Clinical Trials in a Globalized Society
-Building an Effective Cancer Clinical Trials System-

Current Issues of Investigator-initiated Cancer Clinical Trials in Japan and Our Challenge to overcome them

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NEWS & VIEWS

EXPERIMENTAL THERAPIES

Investigator-initiated cancer trials with INDs for approval in Japan

Chiyo K. Imamura, Naoko Takebe, Seigo Nakamura, Hideyuki Saya and Naoto T. Ueno

In Japan, it is quite rare for an investigator to submit an investigational new drug application to initiate a clinical trial and obtain approval of a drug on the basis of clinical trial results. This means that development of new therapies is currently driven almost entirely by pharmaceutical companies as opposed to independent investigators. Here, we provide our perspective on the reasons for this situation and advocate investigator-initiated cancer drug development as a means of increasing access to better therapies for Japanese cancer patients.

In the US, an investigational agent may not be administered to patients for research unless an investigational new drug application (IND) has been submitted to the US FDA. However, there are IND exemptions for studies of lawfully marketed drug or biological products for the treatment of cancer.[1] This is provided that the investiga-

in 2005. These data indicate that the vast majority of investigator-initiated cancer clinical trials in Japan are not designed to collect data required to obtain approval of agents for new indications.

We speculate that the main reason why investigator-initiated cancer clinical trials with INDs are so rare in Japan is that the govern-

reviewing protocols, filing INDs, supplying agents under agreement with pharmaceutical companies, and assists with monitoring and auditing. Major academic institutions in the US also have support systems for conducting clinical trials. By contrast, Japan does not have an effective system in place to support investigator-initiated clinical trials requiring INDs. It is a major challenge for Japanese investigators to plan a clinical trial with an IND because they do not have access to free advice from experts on issues such as protocol development, regulatory affairs and statistical analysis. Furthermore, there are limited government budgets for grants for new drug development, including clinical trials. Therefore, investigators who wish to conduct clinical trials that may lead to new drug development must find funding from public and private sources. Implementing a clinical trial with an IND is more expensive than implementing a clinical trial without an IND because of significant differences in quality control and quality assurance requirements between trials with and without an IND. In fact, the quality control and quality

Regulation of Clinical Trial Notification

Investigational New Drug Application (IND)

Any organization seeking to sponsor clinical trials with experimental agents must first submit an IND to the FDA . The IND is the legal mechanism under which experimental agent research is performed in the United States. No experimental agents may be administered to patients for research in the US without an IND.

CTEP Investigator's Handbook

IND in the US

- Commercial IND：販売用 IND
- Research (non-commercial) IND：研究用 IND

- Treatment Use IND：治験外使用 IND
- Emergency IND：治験外緊急使用 IND

IND must contain information in three broad areas ;

1. Animal pharmacology and toxicology studies
2. Manufacturing information
3. Clinical protocols and investigator information

In Japan, it is not necessary to submit an IND to the PMDA to perform clinical trials

- IND must be submitted only if the objective of the clinical trial is to collect data for a new drug application.
- A clinical trial without IND don't need to observe GCP.

✓ In 2003, the Pharmaceutical Affairs Law was revised to allow investigators to conduct clinical trials requiring INDs.

✓ 900 investigator-initiated cancer clinical trials have been registered and disclosed to the university hospital medical information network (UMIN) Clinical Trials Registry in Japan since it was established in 2005.

Investigator-initiated cancer clinical trials with INDs for approval in Japan

Treatment	Type of malignancy	Phase	Year of IND	PI and affiliation
Imatinib	Relapsed or refractory sarcomas with c-kit or PDGFR expression	II	2004	Y. Fujiwara, National Cancer Center Hospital
HLA-mismatched hematopoietic stem cell transplantation using alemtuzumab	Hematological malignancies	I/II	2004	Y. Kanda, University of Tokyo Hospital
Irinotecan	Refractory pediatric solid tumors	I/II	2005	A. Makimoto, National Cancer Center Hospital
Neoadjuvant chemotherapy and trastuzumab	Operable breast cancer with HER2 overexpression	II	2007	M. Ando, National Cancer Center Hospital
Chemoradiotherapy concurrent with S1 and cisplatin	Stage II or III esophageal carcinoma	I/II	2007	A. Ohtsu, National Cancer Center Hospital East
Carboplatin and paclitaxel with bevacizumab (GOG 0218)	Stage III or IV ovarian epithelial, primary peritoneal cancer, or fallopian tube cancer	III	2007	N. Katsumata, National Cancer Center Hospital
BK-UM (Anti-HB-EGF)	Advanced or recurrent ovarian cancer	I	2007	S. Miyamoto, Fukuoka University Hospital
Talc pleurodesis	Malignant pleural effusions	II	2009	H. Saka, National Hospital Organization, Nagoya Medical Center

Why are investigator-initiated cancer clinical trials with INDs rare in Japan?

