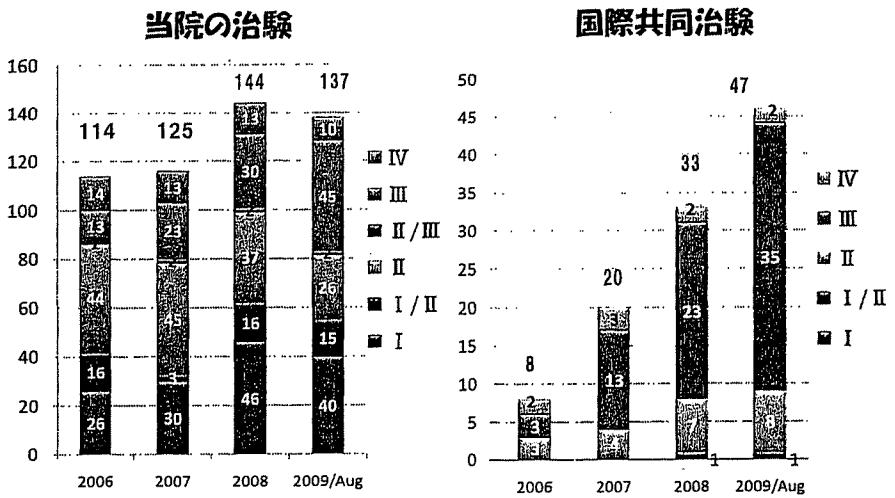
抗がん剤の国際共同治験の実態

国立がんセンター中央病院
臨床試験・治療開発部長
藤原康弘

2009/12/03　　第30回日本臨床薬理学会年会 シンポジウム4

国立がんセンター中央病院での治験の現状



PROACTトライアル　乳癌　術前内分泌療法

登録期間 2000年8月～2002年9月

登録例数 451例(うち日本人97例)

Comparison of Anastrozole versus Tamoxifen as Preoperative Therapy in Postmenopausal Women with Hormone Receptor-Positive Breast Cancer

The Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) Trial

Luigi Cataliotti, M.D.[1]
Aman U. Buzdar, M.D.[2]
Shinzaburo Noguchi, M.D.[3]
Jose Bines, M.D.[4]
Yuichi Takatsuka, M.D.[5]
Katerina Petrakova, M.D.[6]
Pierre Dube, M.D.[7]
Celia Tosello de Oliveira, M.D.[8]

[1] Clinica Chirurgica 1, University degli Studi di Firenze, Firenze, Italy.
[2] Department of Breast Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston Texas.
[3] Department of Breast and Endocrine Surgery, Osaka University Medical School, Osaka, Japan
[4] Breast Cancer Unit, National Cancer Institute, Rio de Janeiro, Brazil.
[5] Department of Surgery, Kansai Rosai Hospital, Hyogo, Japan.
[6] Department of Oncology, Masaryk Oncological Institute, Brno, Czech Republic.
[7] Department of Surgery, Hopital Maisonneuve-Rosemont, Montreal, Quebec, Canada.
[8] Departamento de Quimioterapia, Instituto Brasileiro de Cumbele ao Cancer, Sao Paulo, Brazil.

This study was funded by AstraZeneca, Wilmington, DE.

Dr. Buzdar has received research grants, travel awards and honoraria from AstraZeneca.

BACKGROUND. The Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) study was a randomized, multicenter study comparing anastrozole with tamoxifen as a preoperative treatment of postmenopausal women with large, operable (T2/3, N0-2, M0), or potentially operable (T4b, N0-2, M0) breast cancer. The effect of preoperative endocrine therapy in patients scheduled for mastectomy or with inoperable tumors at baseline was also investigated.

METHODS. Patients with hormone receptor-positive breast cancer received anastrozole ($n = 220$) or tamoxifen ($n = 223$) with or without chemotherapy for 12 weeks before primary surgery.

RESULTS. Objective responses for anastrozole and tamoxifen occurred in 59.5% and 55.4% of patients, respectively (ultrasound measurements), and 50.0% and 40.2% of patients, respectively (caliper measurement). In hormonal therapy-only patients ($n = 314$), feasible surgery at baseline improved after 3 months in 42.0% of patients receiving anastrozole and 30.0% receiving tamoxifen ($P = .04$). In the intent-to-treat population, improvement in feasible surgery at baseline to actual surgery at 3 months was found to be numerically higher in the anastrozole group compared with the tamoxifen group, although this difference did not reach significance. Drug-related adverse events were reported in 20.2% and 16.1% of patients, respectively, in the anastrozole and tamoxifen groups.

CONCLUSIONS. Anastrozole is an effective and well-tolerated preoperative therapy, producing clinically beneficial tumor downstaging and reductions in tumor volume. These effects enable more minimal surgical interventions in patients scheduled for mastectomy, and mastectomy in patients with previously inoperable tumors. Anastrozole appears to be at least as effective as tamoxifen in this setting, and more effective than tamoxifen in certain clinically relevant subgroups. *Cancer* 2006;106:2095–103. © 2006 *American Cancer Society*.

