Considering A Bridging Strategy Driven By Patient Need and Contemporary Science

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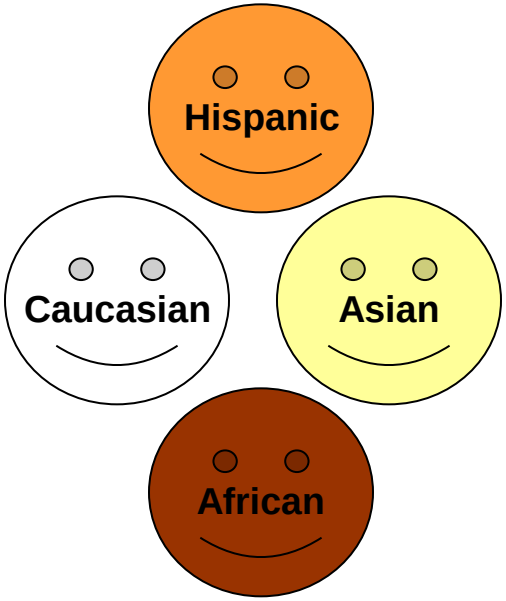
The 'Ethnic Drug Development and Approval Paradigm' as I see it

- **Disease differences between regions** are not adequately considered in global development plans or approval guidelines
- **Ethnic diversity in a very large number of PK, PD, efficacy & safety variables** makes conventional development planning difficult
- If one accepts these thoughts, then there may be some fundamental changes in how we develop and approve drugs

Disease

- Mechanism(s)
- Pathophysiology
- Morbidity & mortality



Race (Black, Asian, Caucasian) **& Ethnicity** (Hispanic)

Drug

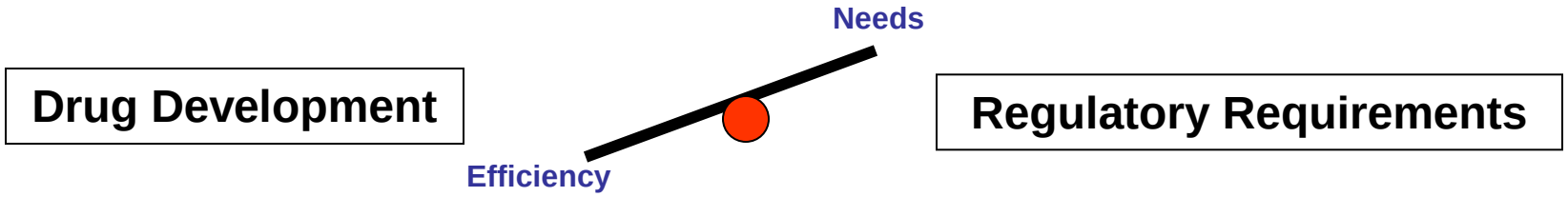
Pharmacokinetics (PK)
- Absorption
- Distribution
- Metabolism
- Excretion

Pharmacodynamics (PD)
- target mechanism(s)
- off-target mechanism(s)
- Receptor(s)
- Biomarker(s)
  - Linked to mechanism
  - Linked to outcome

Countries (i.e., China): **racial & ethnic mix, culture, economy, environment**

- Race, ethnicity & nationality: known differences in disease and drug PK & PD
- Drug efficacy & safety related to country (e.g., French), region (EU), ethnicity, gender…
- Drugs approved both by countries and regions representing their populations

Finding the Right Balance (local vs global)



Phase 1-3 development

- **Inefficient and too expensive to duplicate in each country**
- **Research must meet minimum global quality standards (GCP, GLP)**

Country regulatory requirement for NDA approval

- **Country experience required to support approval?**
- **Are Japanese or Chinese patients ≈ Asian patients?**
- **Is there a need to revise ICH5 or write a Global development guideline?**
- **Should regulatory dialogue on global drug development strategy occur early?**
- **Should simulation be encouraged to support planning (e.g., trial design)?**

Pharmaceutical companies can

- **Create global development plan based on known differences**
- **Implement learn-simulate-confirm cycle in drug development to account for global variables influencing disease, pharmacokinetics, pharmacodynamics**

Outline

- Bridging need
- Bridging potential issues
- International & local bridging guidelines
  - ICH-5
  - Japan
  - China
  - U.S.
- Are current assumptions correct?
- New approach to global drug development
- Scenarios

Key Questions for Developers & Regulators

between country-ethnic differences?
NDA population sample & bridged country population?

- **Disease**
  - Is disease the same (e.g., mechanism, pathogenesis, progression, morbidity & mortality)?
  - Is medical practice the same (e.g., diagnostic criteria)?
  - Is disease severity the same?
  - Are co-morbidities the same?
- **Pharmacology (efficacy-safety)**
  - Is efficacy-safety dose-response (PK-PD) the same?
  - Is the link between biomarkers and efficacy-safety the same?
- **Benefit-Risk**
  - Are benefits and risks perceived the same between ethnic groups?

Issues

- Regulatory requirements are formulaic such as specifying a pharmacokinetic study + a fixed number of patients in phase 3 trials for all diseases and drug classes
- Country drug approval strategies may not account for ethnic or regional differences
- Efficient global drug development strategy balancing local patient needs and global development financial expense
- Opportunities for between country collaboration

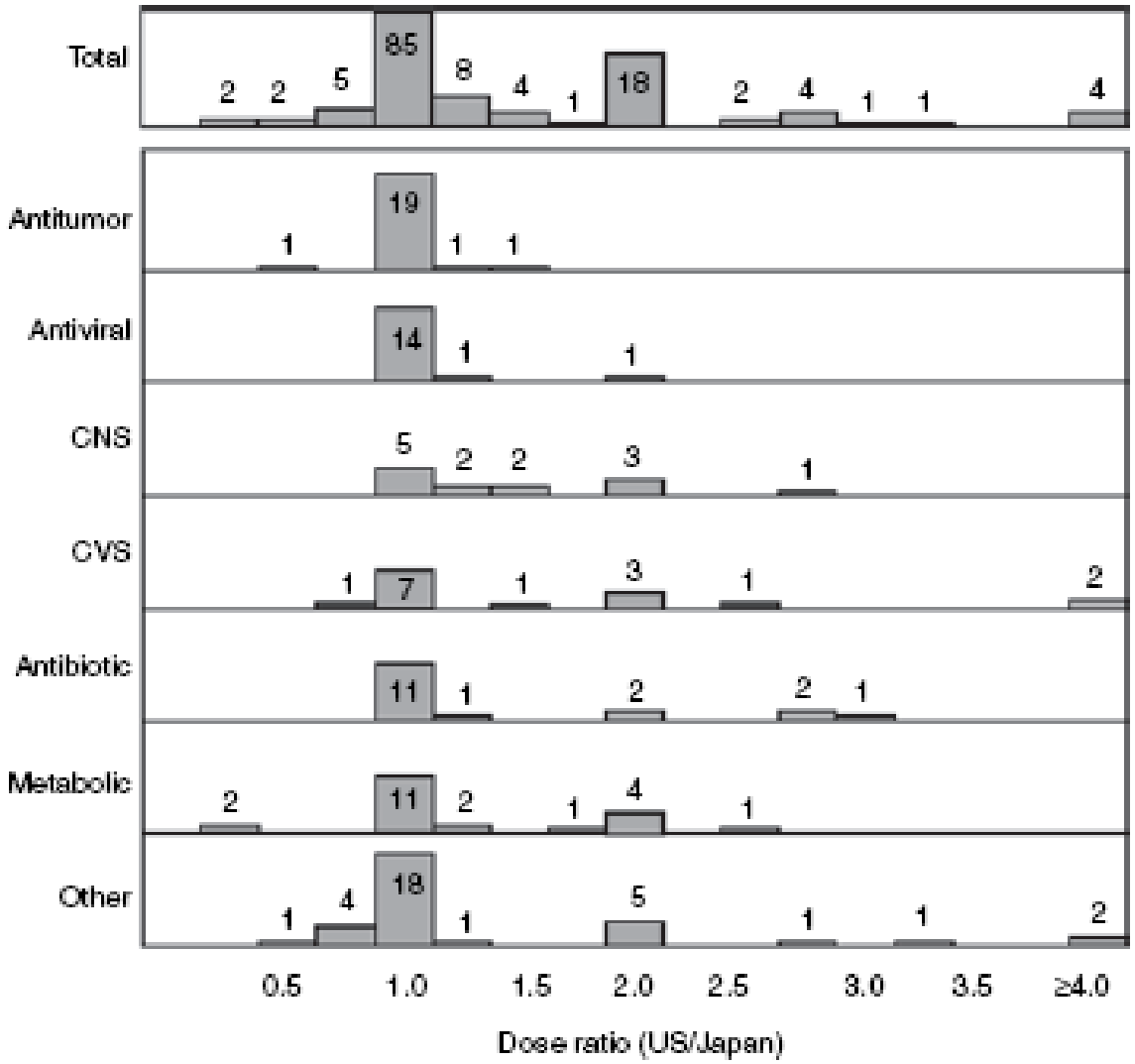
International & local bridging guidelines