- Japan does not have an effective system in place to support investigator-initiated clinical trials requiring INDs.
  - In the US, NCI/CTEP supports investigator-initiated clinical trials. Major academic institutions also have support systems for conducting clinical trials.
- There are limited government budgets for grants for new drug development, including clinical trials.
  - In the US, the NCI has a funding system for implementation of clinical trials.

Influence of Universal Health Care System on Investigator-initiated Clinical Trials

In the US, off-label drug use is sometimes acceptable for cancer treatment on the basis of robust clinical evidence.

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ASCO SPECIAL ARTICLE

Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications

Revised February 27, 2006, by the American Society of Clinical Oncology

From the American Society of Clinical Oncology, Alexandria, VA.

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Effective Date: February 27, 2006, approved by the ASCO Board of Directors.

Address reprint requests to American Society of Clinical Oncology, Cancer Policy and Clinical Affairs, 1900 Duke St, Suite 200, Alexandria, VA 22314; e-mail: sastryb@asco.org.

A B S T R A C T

Approximately half of the uses of anticancer chemotherapy drugs are for indications other than those referenced in the United States Food and Drug Administration approved label. Some managed care organizations and private health insurance plans have declined to reimburse the cost of drugs used off-label to treat cancer on the ground that these uses are "experimental" or "investigational."

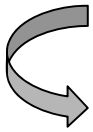
Cancer patients and their providers have experienced similar problems in the Medicare and Medicaid program. To a large extent, these issues have been addressed through legislation enacted in 1993 that requires coverage of medically appropriate cancer therapies including off-label uses recognized by established drug compendia and peer-reviewed literature. Congress has fashioned a system that has worked well, as reflected in improvements in cancer morbidity and mortality.

Now, however, after more than a decade of success, the system requires attention. This statement of policy from the American Society of Clinical Oncology encourages the Secretary of the United States Department of Health and Human Services to address these unmet needs in order to ensure that patients with cancer have access to clinically appropriate treatment, as reflected in timely compendia listings and reports of studies in the medical literature.

J Clin Oncol 24:3206-3208. © 2006 by American Society of Clinical Oncology

In Japan, product labeling is critical under universal health care system.

If there is evidence in the peer-reviewed literature that a drug is effective for a given indication but that indication is not listed in the product labeling, the drug cannot be used for that indication in day-to-day patient care in Japan.

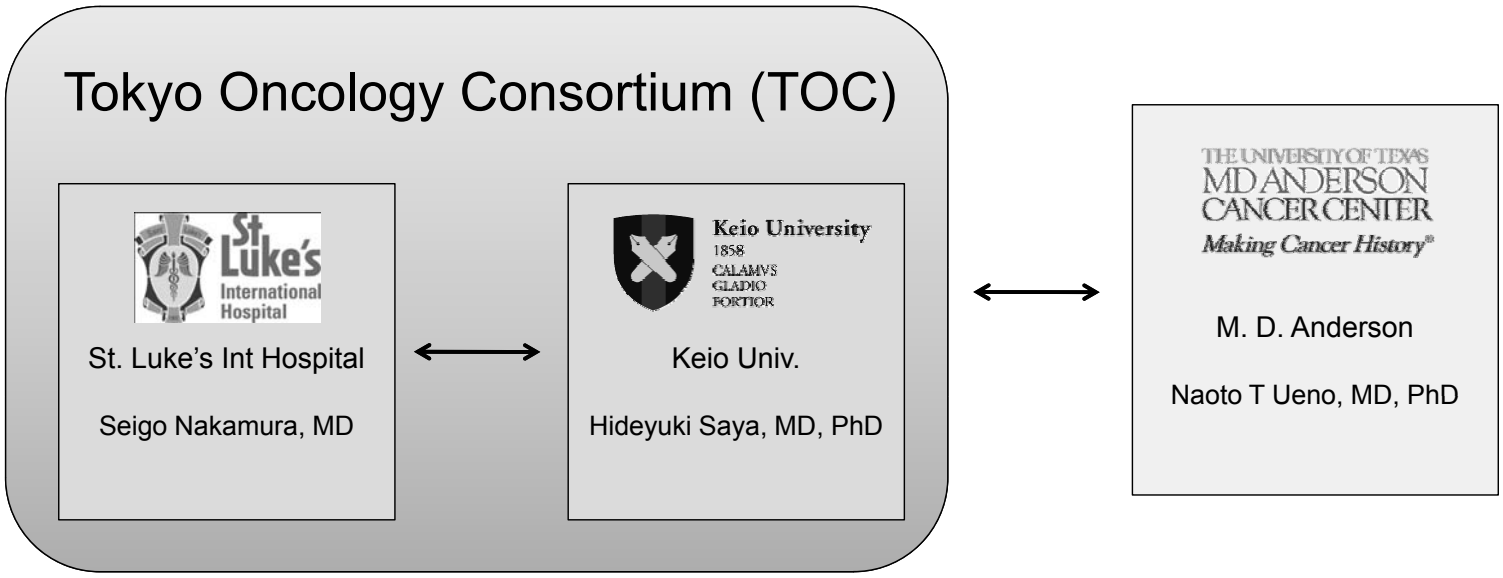


Clinical trials to obtain drug approval for some indications are more significant in Japan than in the US.