KEYWORDS: anastrozole, estrogen receptor, breast

Cancer 106: 2095-3103, 2006

HERAトライアル　乳癌　術後補助療法

登録期間 2001年12月～2005年3月

登録例数5081例 (うちAsian pacific&Japan 405例)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812　　OCTOBER 20, 2005　　VOL. 353 NO. 16

Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer

Martine J. Piccart-Gebhart, M.D., Ph.D., Marion Procter, M.Sc., Brian Leyland-Jones, M.D., Ph.D., Aron Goldhirsch, M.D., Michael Untch, M.D., Ian Smith, M.D., Luca Gianni, M.D., Jose Baselga, M.D., Richard Bell, M.D., Christian Jackisch, M.D., David Cameron, M.D., Mitch Dowsett, Ph.D., Carlos H. Barrios, M.D., Gunther Steger, M.D., Chiun-Shen Huang, M.D., Ph.D., M.P.H., Michael Andersson, M.D., Dr.Med.Sci., Moshe Inbar, M.D., Mikhail Lichinitser, M.D., István Láng, M.D., Ulrike Nitz, M.D., Hiroji Iwata, M.D., Christoph Thomssen, M.D., Caroline Lohrisch, M.D., Thomas M. Suter, M.D., Josef Rüschoff, M.D., Tamás Suto, M.D., Ph.D., Victoria Greatorex, M.Sc., Carol Ward, M.Sc., Carolyn Straehle, Ph.D., Eleanor McFadden, M.A., M. Stella Dodwell, and Richard D. Gelber, Ph.D., for the Herceptin Adjuvant (HERA) Trial Study Team

ABSTRACT

BACKGROUND

Trastuzumab, a recombinant monoclonal antibody against HER2, has clinical activity in advanced breast cancer that overexpresses HER2. We investigated its efficacy and safety after excision of early-stage breast cancer and completion of chemotherapy.

METHODS

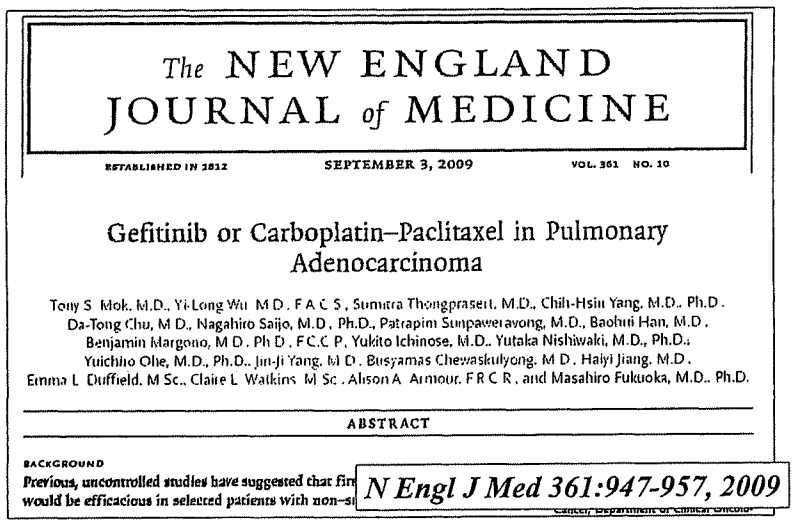
This international, multicenter, randomized trial com... zumab given every three weeks with observation in p... either node-negative or node-positive breast cancer w... therapy and at least four cycles of neoadjuvant or adju...

Address reprint requests to Dr. Piccart-Gebhart at the Medicine Department, Jules Bordet Institute, Bld de Waterloo 125, 1000 Brussels, Belgium, or at martine.piccart@bordet.be. The authors' affiliations are listed in the Appendix.

N Engl J Med 353:1659-1672, 2005

IPASSスタディー 進行肺腺癌

登録期間 2006年3月～2007年10月
登録例数 1217例（うち日本人 233例）



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 3, 2009 VOL. 361 NO. 10

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Jin-Ji Yang, M.D., Busyamas Chewaskulyong, M.D., Haiyi Jiang, M.D., Emma L. Duffield, M.Sc., Claire L. Watkins, M.Sc., Alison A. Armour, F.R.C.R., and Masahiro Fukuoka, M.D., Ph.D.