- **ICH5** (http://www.ich.org/LOB/media/MEDIA481.pdf)
  - **Premise**.
    - Development efficiency- sharing development data for regulatory decisions between regions
    - 'Acceptability of the foreign clinical data component of the complete data package depends then upon whether it can be extrapolated to the population of the new region.'
  - **Focus**. Pharmacokinetics, pharmacodynamics, dose-response, efficacy, safety, clinical trial standards.
  - Disease topics
    - Endpoints for assessing treatment effectiveness
    - Medical and diagnostic definitions acceptable to the new region
  - **Recommendation**. Amend ICH5 to gain an assessment of
    - Disease differences, if any and clinical significance, if any
    - How to manage drug development if the disease difference is deemed to be clinically significant

International & local bridging guidelines
(1st approved elsewhere scenario)

- **Japan**
  - **Bridging experience** (Clin Pharm Ther 87:362, 2010)
    - In 2006 2.5 year drug lag (compared to USA) sequential rather than parallel development
      - ICHE5 guideline implementation in Japan may have led to the 2.5 year lag starting ~late 90s. (Drug Info J 43:3, 2009)
        - » Wanted only Japanese, not Asian patients
        - » Japanese patients in every development phase
    - Lower doses in Japan (vs USA-EU) 31.2% approved new drugs 2003-7 (n=41)
  - **Global Clinical Trial recommendation 2007** (http://www.pmda.go.jp/english/service/pdf/notifications/0928010-e.pdf)
      - Definition. 'A trial designed for a new drug aiming for worldwide development and approval, having multiple countries, regions, and medical institutions participating in a single clinical trial and conduct concurrently in accordance with a common clinical trial protocol.'
      - Recommend Japanese participate in dose finding studies
      - Japanese patients 15-20% of total

Japanese Approved (2001-7, N=137) Drug Dose Ratios (US/Japan)



Clin Pharm Ther 87:714, 2010

International & local bridging guidelines (1st approved elsewhere scenario)

- Japan
- China
  - PK study-mainland
  - ≥100 pairs Chinese patients-mainland
- USA
  - Case by case basis with CDER division
  - Concern when all data foreign
  - No guideline, but ≥25% U.S. patients target my advice

Height by Location

(descending male cm)

	Male (cm)	Female (cm)
Netherlands	185	169
Sweden	180	167
Finland	178	165
Germany	178	165
USA	178	164
Japan	171	159
Hong Kong	170	159
Mexico	167	155
China	165	155
Philippines	164	152

http://www.disabled-world.com/artman/publish/height-chart.shtml

Evidence for Differences

Chronic Hepatitis B

Criteria	USA, EU	Asia
Transmission	Adult > Perinatal	Perinatal ≥ Adult
Virus genotype- (predominant)	A	B,C
HIV co-infection	5-10%	20-30%
Cirrhosis risk		lower
Hepatocellular carcinoma risk		greater
Genotype Interferon alpha 2b HbeAg & HbsAg seroconversion	A>B>C>D	

J Hepatol 48:355, 2008 & NEJM 359: 1486-500, 2008

Evidence for Differences

Lung Cancer

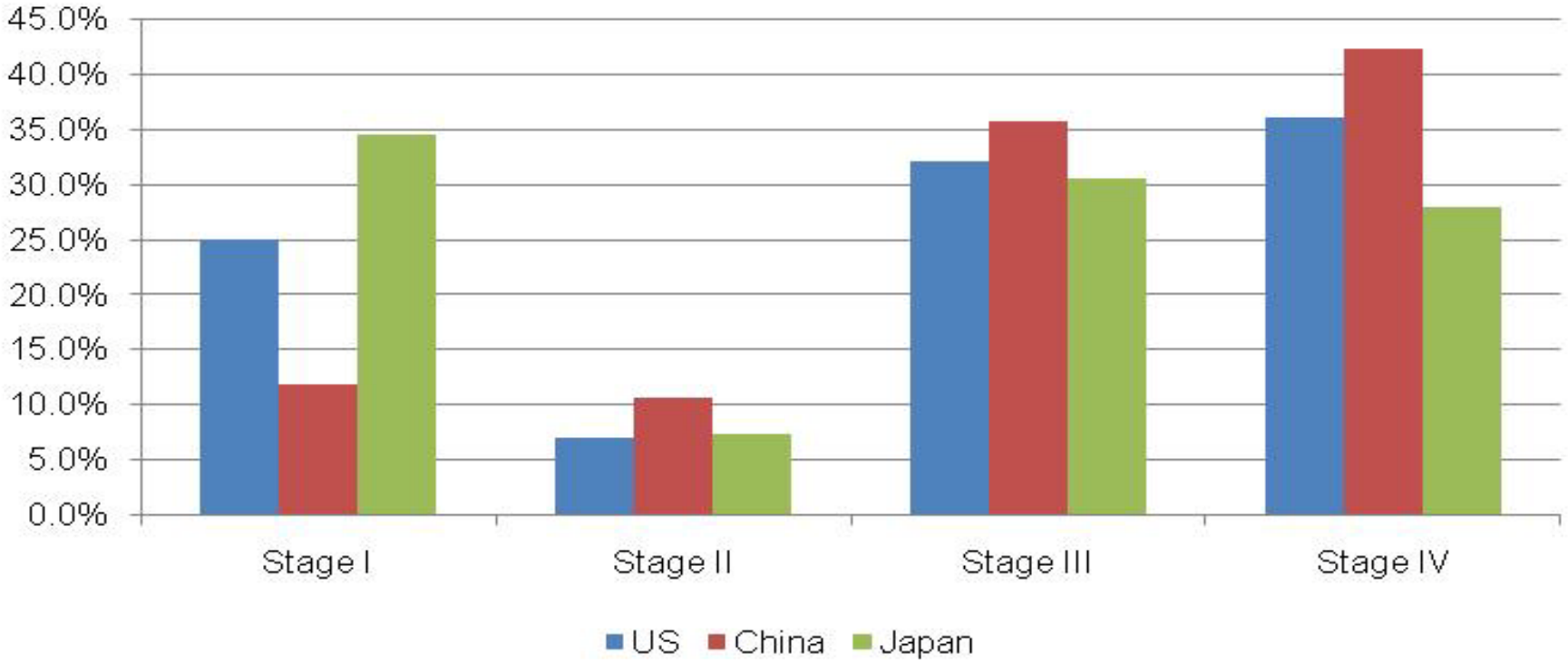
	Western	Asian
Efficacy		
–NSCLC		
• EGFR Mutations		
–All patients	7%	31%
–Adenocarcinoma	13%	47%
–Non-smokers	35%	56%
• Efficacy response		
– Erlotinib	10%	28%
– Gefitinib	5.5 mo MST★	9.5 mo MST★
Toxicity (grade 3-4)		
–Carboplatin + paclitaxel		
• Neutropenia	6-65%	88%
• Febrile neutropenia	0-4%	16%
– Cisplatin + vinorelbine		
• Neutropenia	37-83%	88%
• Febrile neutropenia	1-22%	18%