If the effectiveness of a drug was revealed by investigator-initiated clinical trial and it is used as a standard therapy without indication on the basis of robust clinical evidence in other countries, Japanese patients would not be able to receive it without investigator-initiated clinical trial with IND for approval in Japan.

Our Challenge for Implementing a Investigator-Initiated Clinical Trial with IND for Approval as a Collaboration Study with NCI/CTEP

St Luke's international hospital and Keio University are sister institutions of M.D. Anderson Cancer Center



TOC will implement an investigator-initiated clinical trial with IND for approval collaborated with NCI/CTEP

- Treatment : Neoadjuvant therapy
- Type of disease : Breast cancer
- Phase : II
- Year of IND : 2011 (January or February, hopefully)
- Fund : Japan Medical Association

This study is the first independent study collaborated with CTEP.

We hope our challenge can propose a novel style of investigator-initiated clinical trials with IND for approval in Japan.

Clinical Trials in a Globalized Society – Building an Effective Cancer Clinical Trials System

May 25, 2010
British Embassy, Tokyo

Byung-Ho Nam
National Cancer Center, Korea(NCCK)

Contents

International Collaboration

- Need: for public benefits
  - differences do exist
    - Cancer Incidence
    - Response to drugs
    - Genetic difference
    - Environmental difference – life style
- How?: challenging!
  - Government supported system
    - Centralized Coordinating infra-structure
    - Common(exchangeable)platform