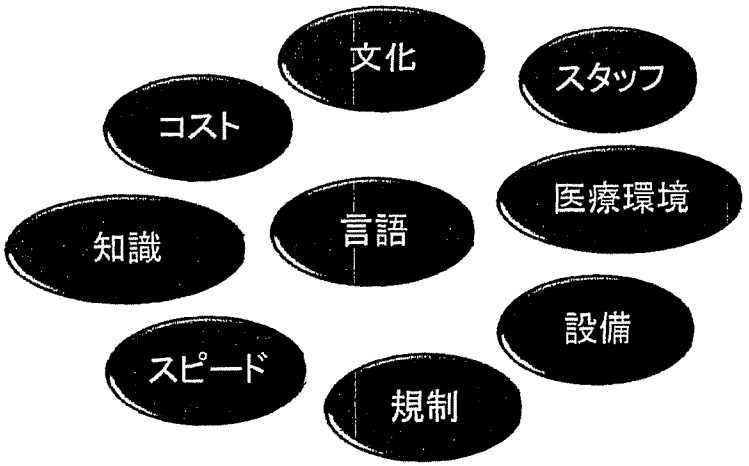
ABSTRACT

BACKGROUND

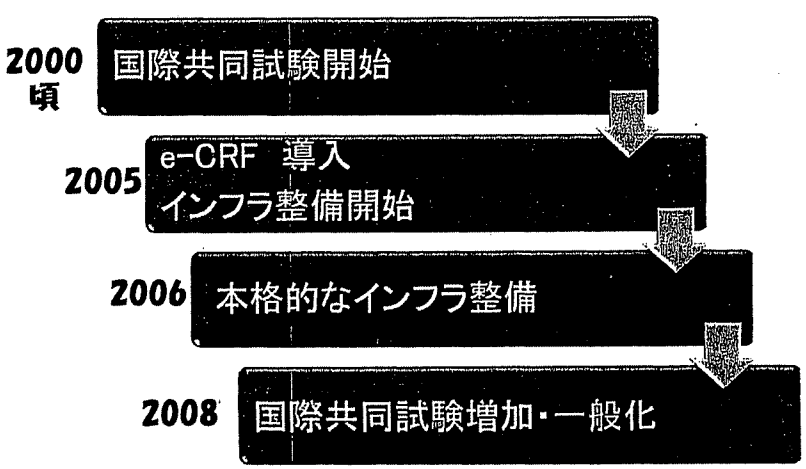
Previous, uncontrolled studies have suggested that fir... would be efficacious in selected patients with non-si...

N Engl J Med 361:947-957, 2009

国際共同治験の受託にあたり施設として考えていた問題点



国立がんセンター中央病院における国際共同治験の取り組みの経緯



言語の問題点（当初の経験から）

- プロトコール、概要書、手順書等
  - 翻訳版が必要
- 症例報告書
  - 英語の読解と入力
- IRB申請書類
  - 翻訳版が必要
- 診療記録
  - 依頼者によっては日本語での記載に加えて英語記載が必須と要求
- IVRS
  - ガイダンスは日本語だが、トラブル時は英語で対応

医療環境の違いの問題点

- 治験薬取扱い
  - 管理の違い
  - 患者への提供方法
- 中央検査
  - 二重の検査と二重の結果
  - 検査方法と検査機器・資材の違い
- 頻回な生存調査
  - 調査の限界
- 登録スピード

規制の問題点

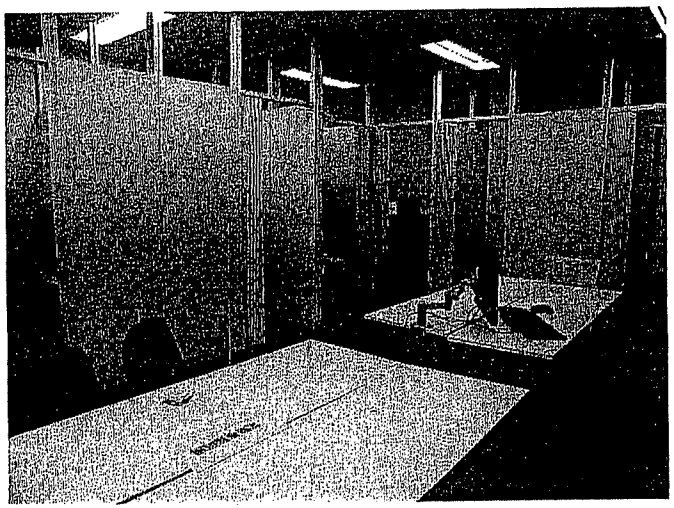
- 原データ
  - オリジナルデータの取り扱いの違い
  - 文書保管(15年間)
- 重篤な有害事象(SAE)
  - 日本語と英語の報告書
  - e-CRFの報告
    企業への報告は24時間以内という時間制限
- FDAからの実地調査

問題解決のために当院で行ったこと

- インフラ整備
  - 各通信回線、海外対応のソフトウエア設置
  - 各回線の簡便な使用場所と各資材・機器保管場所の拡充
  - 国内試験と共通の業務手順の作成
    - 各部署(主に薬剤部、臨床検査部、診断部、看護部)との協同
  - 電子カルテのシステム構築(臨床試験システム/C-DISC対応)中
  - IRB申請～承認までの短縮(IRBシステム構築)中
- 院内教育
  - 臨床試験プログラム
- 経験を積む
  - 柔軟な受け入れ
  - 言語の研鑽

当院の主なインフラ整備の内容

通信環境	• 直通国際電話回線 • 光ファイバー • Web環境の整備
SDV対応	• 20部屋(光ファイバー対応)設置 • 直接閲覧用電子カルテ55台 • 電子カルテ内に直接閲覧システム構築
検査実施	• 各検査部に治験担当者配置 • 全試験共通のルール作成 • 新医療機器の導入 • 各試験毎の搬入機器保管場所設置
薬剤管理	• 各試験温度管理対応 (新冷蔵庫、温度計、温度記録計設置)



施設だけでは解決できないこと

- 各書式の簡便化
- 治験依頼者の意向に伴う診療録の英語記載
- 生存調査における自治体や法務局の協力
- ICH-GCPとJ-GCPの相違の解釈の統一化
- 経験のないFDAによる実地調査対策