★ Median Survival Time

Br J Cancer 99:1757-62, 2008

Evidence for Differences

Lung Cancer Stage



Data from Draco Epidemiology Study, 2008

Evidence for Differences

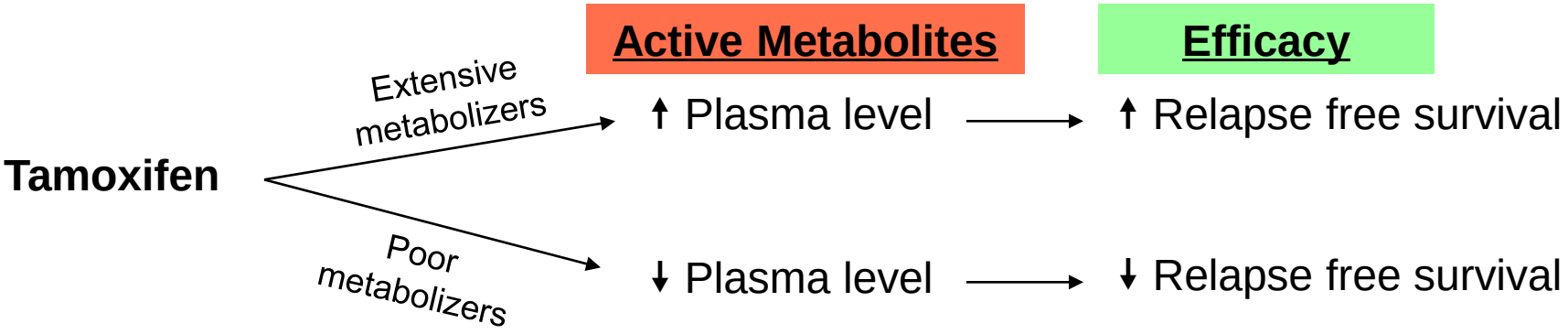
Breast Cancer

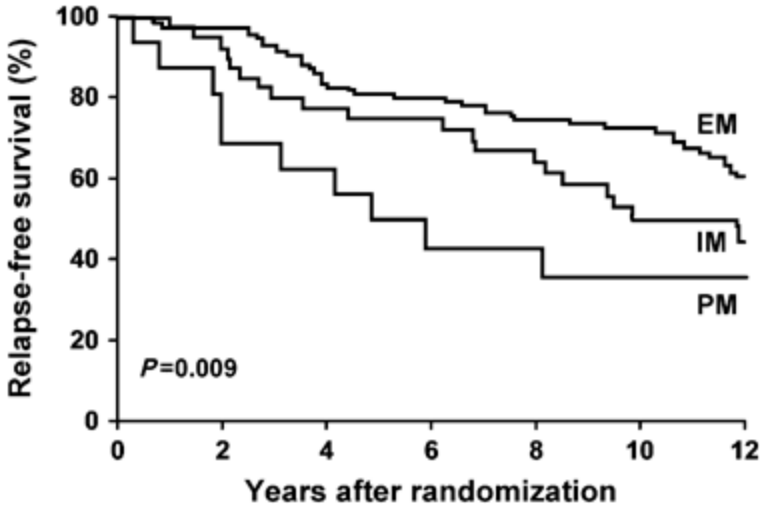
	Western	Asian
Incidence	$101/10^5$	$60/10^5$ and ↑
Demographics	Post>Pre-menopause	Pre>Post menopause
Receptors status (Estrogen, progresterone, p53, HER-2/*neu*))	similar	Similar, ↑ HER-2/*neu*
Prognosis	73% 5 year survival	• 58-84% 5 year survival depending on resources • later stage dx → ↓ survival

Cancer 98: 1587, 2003; Cancer 112: 171, 2008; Breast Ca Res 11: 1, 2009

Tamoxifen in Breast Cancer

Tamoxifen indicated for estrogen (+) breast cancer to prevent recurrence after surgery





EM- extensive metabolizers

IM- intermediate metabolizers

PM- poor metabolizers

- **15-21% Caucasian**
- **~ 57% Asian**
- **20-34% African-African American**

Breast Cancer Res Treat 101: 113, 2007

Diet, Exercise & Lifestyle

Comparing Japanese-Americans to Native Japanese

30 year longitudinal study healthy & type 2 diabetics ~ currently or originally from Hiroshima

	Japanese-Americans	Japanese
Diet & exercise	• ↓ complex carbs • ↑ animal fat • ↓ exercise	• ↑ complex carbs • ↓ animal fat • ↑ exercise
Diabetes Diagnosis @ 40 yrs (1978-88)	• 18.9% Hawaii (n=873) • 13.7% LA (n=1175)	6.2% (n=2510)
Biochemistry (serum)	• Cholesterol 2x • Triglycerides 1.5 x • ↑ glucose fasting	
Ischemic heart disease mortality	44% (n= 2551)	12.3% (n=9737)

Biomedicine & Pharmacol 58: 571, 2004

Evidence for Differences

Type 2 Diabetes

	Asian relative to Caucasian
Demographics	• Younger • Prevalence less but rapidly increasing
Body	• Normal to <overweight using BMI • Diabetes risk increased at lower BMI • More visceral fat than Europeans at same BMI
Complications	End stage renal disease & stroke more common
Genetics	No clear difference
Drug response	No known differences

JAMA 301:2129, 2009

Disease Summary

- Significant disease differences exist
- All differences need to be placed in clinical significance context
- Many diseases have either not been as thoroughly investigated in Asians relative to U.S. and Europe
- Asian government-academic opportunities

Pharmacokinetics

Ethnic differences

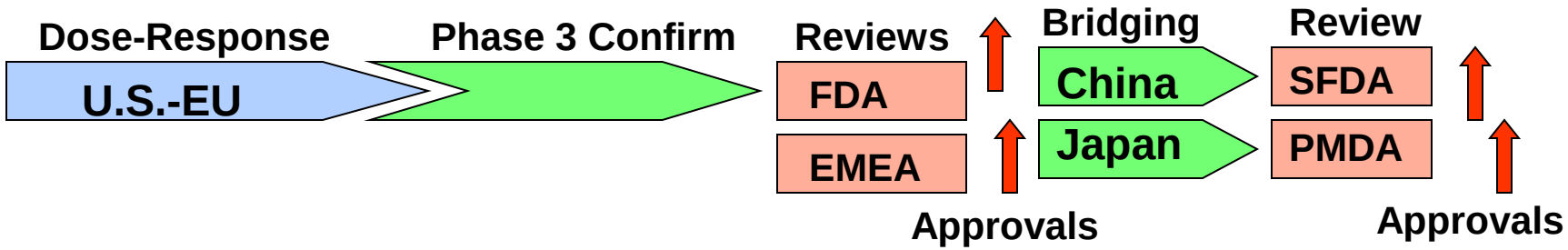
- **Absorption**
  - Passive: no differences
  - Active (transporters): potential
- **Metabolism**
  - Phase 1: >300 alleles various enzymes. Ethnic differences. Some clinically significant
  - Phase 2: >13 alleles different enzymes. Differences.
- **Distribution & excretion**
  - Passive: no difference
  - Active (transporters): potential
- **Human Pharmacokinetics**
  - Differences reflecting active processes
  - Small N~12 in studies
  - No guidance on patient selection, number, design
  - Not in drug development decision pathway. Not predictive of dosing

Dilemma

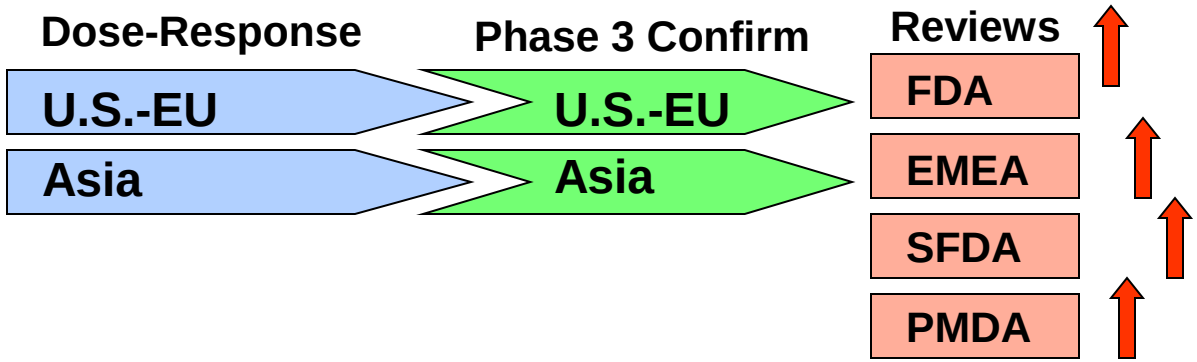
- Current bridging path is too simplistic to guide drug use and dosing in bridged population
- Potential variables influencing efficacy and safety are too many and complex to effectively and efficiently create development plan and trial designs
- Regulators worry about disease differences, but little guidance available
- So, what to do?