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International Collaboration

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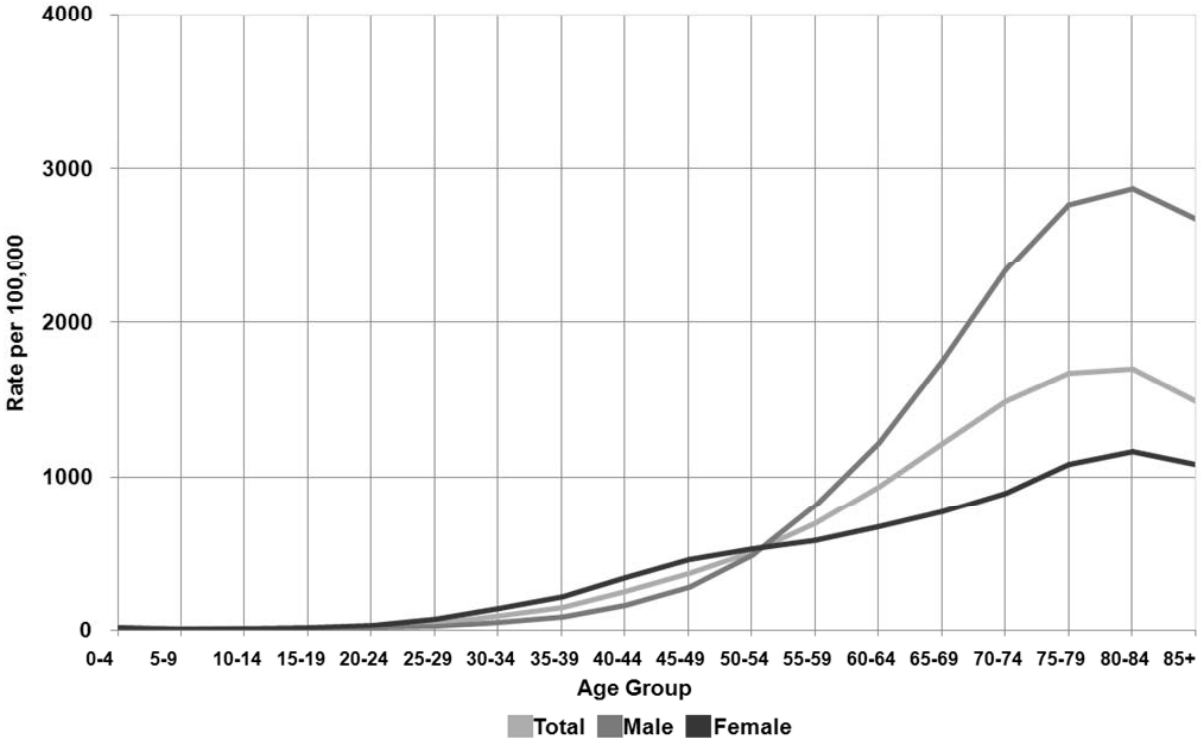
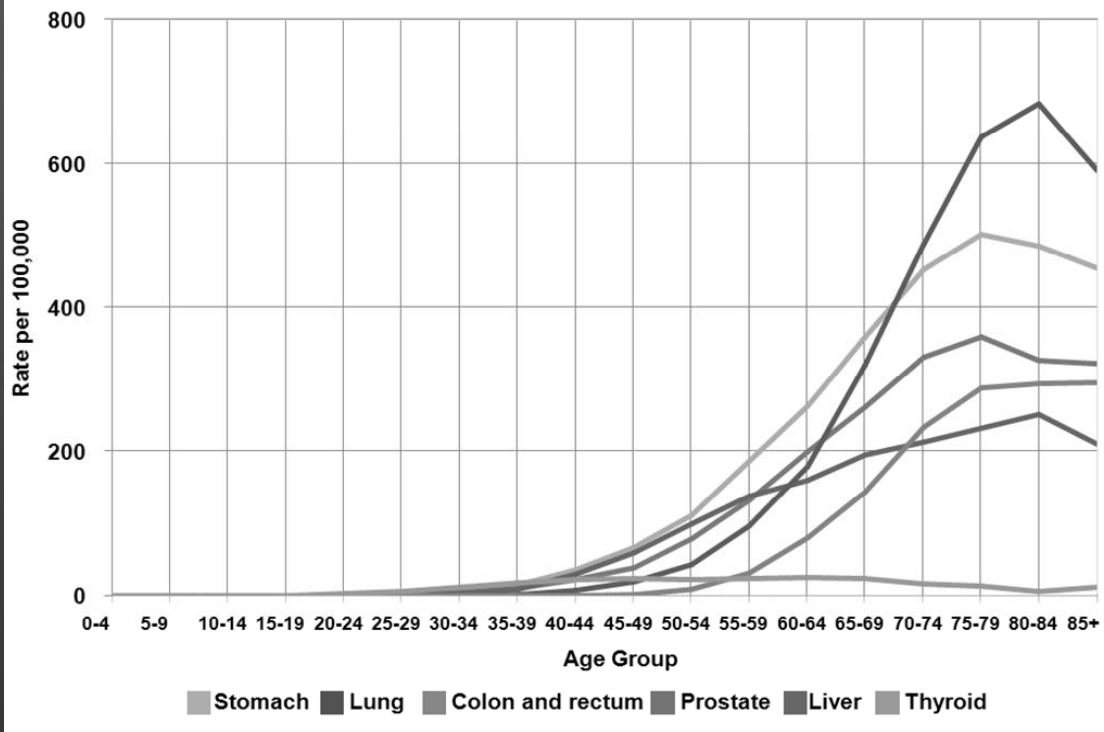
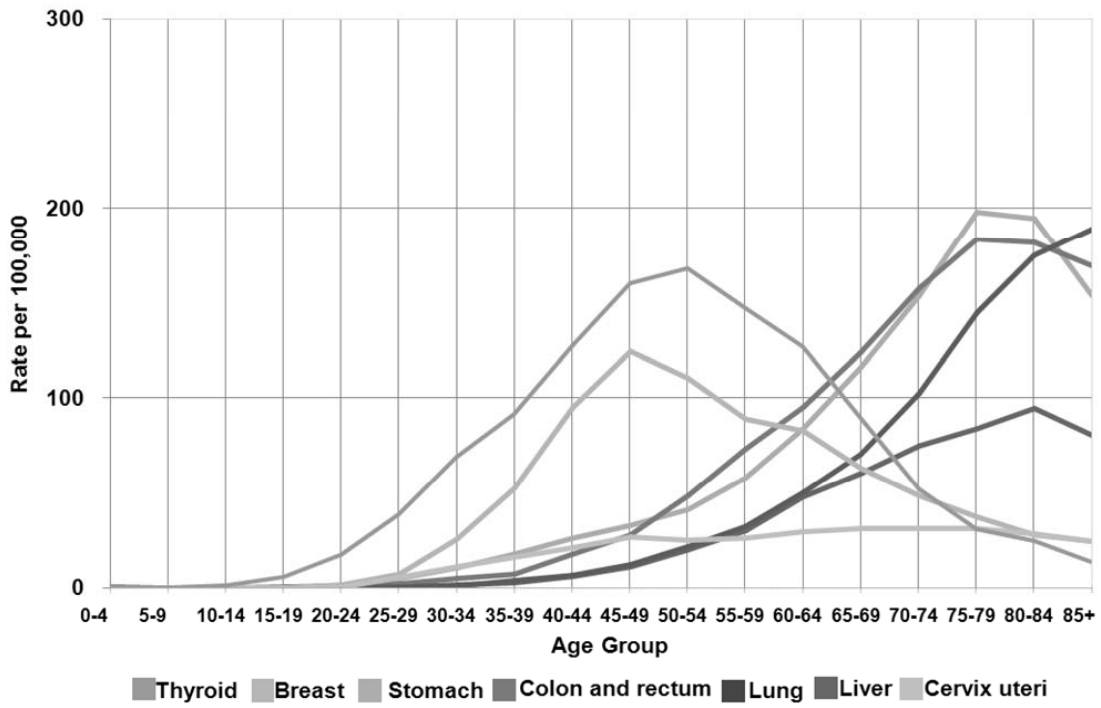
Age-specific incidence rates by sex, 2007, Korea