原資料の取り扱い違いで当院が困ったこと

ICH-GCP 1.52	J-GCP 運用通知 第2条3
• Original documents, data, and records →最初に記録されたデータ？ 範囲が広い	• 症例報告書等の元となる文書、データ及び記録 →最初のものを指していない？ 範囲が狭い

- 入院中のナースが配薬管理しているナース使用の配薬・残薬管理表は原資料と扱わず、退院後破棄した
- 速報より後から届いた原本だけを残し、速報にタイムリーな確認サインもなかった
- 何がOriginal documentなのか、どこに記録の不備があるのか明確に把握できていない

治験に係る文書又は記録の保管の違いで当院が困ったこと

ICH-GCP 4.9.5	J-GCP 1.26
• Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. → 約15年程	• 製造販売承認をうける日又は治験の中止若しくは終了の後3年を経過した日 → 約3～5年程

保管場所の確保 / 15年保管した経験がない

治験に係る文書または記録について当院が困ったこと

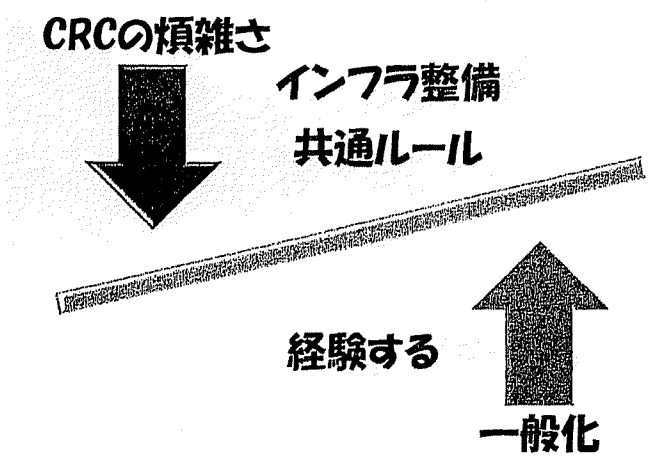
ICH-GCP 8.2.10	J-GCP 運用通知 10.1.5
• Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub investigator(s)	• 治験責任医師となるべき者がその要件を満たすことを証明した履歴書及びその他の文書並びに治験分担医師となるべき者の氏名リスト(求めがあった場合には治験分担医師の履歴書)

治験分担医師だけでなくCRCの履歴書も要求される場合がある

施設の今後の課題

- コスト削減
- 英語書式・英語書類だけの実施
- 知識の習得
  - 規制の相違
- さらに効率的な業務の標準化
  - 経験を集約
- プロジェクトマネージメント
- 時代に合わせたインフラ整備の継続

Things to be solved



国内治験も国際共同治験もCRCがやるべきことは同じ

私見

- 薬事法承認は医師の診療内容を規制するものではない; compendium 制度の導入
- 国際共同治験の議論より、国際共同臨床試験をいかにリードできるかが大事; 中核的医療機関はacademic research organizationたるべし(医療従事者を4倍に!)
- 外的要因は承認後の医師主導の臨床試験(国際共同研究)で検討すればよい; conditional approval の制度導入

ご静聴ありがとうございました

Globalization of Clinical Studies in Japan: Perspective from a Global Multinational

Mike Ferris, M.A., D.Phil.,

Managing Director, Head of Development Division,

Novartis Pharma K.K.

29th January 2010

NOVARTIS

Comment from our HQ: In the Past...

- Traditional stand alone clinical drug development in Japan
- High quality standards in clinical drug development in Japan

but

- Deferred access to new medication for patients in Japan
- Limited global visibility of Japanese scientific contribution and performance in clinical trials

In the Past...

- "Japan can rightfully be proud of its achievements in the area of public health...Yet though Japanese doctors are quite active on the international scene...the medical care system, its development, medical practice itself and clinical trials have been shaped profoundly by internal factors based on Japanese cultural norms which are also reflected in government and regulatory policies. These norms at times may be in sharp contrast to established international medical practice or more specifically Western medical practice."

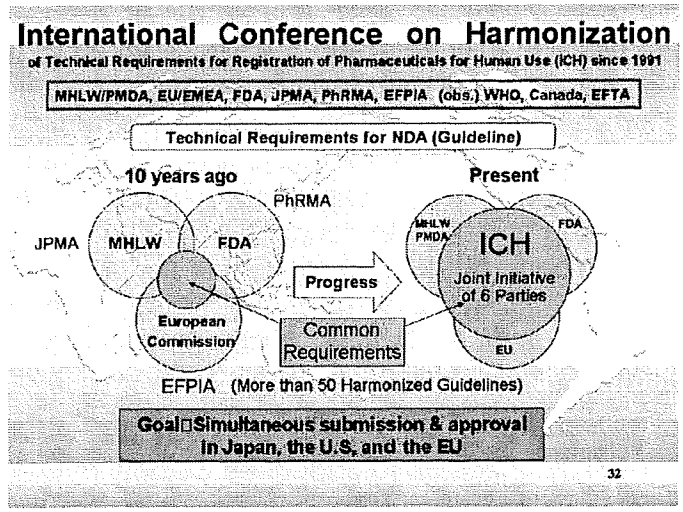
Kiyoshi Kurokawa, lecture to Japanese Society of Clinical Pharmacology, December 1997