Development-Regulatory Scenarios

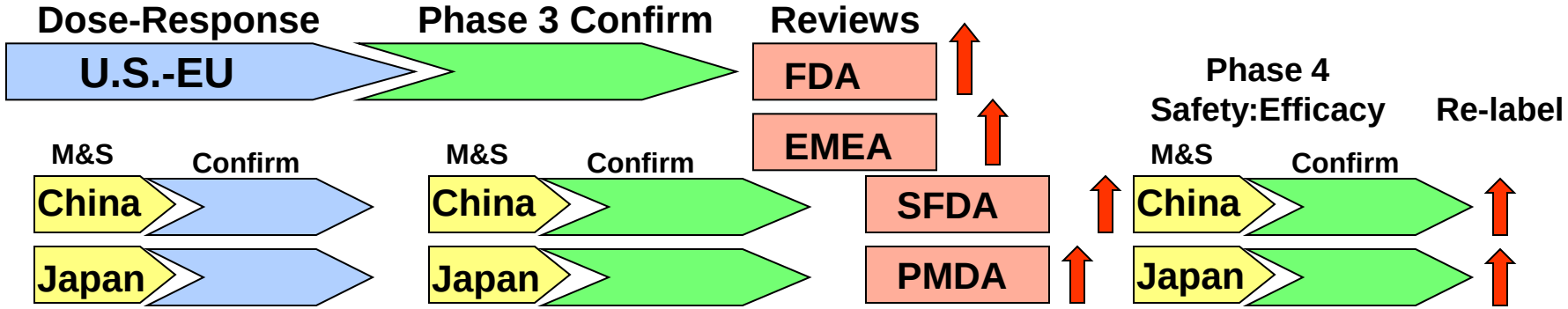
1. Sequential: approve elsewhere, local bridge



2. Parallel: Global development plan & Phase 3 trial(s), simultaneous approvals



3. Modeling & Simulation (M&S)-confirmation based

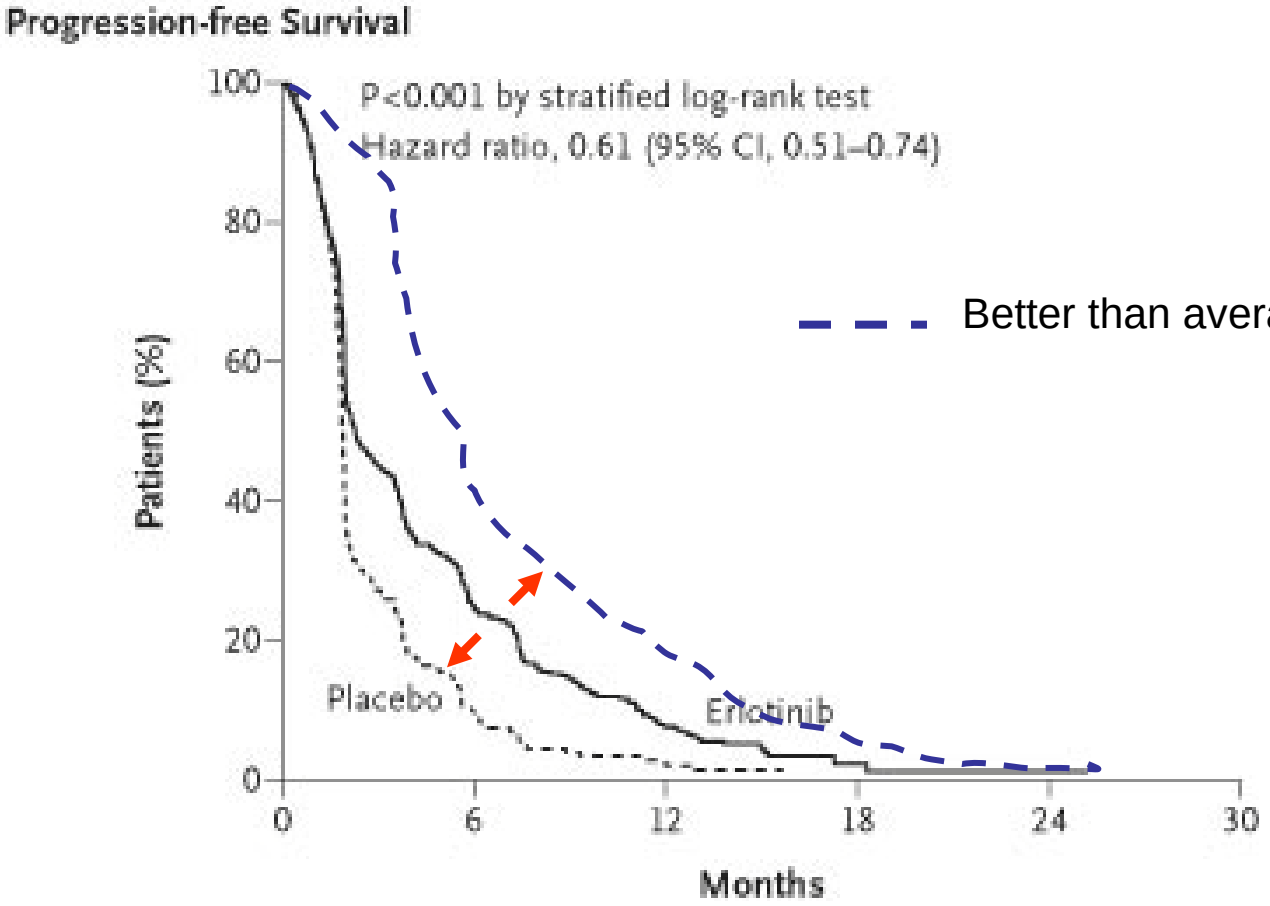


Scenario Comparisons

	1. Sequential	2. Parallel	3. Simulation-Confirm
Time to market	4-5 years longer than 2.	fastest	0.5-1 year longer★ than 2.
Expense	$$	$$$$$	$$$★
Dose-Response	Poor	Good	Best
Efficacy	Poor	Good	Best
Safety	Poor	Good	Best
Regulatory Change?	No	Yes	Yes

★ Could be less time and expense

Example
Are Asians Better (↑) or Worse (↓) than Average Drug Response in NSCLC ?



N Engl J Med 353: 123, 2005

Modeling & Simulation

- **Model**
  - **Disease** mechanistic or empirical relationships to primary disease endpoints
  - **Pharmacology**: known prior dose-response (PK-PD) relationships to biomarkers, intermediate or primary endpoints (Phase 1,2)
  - **Asian** phenotypes & genotypes (disease, adme, PD)
  - **Prior knowledge** (publications, NDA reviews) with disease & drug class
    - Baseline
    - Dropout
- **Simulate**
  - Asian clinical trial design(s) for Phase 2, 3, 4

Non-Small Cell Lung Cancer Model

(Yaning Wang et al)

- 4 NSCLC registration trial data used to develop model linking survival to risk factors and tumor size change during treatment
- Reason. To facilitate drug development decisions regarding trial design and treatment effect (high trial failure rate)
- Registration trials: bevacizumab, docetaxel, erlotinib, pemetrexed
- Number of patients: 3,398 total; 2,445 with baseline & week 8 post-Rx start
- The full model

$$\log(T) = \alpha_0 + \alpha_1 \times ECOG + \alpha_2 \times (Baseline - 8.5) + \alpha_3 \times PTR_{wk8} + \varepsilon_{TD}$$

T = time to death (days)

$\boldsymbol{\alpha_0}$ = intercept

$\boldsymbol{\alpha_1}$, $\boldsymbol{\alpha_2}$,$\boldsymbol{\alpha_3}$ = slopes for ECOG

