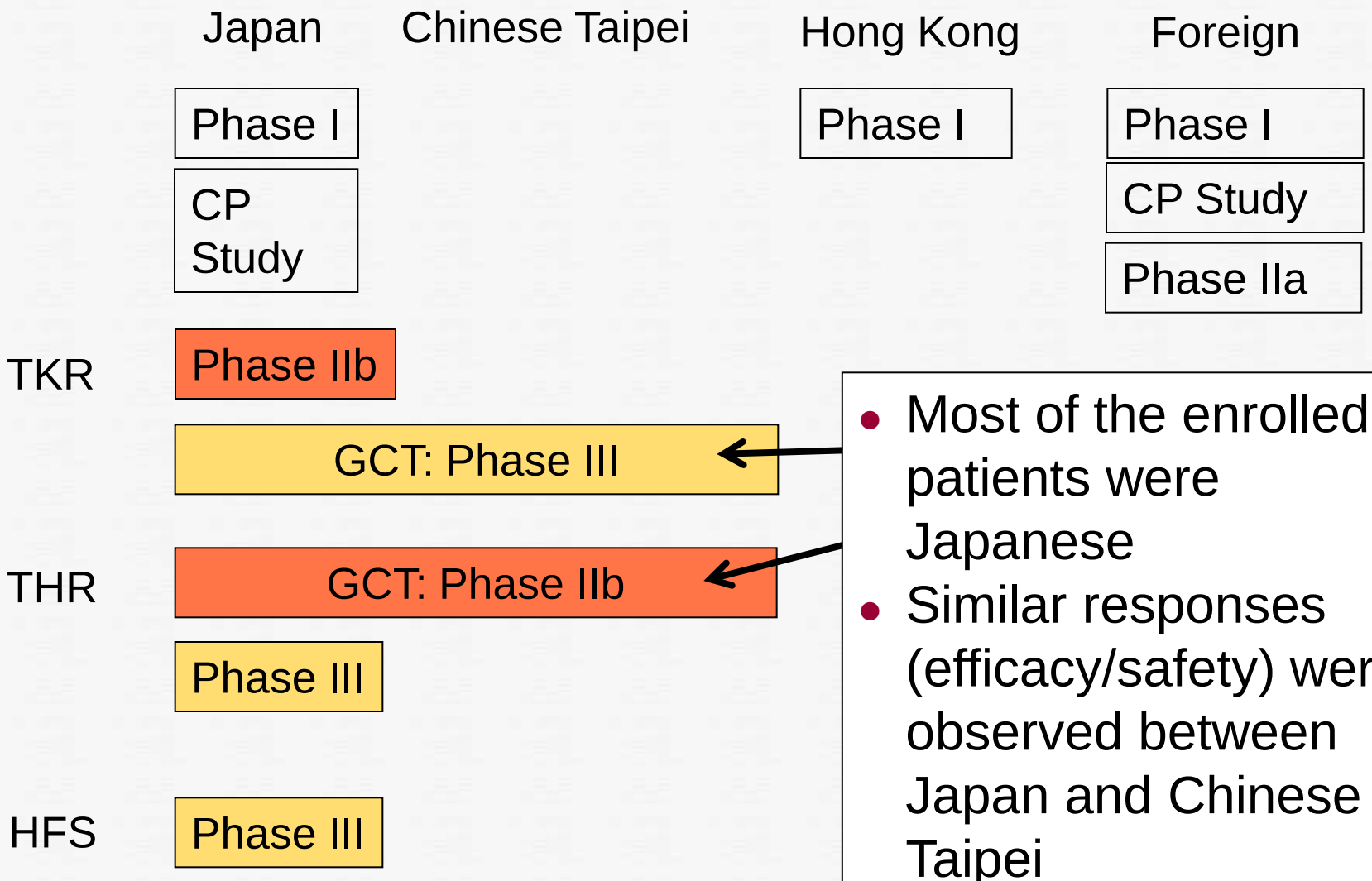


The indication of gefitinib was revised to limit to the EGFR(+) patients

Example 2:

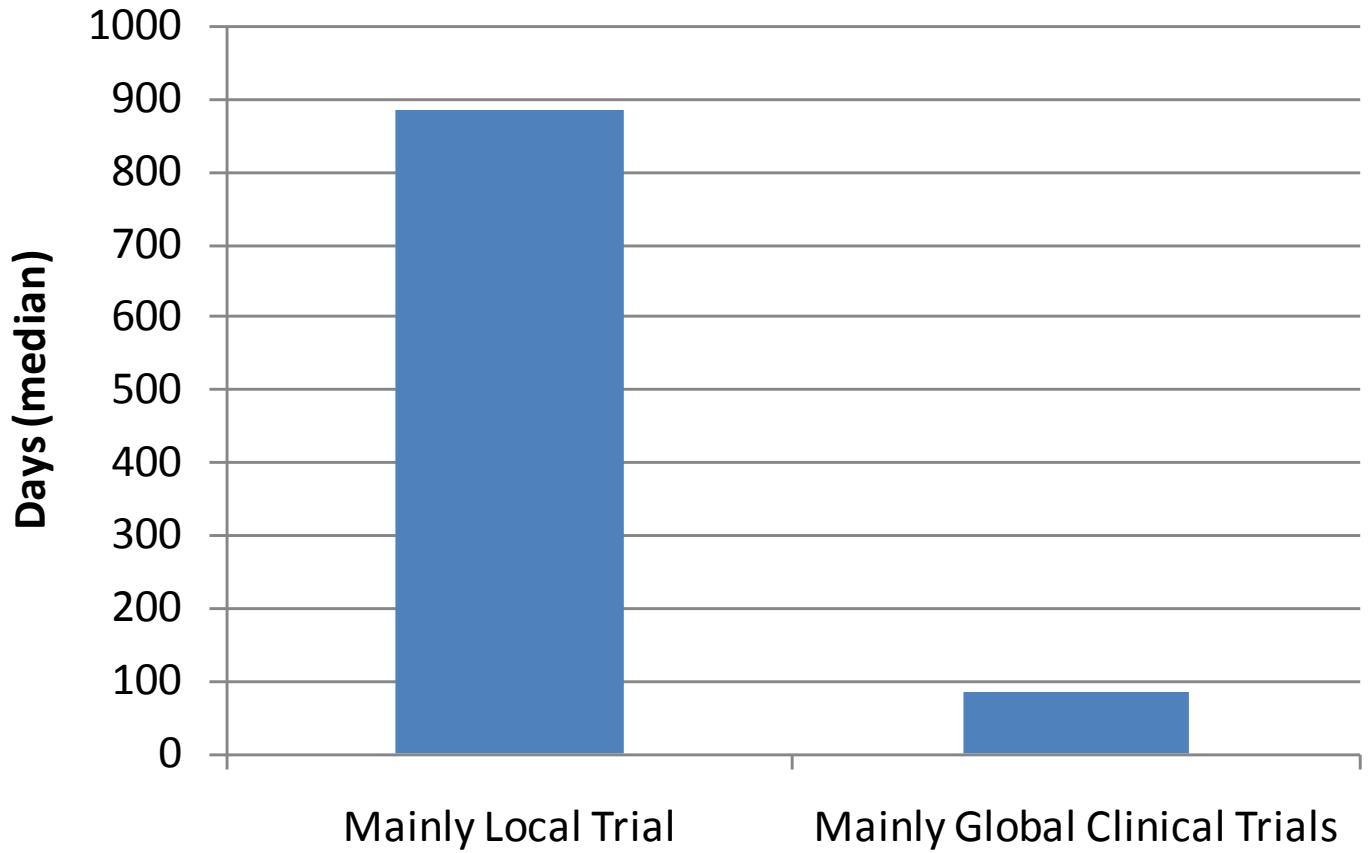
Edoxaban for the prevention of venous thromboembolism (VTE) in patients with total knee arthroplasty, total hip arthroplasty and hip fracture surgery

Clinical Data Package



GCTs contributes to resolve Drug Lag

Approved in FY2009-FY2011（as of Sep. 30th)



*: Difference of NDA application date between USA and Japan is calcualted.
The difference is asuumed 0, if a drug is not approved in USA.

New Guidance
"Basic Principles on Global Clinical Trials (Reference Cases) (Draft)"

- MHLW/PMDA is preparing to publish another new guidance document
- Contents of the document is based on recently accumulated scientific data and our experiences
- The document is intended to further promote an understanding of the 2007 notification and ensure Japan's smooth participation in global drug development activities at an early stage as well as smooth and proper implementation of East-Asian global clinical trials

Examples of Expected Discussion Points (1)

- Points to consider in conducting East-Asian global clinical trials
- Recommended therapeutic area for East-Asian global clinical trials
- How to develop global drug development strategies based on data of interethnic comparison of pharmacokinetics
- Points to consider in comparing PK data between different ethnicities
- Points to consider in evaluating the results of a global clinical trial

Examples of Expected Discussion Points (2)

- Points to consider in conducting a global clinical trial when PK exposure is different between Japanese and non-Japanese subjects
- Points consider in evaluating the data of Japanese subjects living overseas enrolled in overseas studies
- Points to consider when the target sample size of Japanese is not achieved in a global clinical trial
- Points to consider in participating in a large-scale global clinical trial using a true endpoint such as survival time
- Points to consider in the required Japanese sample size to evaluate long-term safety of a drug that clinical trials are mainly conducted as a global clinical trial

Conclusion

- For a better assessment regarding effects of ethnic factors on drug efficacy and safety, more scientific data should be accumulated.

- A GCT under the same protocol will provide valuable information to examine ethnic similarities/differences for regulatory review

Acknowledgement

- Dr Kawai, S (Toho University)
- Dr Tohkin, M (Nagoya City University)

Thank you for your attention