The Road to Harmonization

- 1985 Market Orientated Sector Selective (MOSS) talks signalled the beginning of change

  - **"Action Program for Improved Market Access"**

1991 "First International Conference on the Harmonization of Technical Requirements for the Testing of Pharmaceuticals"



Source: PMDA

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Harmonization spanning 3 decades

- 1980s – The Age of Preclinical Harmonization ("a rat is a rat")
  - **Toxicology Guidelines**
  - **General Pharmacology Guidelines**
- 1990s – CMC and Clinical Harmonization (Step 1) (" a tablet is a tablet")
  - **Stability guidelines**
  - **ICH E5 "Ethnic Factors"**
  - **ICH GCP**
- 2000s – Regulatory Harmonization and Clinical Harmonization (Step 2) ("CDROMs and CTDs")
  - **Electronic Submissions**
  - **Common Technical Document**

Study Group Meeting, 29th January 2010, Tokyo

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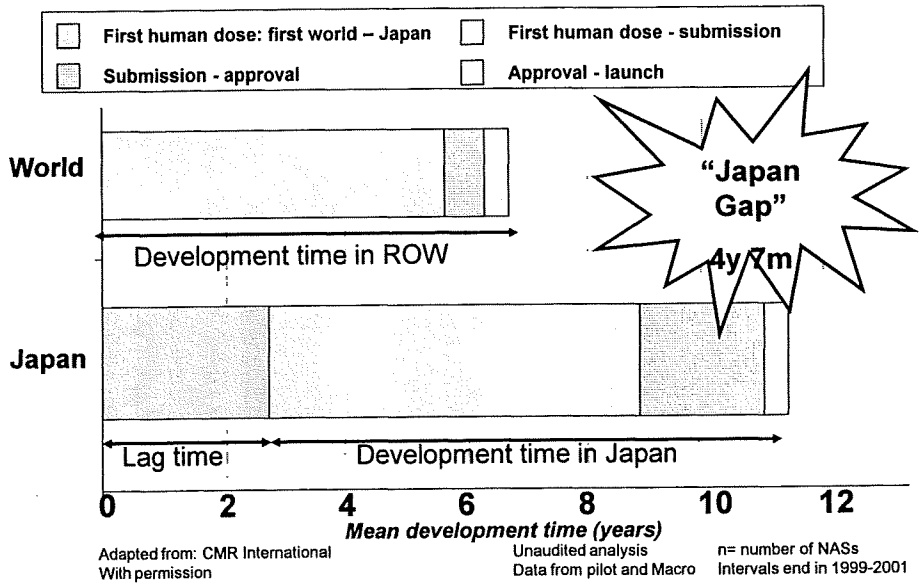
Clinical Development "First Age" - The "Japan Gap"



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Clinical Trials – landmarks in evolution

- 1989 First Japanese Good Clinical Practice
  - **Introduction of Informed Consent**
  - **Basic Scientific Standards**
- 1997 Update to ICH Good Clinical Practice
  - **Introduction of Written Informed Consent**
  - **Clarification of roles/responsibilities, in particular of Sponsor**
- 1998 ICH E5 Guideline "Ethnic factors in the acceptability of Foreign Clinical Data"
  - **Concept of Bridging**

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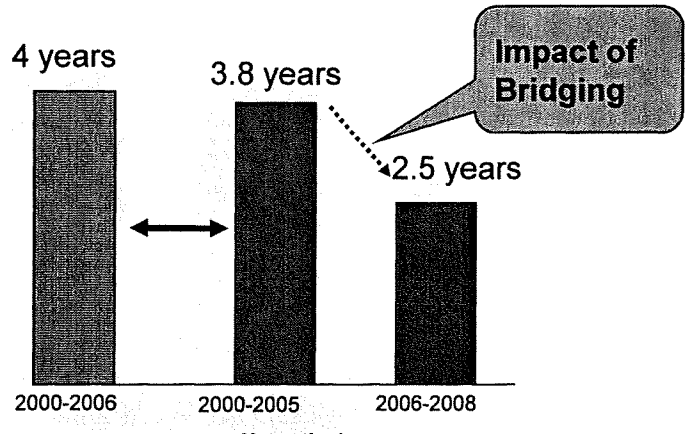
Clinical Development in the "Second Age"

The Japan Gap*



* Time between first approval and Japan approval

Source: In house data

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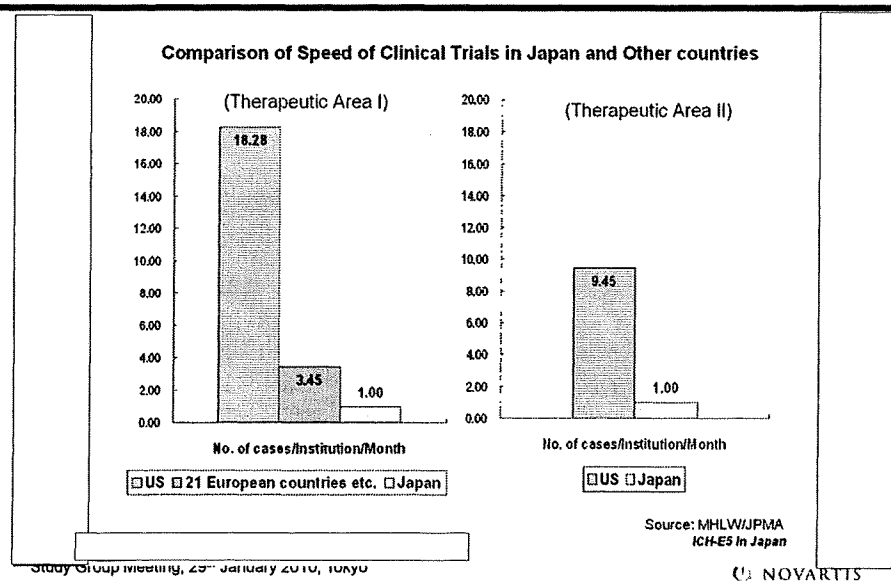
Clinical Development in the "Second Age"
Slow Speed an Issue