ECOG = Eastern Cooperative Oncology Group performance score

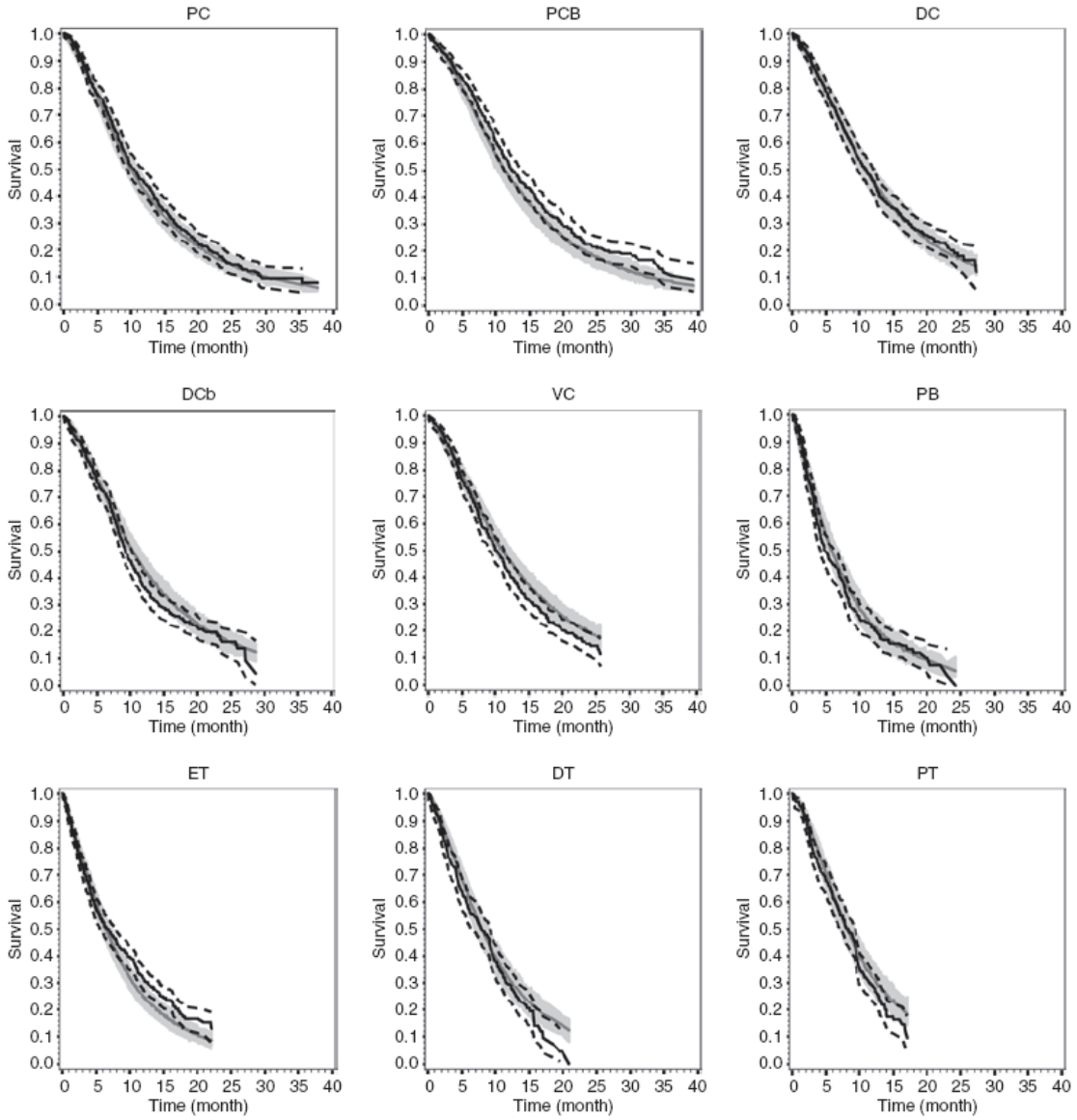
PTR_{wk8} = % tumor reduction from baseline

$\boldsymbol{\varepsilon_{TD}}$ = residual variability

Clin Pharmacol Ther 86: 167, 2009

NSCLC Patient Survival Curves Predicted vs Observed

(Solid & broken black lines: survival curve & 95% CI: Gray line & shaded area: predicted)



Clin Pharmacol Ther 86: 167, 2009

Model Based Non-small Cell Lung Cancer Development in Asia

Disease Model
(NSCLC)

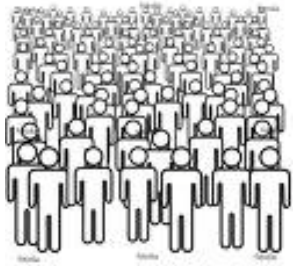
Drug Model Library
- Erlotinib
- Gefitinib
- Docetaxel
- Platins
- Combinations

+

Situation Models
(clin trials, market population)

Economic Models

Virtual Populations



Phenotypes & Genotypes
- Chinese
- American
- European

Simulation Opportunities
- Trial design
- Efficacy-Safety
- Personalized medicine
  - Dosing
  - Combo's
  - Biomarkers
- Target selection

Decisions

Learning
- Completed Trials
- Post-market surveillance
- Mechanistic research

Steps to ↑ Regional Drug Development Quality

Pharma Industry

1. Determine if ICH5 (possibly others) needs revision to account for regional disease differences
2. Create global disease assessment accounting for ethnic & regional differences if any
3. Create global development plan accounting for significant disease, PK-ADME, & PD differences by region
4. Recommend regional development path based on clinical, regulatory & commercial character

Regional Regulatory Agencies

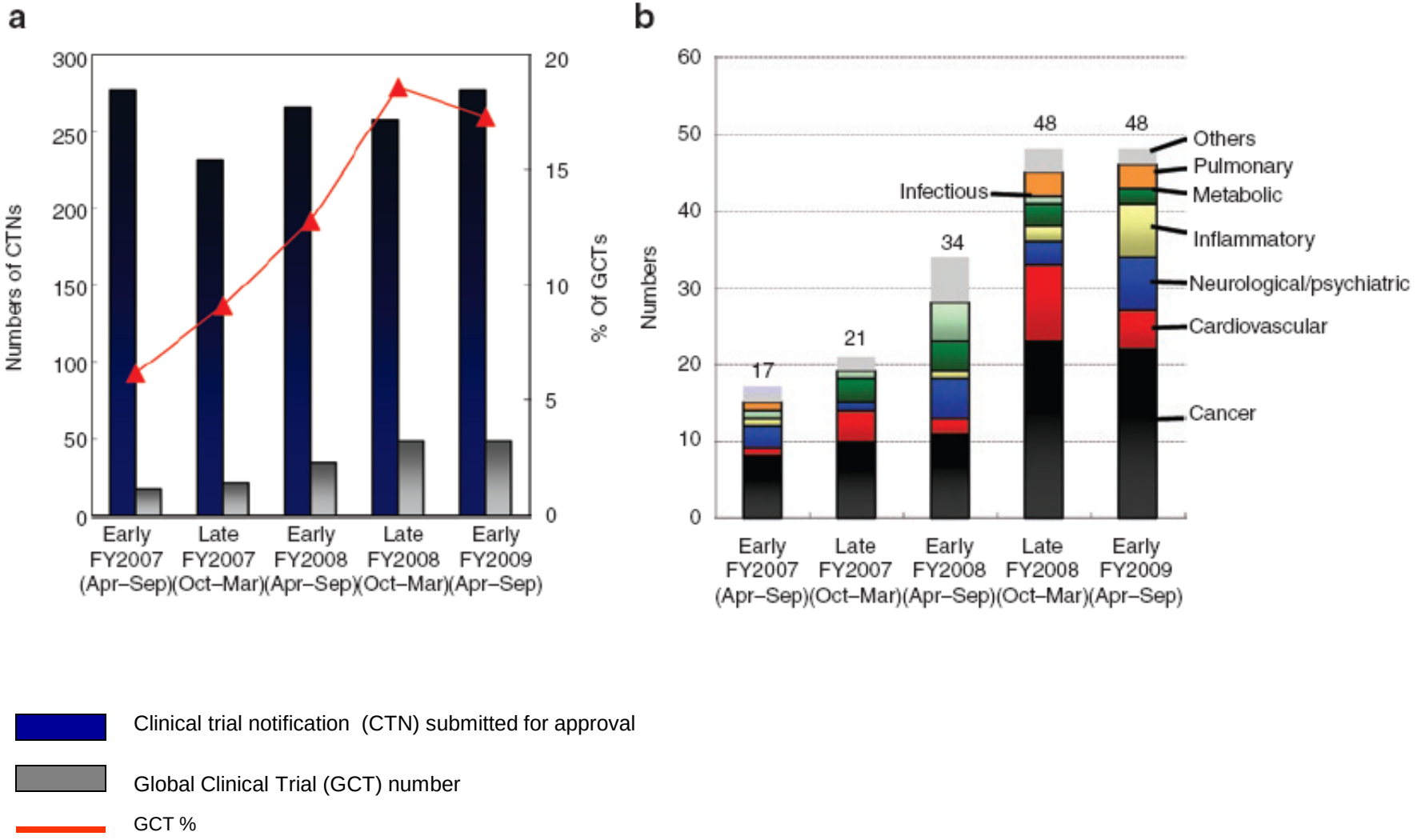
1. Determine if ICH5 (possibly others) needs revision to account for regional disease differences
2. Decide local experience required & principles for
   - When to engage company on development strategy
   - Willingness to accept simulation to justify plans
   - Dose-response strategy
   - Confirmatory Phase 3 strategy
   - Willingness to use Phase 4 commitment to gain efficiency
3. Decide if collaboration between regional countries will be synergistic?