Age-specific incidence rates by cancer sites Male, 2007, Korea



Age-specific incidence rates by cancer sites Female, 2007, Korea



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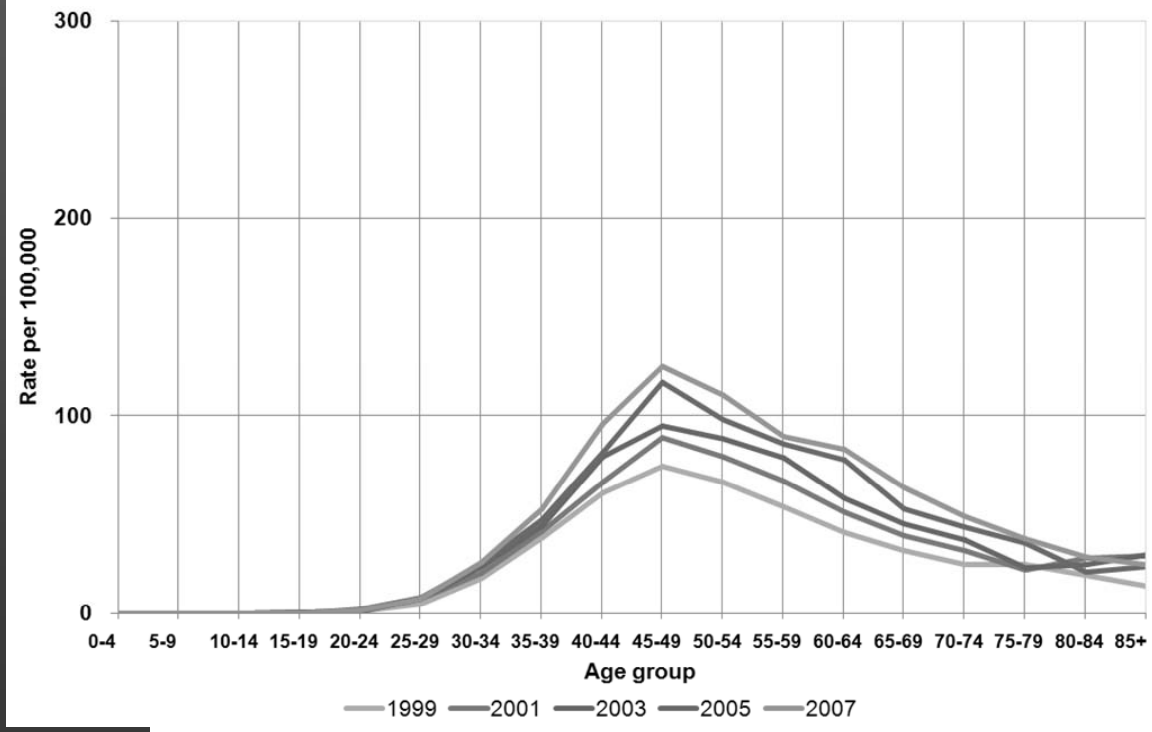
Age-specific rates of breast cancer: Female, Korea