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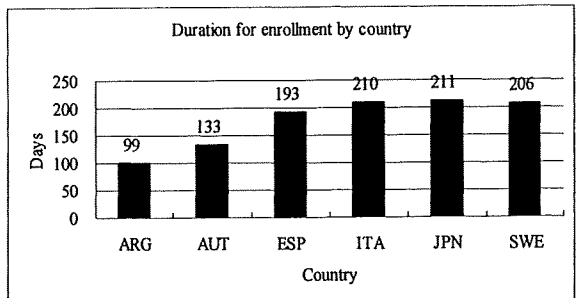
Clinical Development in the "Third Age"

- Revision of J-GCP towards ICH GCP provided a trigger for enhancing the quality and efficiency of clinical trials

Clinical Development in the "Third Age"

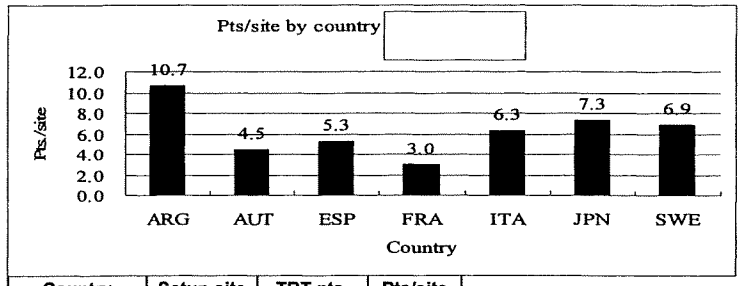


Enrolment speed: Japan is catching up European countries

Country	FPFV	LPLV	Duration
ARG	2005/8/16	2005/11/23	99
AUT	2005/6/9	2005/10/20	133
ESP	2005/5/16	2005/11/25	193
ITA	2005/4/26	2005/11/22	210
JPN	2005/4/28	2005/11/25	211
SWE	2005/5/2	2005/11/24	206

Source: In house data

Clinical Development in the "Third Age"



Country	Setup site	TRT pts.	Pts/site
ARG	6	64	10.7
AUT	2	9	4.5
ESP	14	74	5.3
FRA	20	59	3.0
ITA	9	57	6.3
JPN	6	44	7.3
SWE	7	48	6.9
Total	64	355	5.5

Number of patients per site: Similar to those of European countries

Source: In house data

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The Biggest Jump: from Harmonization to Globalization

- **5 Year Strategy for the Creation of Innovative Pharmaceuticals and Medical Devices***
  - ➢Concentrated Investment in Research
  - ➢Development of Venture Capitals, etc.
  - ➢Improvement of the Clinical Research/Trial Environment
  - ➢Tie-ups with Asia
  - ➢Acceleration and Improvement of Reviews
  - ➢Fair Assessment of Innovation

*April 26, 2007: Cabinet, Ministry of Education, Culture, Sports, Science and Technology (MEXT); Ministry of Health, Labor and Welfare (MHLW); Ministry of Economy, Trade and Industry (METI)

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The Dawn of Globalization

Guidance document for global studies

Japanese version

English version

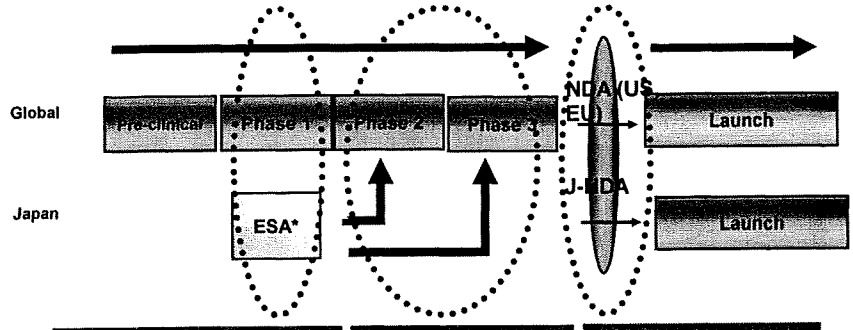
http://www.pmda.go.jp/operations/notice/2007/file/0928010.pdf

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

East Asian Pharmaceutical Regulatory Symposium 2008

Presentation of Mr.Mori

Global Clinical Development



ESA conducted before Global Phase II

Japan joins Global Phase II dose-finding and/or Phase III

Target is simultaneous filing (US/EU/Japan)