Recommendations

- **Disease ethnic difference research** (pathogenesis, epidemiology, treatment). Governments
- **Need public meetings** on global development strategy & regulatory congruence
- **In silico demonstration project**. Pick a disease & therapeutic target. Develop disease-drug models & virtual patient-ethnic population. Government, Industry, Academia
- **Change regulatory policy** in stepwise manner.
- **International transparency** on regulatory decisions to promote synchronization
- **Change drug development practice** starting at Phase 0
- **Regional regulatory collaboration** could balance local needs & development efficiency

Backups

Global Clinical Trials (GCT) in Japan 2007-2009



Clin Pharmacol Ther 87: 362-366, 2010

Scenario Planning for Development
(front-loading knowledge & planning)

- Pre-IND
  - Critical disease review relative to dose-response, efficacy & safety linked to Phase 1-3 development plan
  - Customize international plan according to ethnic and country-regional differences in disease, demographics, values & practices
    - No disease difference. Verify & confirm with regulators early
    - Differences in disease &/or demographics, then simulate & confirm

Scenario Planning for Development
(front-loading knowledge & planning)

- Phase 1
  - Conduct single dose-multiple dose PK-PD
  - No ethnic study until full scale development decision
  - Design phase 2 a&b trials with disease modeling & trial simulation
- Phase 2
  - **2a**. PK-PD driven if possible
    - End of phase 2a meeting with regulators. Simulate 2b-3 designs
  - **2b**. Adaptive design if possible. Seamless to 3?
  - **Ethnicity**. Conduct PK-PD driven comparative study to set dosing in Global Phase 3 trial. Patients from target countries (Asians from Asia)
  - Simulate Phase 3 global design

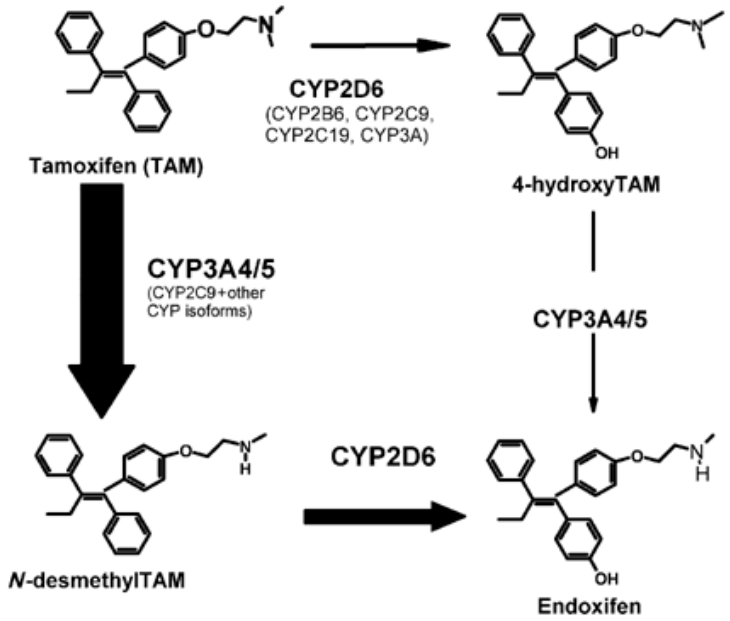
Scenario Planning for Development
(front-loading knowledge & planning)

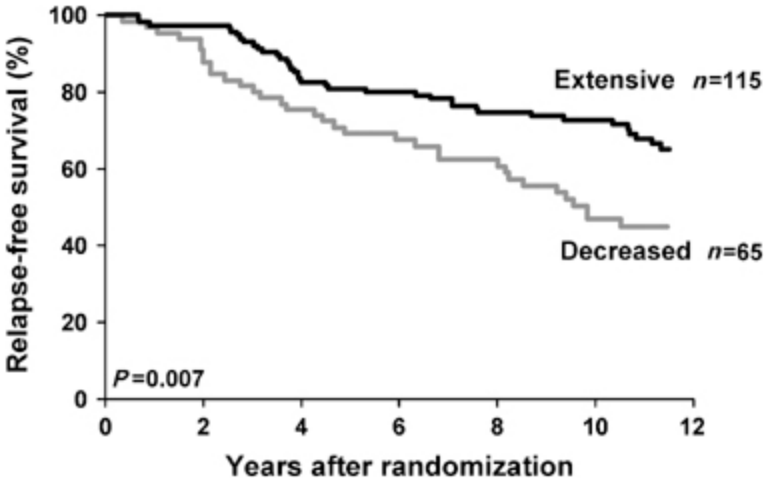
- Phase 3 trial recommendation
  - One trial designed to optimize finding efficacy & minimize uncertainty (e.g., enrichment, fewer sites)
  - One global trial designed to find efficacy & safety in global population
- Phase 4 (view as continuum from 1-3 r&d driven)
  - Confirm safety in passive + structured surveillance studies
  - Confirm efficacy in local patients with varying disease severity, age and other factors that makes sense

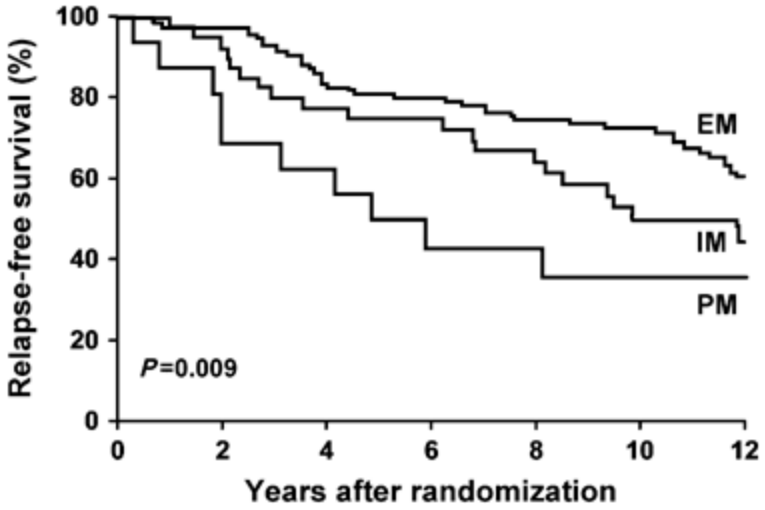
A New International Drug Development Strategy