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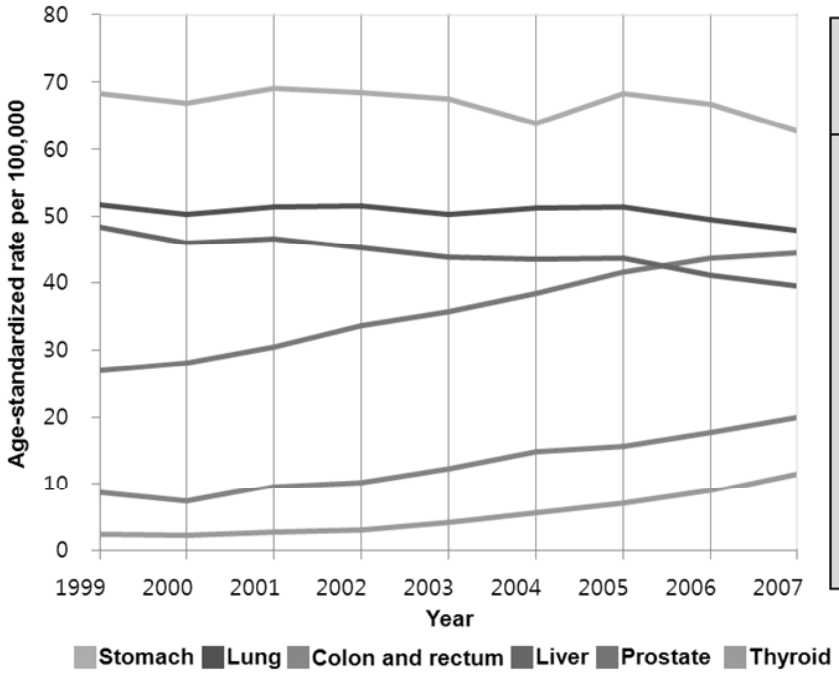
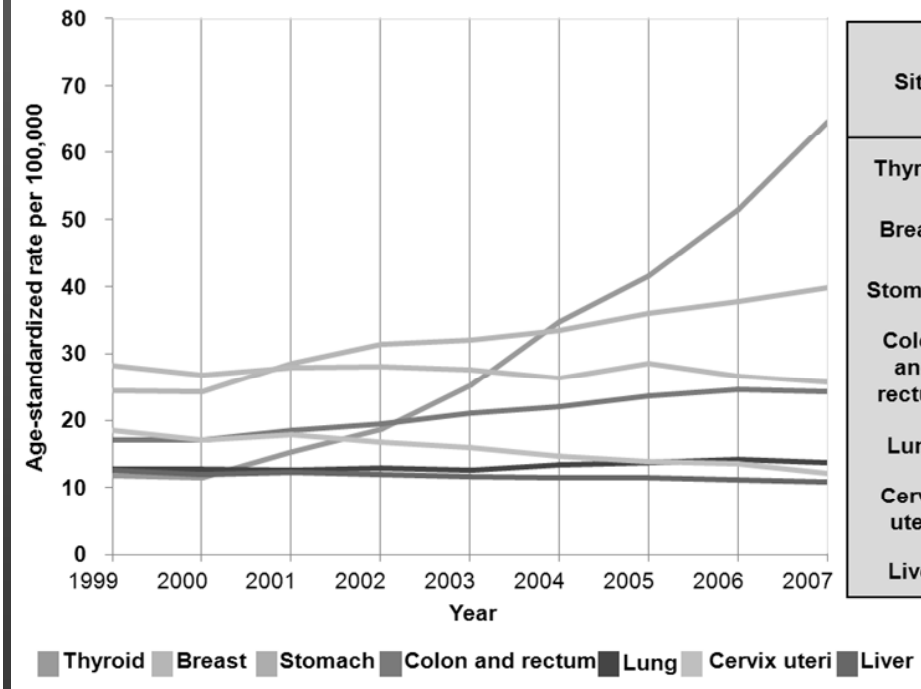
Trend of Major Cancers in Korea, Male



Site	Year		Annual Percent Change (%)
	1999	2007	
Stomach	68.4	62.8	-0.7
Lung	51.9	48.1	-0.6
Colon and rectum	27.0	44.5	7.0 *
Liver	48.5	39.6	-2.2 *
Prostate	8.5	20.1	13.2 *
Thyroid	2.3	11.6	24.5 *

* P < .05

Trend of Major Cancers in Korea, Female

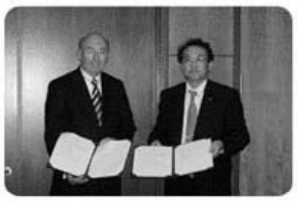


Site	Year		Annual Percent Change (%)
	1999	2007	
Thyroid	11.9	64.8	26.0 *
Breast	24.5	39.9	6.6 *
Stomach	28.3	25.7	-0.7
Colon and rectum	17.1	24.3	5.3 *
Lung	12.9	13.7	1.2 *
Cervix uteri	18.6	12.2	-4.9 *
Liver	12.6	10.9	-1.6 *

* P < .05

NCCK's Effort for International Collaboration

- LOI between NCCK and NCI(2006)
- WHO Collaborating Center(2005)
- MOU with IARC(2008)
- Asian National Cancer Centers Alliance(ANCCA)



LOI Exchange at NCI in July 2006

ANCCA Inauguration Meeting

WHO Collaborating Centre

MOU with the IARC

NCCK's Effort for International Collaboration

- Collaboration between NCCK and NCI
  - In Clinical trials:
    - NCCK's participation in NCI's supported clinical trials
      - Collaborating with South West Oncology Group (SWOG)
        - ✓ Start with lung cancer
    - KGOG (and JGOG) are members of GOG

NCCK's Effort for International Collaboration

■ **Collaboration between NCCK and NCI**

➢ **In B&D(Bridge and Development) project for cancer drug development**

◆ **Advice & Support from the global leader**

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Multinational Clinical Trials

➢ **Introducing a web based clinical trial management system: Velos (USA)**

- **Rapid increase of multi-center, multi-national clinical trials – need for better systematic management platform (Web-based clinical trial management)**
- **National Cancer Center's role as a leading and coordinating institution for cancer clinical research requires better infra-structure with efficient and effective hardware system**