*ESA: Ethnic Sensitivity Assessment

Source: adapted from M. Inazu, 6th DIA Annual Japan Study Group Meeting, 29th January 2010, Tokyo Meeting

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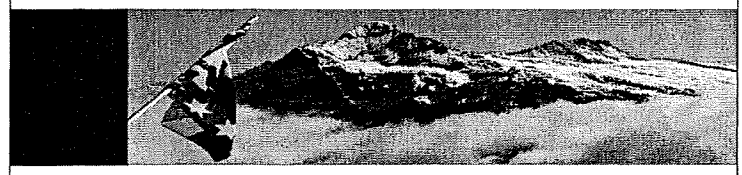
Global Clinical Development in Japan

The view from Basel:



Global Drug Development including Japanese Trial Sites
Basel, 4 November 2009
Helmut Wolf

NOVARTIS

In the Future...

Novartis has begun to integrate Japan into global clinical development for drugs to be launched in Japan.

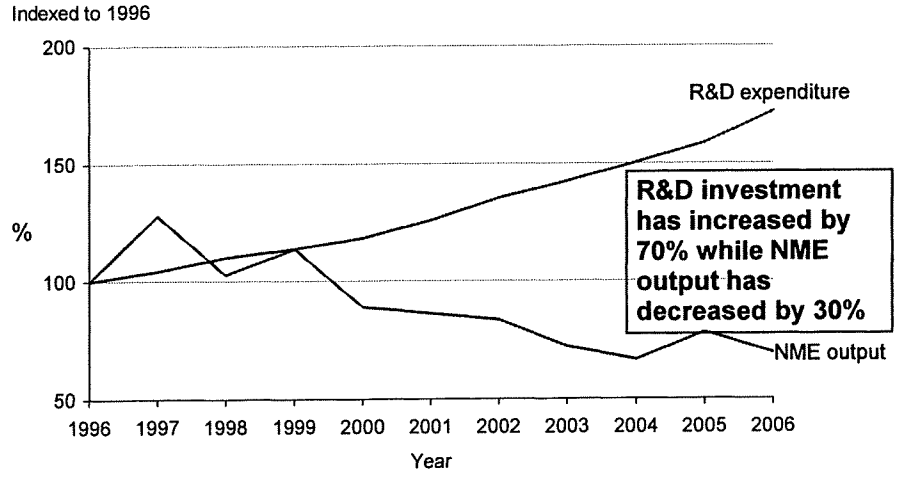
Involvement will encompass all phases of clinical development

Our aim is to make new medications available to all patients worldwide within the same timeframe

Hurdles / concerns to be addressed

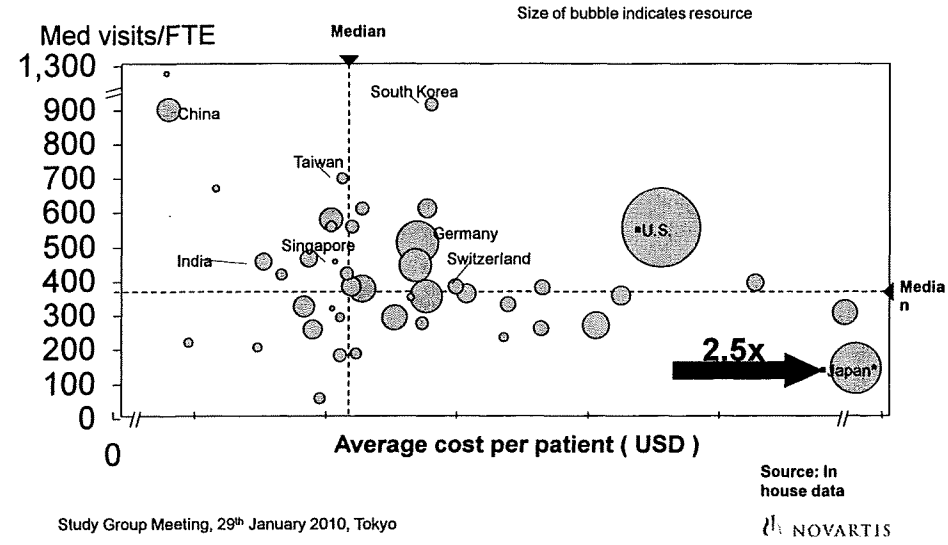
- Several major differences exist:
  - Higher bureaucracy
  - Physicians expect extra support from the CRA
  - High cost per patient
  - Low number of patients per site, long trial approval and recruitment time could lead to delay of global dossier
- Consequently: Low productivity compared to global average

"Why do we always talk about cost?" "Pharma companies are always rich – aren't they?"