1. Is the disease likely to be different in the to be bridged population?
   a) Government-academia.
      I. Conduct pathogenesis & disease progression studies including contemporary genotype-phenotype techniques
      II. Develop and maintain key disease models
      III. Develop virtual patient population based on this information
   b) Company. Prepare comparative ethnic disease review pre-IND. Include likely significant differences in Phase 2-3 & 4 global plan. Power studies and employ inclusion-exclusion criteria based on this information
2. Is dose-response the same relative to efficacy and safety from one country or ethnic group to another? Company will
   a) Simulate studies based on preclinical drug-biomarker relationship for
      I. Single dose or short-term PK-PD trial in bridged and primary population sample
      II. Phase 2a & b trial designs
   b) Use results of each in subsequent trials
3. Are efficacy and safety the same in Phase 3 trial populations? Company will
   1. Simulate Phase 3 trial designs during phase 1-2 based on disease model, drug model and clinical trial data models and desired product profile
   2. Discuss simulations with regulators at End of Phase 2a type meeting. Agree design.
   3. Conduct two different phase 3 trials or one trial with subsets based on simulation results
4. Post-market continue development for additional patient subgroups (e.g., disease severity) and potential safety signals again based on simulation driven decisions

Tamoxifen in Breast Cancer







The Need

- **Efficacy**
  - Quantitatively describe efficacy in terms of patient benefits relative to patient characteristics and dose
  - Individuals. Know who is most likely to respond
- **Safety**
  - Identify and quantitatively describe common and rare risks related to patient characteristics and dose.
  - Individuals. Know who is likely to be at risk and how to decrease it
- **Dosing regimen**
  - Justify based on a thorough understanding of benefit and risk for patient populations and individuals
- **Labeling**
  - Capture the above information in a manner that helps clinicians and patients make optimal therapeutic decisions
- **Cost**
  - Avoid unnecessary duplication in drug development due to high expense
- **Time**
  - Useful drugs should be available as quickly as possible for patients in need

Bridging Definition

- **Definitions (ICH5):**
  - **Bridging Study.** ‘is defined as a supplemental study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the new region. Such studies could include additional pharmacokineitic information.’
  - **Bridging Data Package**. ‘Selected information from the Complete Clinical Data Package that is relevant to the population of the new region, including pharmacokinetic data, and any preliminary pharmacodynamic and dose-response data and, if needed, supplemental data obtained from a bridging study in the new region that will allow extrapolation of the foreign safety and efficacy data to the population of the new region.’

Drug Metabolism

Enzymes & Mutant alleles (large N)
Significant Ethnic Differences

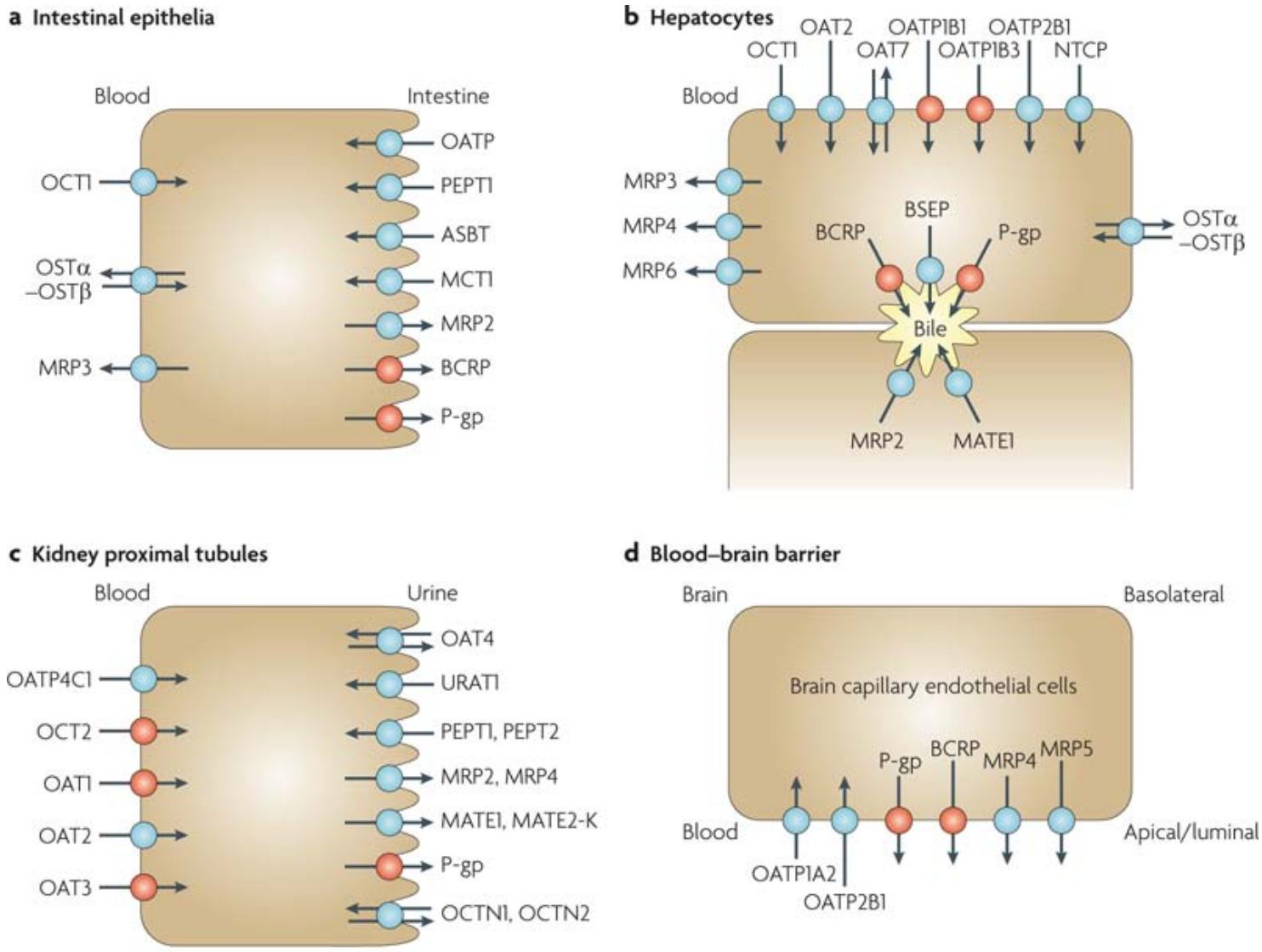
	Allele Number	Asian relative Caucasian	Drug example
Phase 1			
CYP1A1	>15	?	R-warfarin
CYP2B6	11	?	Buproprion
CYP2C8	20	Differences	Paclitaxel
CYP2C9	38	↑ PM	Warfarin, rosuvastatin
CYP2C19	8	↑ PM	Mephenytoin, diazepam
CYP2D6	75	↑ PM	Codeine, tamoxifen
CYP3A4	≥40	?	Irinotecan, gefitinib
CYP3A5	26	?	Nifedipine, tacrolimus
DPD	39	Differences	5-fluorouracil
TPMT	29	Small differences	6-mercaptopurine
Phase 2			
GST	13	Differences	Adriamycin, BCNU
UGT (5 subtypes)	multiple alleles	Differences	Irinotecan, morphine