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Multinational Clinical Trials

- **Velos system: USA**

- Velos system acquired Silver level from the NCI (CDE, CTC, AE report, caBIG compliance)
- Standardization of Electronic Data Capture (EDC) procedure by the NCI: NCI recommends Velos system
- 20 Major Comprehensive Cancer Centers, Major Universities(Duke, Johns Hopkins, Columbia, Michigan, UC San Francisco, MD Anderson etc. are using Velos system

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Training the Velos System Users

Programs what we have

1. **Off-line education – 1 Day & Regular**

Regular (Date)	No.
2007/11	21
2008/03	16
2008/06	17
2008/10	16
2009/03	17
2009/09	17
Total	104

1Day (Year)	No.
2007(1 time)	13
2008(11times)	166
2009(13 times)	206
2010(1 times)	18
Total	403

2. **Web-based education (Cyber)**

e-Learning (Month)	No.
2009/11	34
2009/12	15
2010/01	19
2010/02	9
2010/03	6
Total	83

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Multinational Clinical Trials

- **SOS Study: Phase III trial of 3-weekly vs. 5-weekly schedule of S-1 plus cisplatin combination chemotherapy for first line treatment of advanced gastric cancer (S-1 Optimal Schedule Study)**
  - **Participating country: Korea, Japan(WJOG)**
    - **Institutions: Korea – 13, Japan – about 20~25**
  - **Total patients: 622**
  - **Coordinating Centers:**
    - **Korea: National Cancer Center**
    - **Japan: WJOG Data Center**
  - **Clinical Trial Management Platform: Velos system**

Future Challenges

- **Support from the Government and Policy makers**
- **Academic infra-structures for clinical trials**
- **International Commitment for Cancer clinical trials**

Thank you!

International Collaboration in Oncology Clinical Trials: US NCI CTEP example

Naoko Takebe
Edward Trimble
Cancer Therapy Evaluation Program
DCTD, NCI, NIH
January 29, 2009
Clinical Trials in a Global Society

Overview

- Why is international collaboration in clinical trials important?
- NCI's current activity in international collaboration in clinical trials
- Challenges and success stories

Why we need international collaboration: I

- Improved treatment->improved survival
  - We need a larger sample size to detect further improvements or to define the efficacy of a less toxic regimen
- Use of tumor biology to define patient cohorts
  - We need to cast a wider net to identify patients with the appropriate molecular classification

Why we need international collaboration: II

- We have effective screening for certain cancers
  - The incidence of cancers with advanced stage has fallen; we need to collaborate to complete phase III trials in these patient populations
- Targeted therapy may offer effective treatment for rare tumors and subtypes
  - We need to recruit patients worldwide to conduct definitive trials

Why we need international collaboration: III

- We now have many new investigational agents
  - We need to collaborate on the design and conduct of randomized treatment trials to evaluate these new agents in conjunction with state-of-the-art care as quickly as possible
- Global trials will make trial results broadly applicable and facilitate uptake of new effective treatments.