NME = New Molecular Entity
Source: CMR International & IMS Health (R&D factbook 2007)

Clinical Productivity – is low in Japan



Study Group Meeting, 29th January 2010, Tokyo

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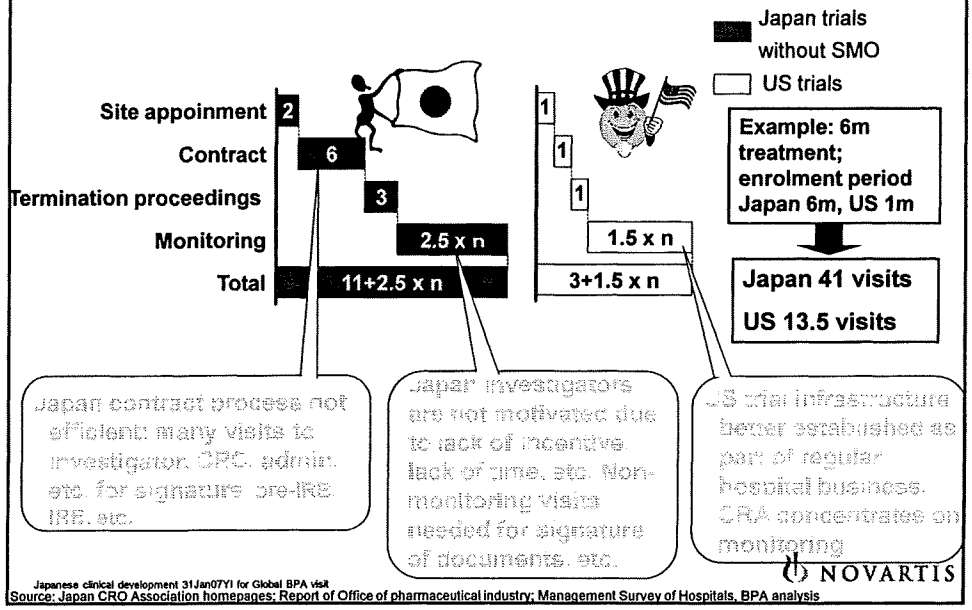
CRAs need to visit their investigators in Japan more times than in US.



Japanese clinical development 31Jan07YI for Global BPA visit

Source: Japan CRO Association homepages; Report of Office of pharmaceutical industry; Management Survey of Hospitals, BPA analysis

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Proposed solutions

- Increased communication and cooperation to understand the needs of all participating parties and work towards solutions
- Reduce unnecessary work / hurdles => standardization of processes / procedures
- Accurate site selection based on reliable feasibility assessment
  - Sites honor commitment : patient numbers + timelines
- CRAs support trial sites in all essential trial specific aspects
  - Allow CRAs access to patient data as needed (time, space)
- Accelerate adoption of new technologies such as remote monitoring

Thank you for your attention

Study Group Meeting, 29th January 2010, Tokyo

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(Multinational) clinical trial operation in relation to GCP

From the view point of productivity

Kikuo Tsukahara, Clinical Operation

29-Jan-2010

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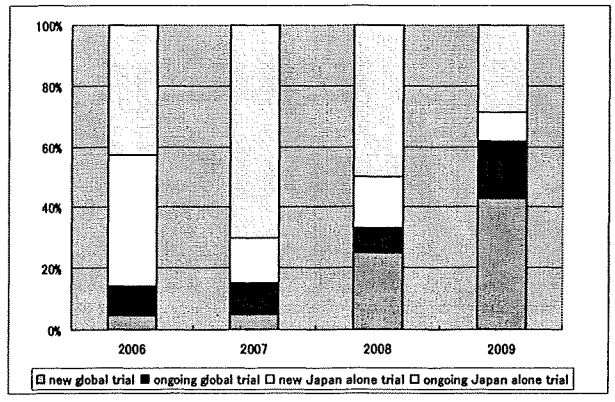
CRAs' perception re. multinational/local trial and GCP

- "Clinical Trial" means "Multinational Clinical Trial"
- GCP: no attention on separation of ICH-/J-GCP



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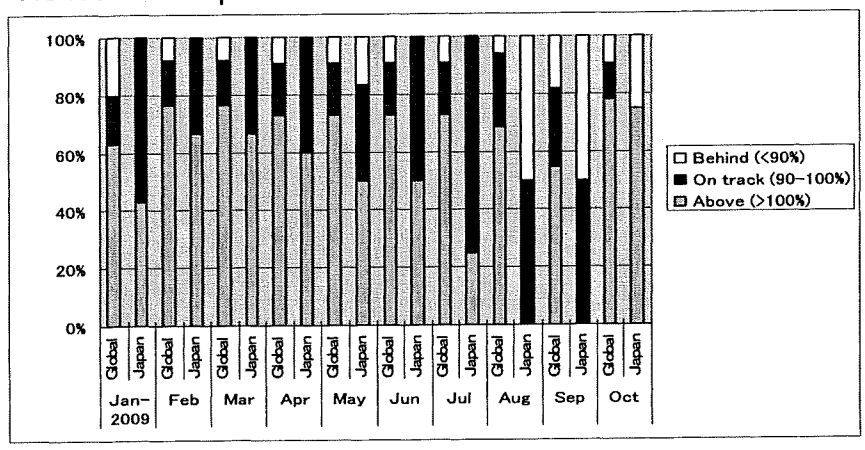
Multinational trials made a comparison between Japan and other countries easy

- No issues in speed



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Multinational trials made a comparison between Japan and other countries easy

- No issues in quality –example-

	Japan	EU1	EU2
Patient number			
Committed	24	32	20
Randomized	25	39	19
Screen failure(%)	17	24	21
Quality			
# of patient with protocol deviation (%)	14(56)	33(85)	19(100)
Days from LPLV to query resolution	22	44	42

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