Importance depends on fractional clearance & therapeutic index

Expert Opin Drug Metab Toxicol 5: 243, 2009

Transporters in Drug Absorption and Distribution

- 19 Known & growing
- Genetically controlled and ethnic differences



Nature Reviews Drug Disc 9:215: 2010

Selected Transporter Drug-Drug Interactions

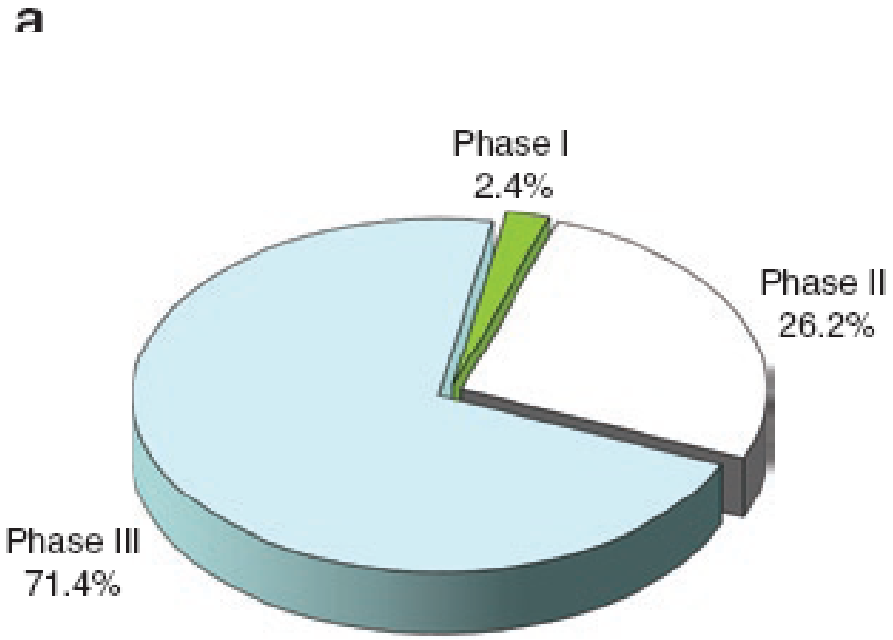
Implicated transporter*	Interacting drug	Affected drug	Clinical pharmacokinetic impact on affected drug‡
Organic anion transporting polypeptides	Cyclosporine	Pravastatin	AUC ↑890% and C_{max} ↑678%[102,204]
	Cyclosporine	Rosuvastatin	AUC ↑610%[205]
	Cyclosporine	Pitavastatin	AUC ↑360% and C_{max} ↑560%[206]
	Rifampicin (single dose)	Glyburide	AUC ↑125%[207]
	Rifampicin (single dose)	Bosentan	C_{trough} ↑500%[208]
	Lopinavir/ritonavir	Bosentan	Day 4: C_{trough} ↑4,700%[208]; day 10: C_{trough} ↑400%[208]
	Lopinavir/ritonavir	Rosuvastatin	AUC ↑107% and C_{max} ↑365%[209]
Organic anion transporters	Probenecid	Cidofovir	CL_r ↓32%[210,211]
	Probenecid	Furosemide	CL_r ↓66%[210]
	Probenecid	Acyclovir	CL_r ↓32% and AUC ↑40%[210,212]
Organic cation transporters	Cimetidine	Metformin	AUC ↑50% and CL_r ↓27%[213,214]
	Cimetidine	Pindolol	CL_r ↓~34%[215]
	Cimetidine	Varenicline	AUC ↑29%[216]
	Cimetidine	Pilsicainide	AUC ↑33%, CL_r ↓28%[217]
	Cetirizine	Pilsicainide	CL_r ↓41%[218]
	Cimetidine	Dofetilide	CL_r ↓33%[219]
P-glycoprotein	Quinidine	Digoxin	CL_r ↓34–48%[220,221]
	Ritonavir	Digoxin	AUC ↑86%[222]
	Dronedarone	Digoxin	AUC ↑157% and C_{max} ↑75%[223]
	Ranolazine	Digoxin	AUC ↑60% and C_{max} ↑46%[224]
Breast cancer resistance protein	GF120918	Topotecan	AUC ↑143%[225]

Nature Reviews Drug Disc 9:215: 2010

Evidence for Differences Pharmacokinetics

- Few differences
- Studies often not designed to find a difference in terms of patient selection criteria or number linked to a critical clearance difference relative to theraputic index (e.g., 25%)
- Studies often not in the decision chain for trial design information (e.g., conducted late)
- A PK difference may not translate to a dosing recommendation, but rather the potential need for dosing data and recommendations
- PD differences (e.g., receptor prevalence, EGFR) may be opportunities for enrichment

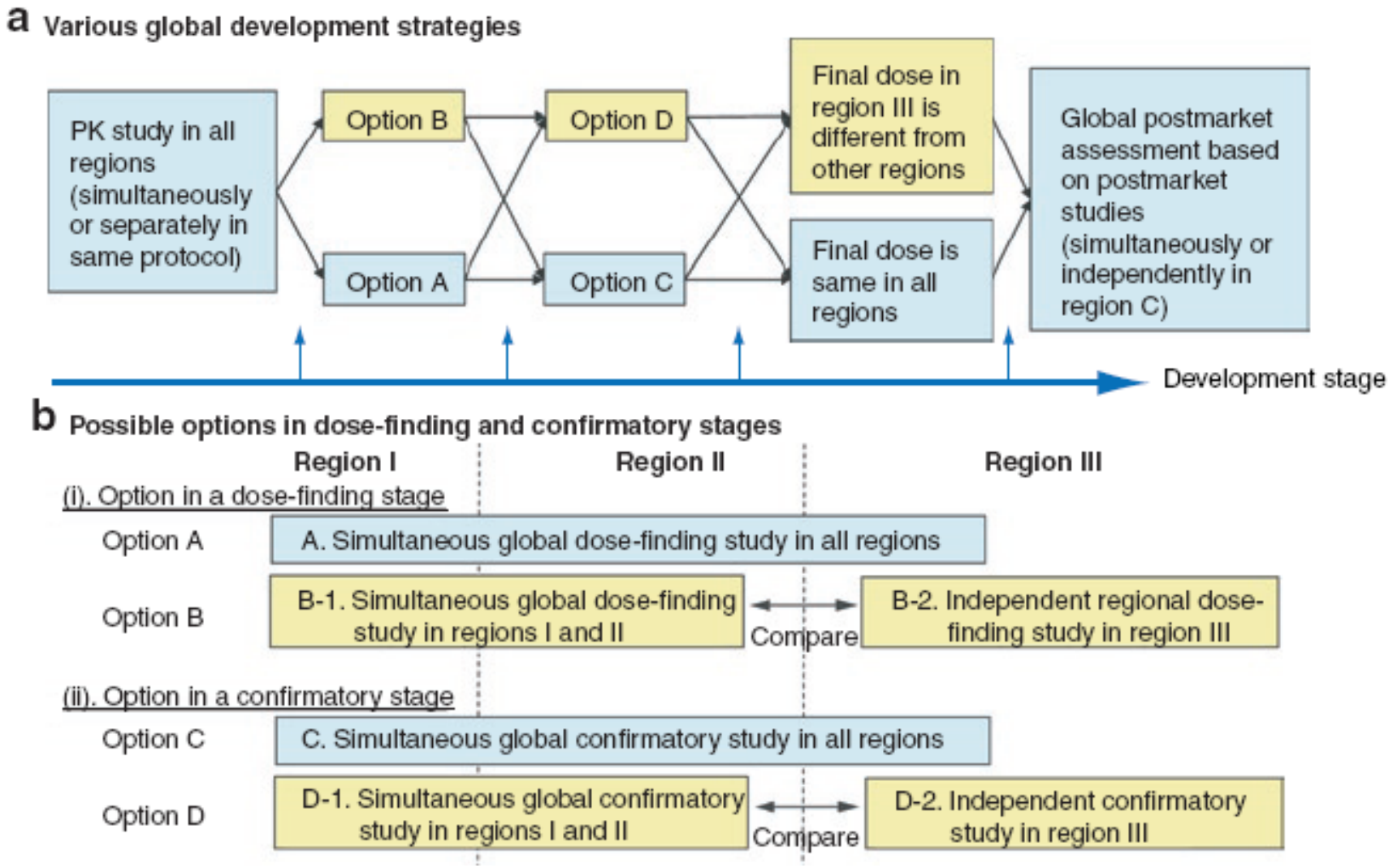
Development Phase for Global Clinical Trials in Japan 2007-2009



Clin Pharmacol Ther 87: 362-366, 2010

Ethnicity Global Strategy

Recommendation from Japan



Clin Pharmacol Ther 87: 362-366, 2010

My assumptions

- I don’t know the extent to which diseases are virtually the same or significantly different between Asia and USA:EU
- There may be a literature bias to show differences
- Even when differences exist, are they clinically significant?
- I’m exploring ways to test this and am looking for curious people

A New Global Drug Development Strategy

Regulatory Considerations

1. Global path needs to support 1st development in EU, USA or Asia
2. Encourage early (e.g., preIND) dialogue on bridging strategy and answers to previous questions.
3. International support for bridging. Develop or amend ICH5
4. Encourage simulation based trial planning meetings (e.g., EOP2a meeting)
5. Facilitate early entry into patients to begin bridging