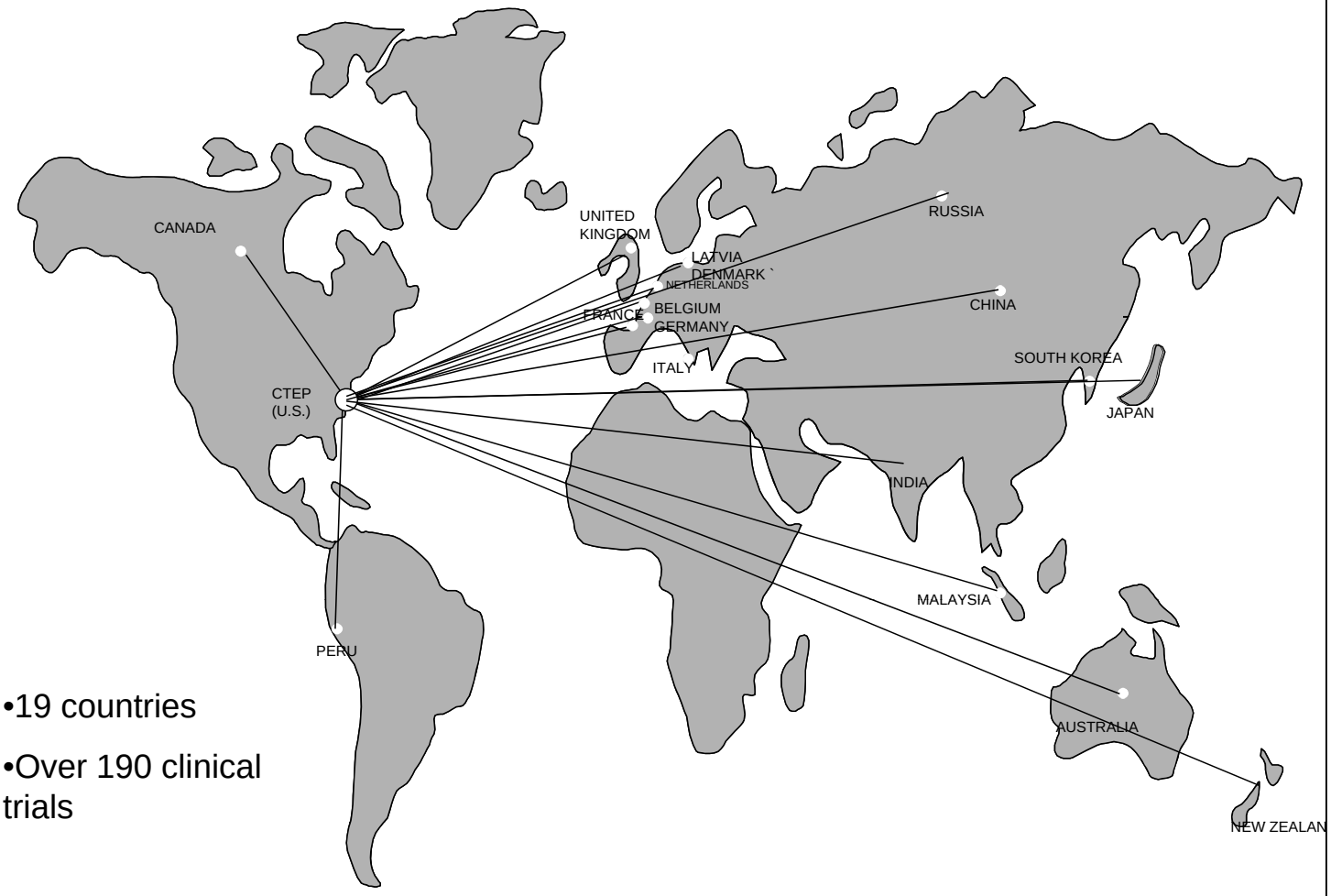
NCI International Partnerships in Clinical Trials

- Canada
- Europe (EORTC)
- All-Ireland Cancer Consortium
- UK National Cancer Research Network
- French Institut National du Cancer
- Korea National Cancer Center
- Latin America

Sites for US groups outside North America

- Australia
- China
- Ireland
- Israel
- Japan
- Korea
- New Zealand
- Peru
- Saudi Arabia
- South Africa
- Switzerland

CTEP'S INTERNATIONAL CLINICAL TRIALS COLLABORATIONS



•19 countries

•Over 190 clinical trials

Accrual by Region

Registering Institution Region	FY2000	FY2001	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007	FY2008	FY2009	Grand Total
Canada	1714	2464	2902	2733	2662	2725	2377	2020	1933	2081	**23611**
International	263	307	359	445	520	644	797	948	983	1070	**6336**
USA	23317	27742	27383	24755	25463	27333	27525	25011	25746	28143	**262418**
Unknown	1528	2212	1341	133	207	282	833	526	304	823	**8189**
Grand Total	**26822**	**32725**	**31985**	**28066**	**28852**	**30984**	**31532**	**28505**	**28966**	**32117**	**300554**

Accrual by Country

Registering Institution Country	FY2000	FY2001	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007	FY2008	FY2009	Grand Total
Australia	67	100	166	188	208	164	139	176	171	162	**1541**
Austria	0	0	0	0	1	0	0	0	0	0	**1**
Belgium	5	5	9	2	2	0	0	8	13	0	**44**
Brazil	0	0	0	0	0	0	0	0	4	8	**12**
Cameroon	0	1	0	0	0	0	0	0	0	0	**1**
Canada	1714	2464	2902	2733	2662	2725	2377	2020	1933	2081	**23611**
China	0	0	0	2	8	7	4	1	2	4	**28**
Denmark	3	7	4	3	1	3	0	0	0	0	**21**
France	0	0	0	0	0	0	0	0	9	0	**9**
Germany	2	6	17	5	1	4	1	1	5	0	**42**
Hong Kong	0	0	0	0	1	3	9	7	6	19	**45**
India	0	0	0	0	0	0	0	0	3	38	**41**
Ireland	1	0	27	63	9	3	109	96	183	325	**816**
Israel	2	7	2	33	39	24	45	70	42	30	**294**

Accrual by Country (cont.)

Registering Institution Country	FY2000	FY2001	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007	FY2008	FY2009	Grand Total
Italy	0	0	0	0	0	4	0	0	0	0	**4**
Japan	0	0	0	1	3	12	20	29	47	39	**151**
Korea (South)	0	0	0	0	1	2	4	6	11	23	**47**
Latvia	0	0	0	0	0	0	0	8	21	0	**29**
Netherlands	40	17	0	0	0	6	2	8	21	5	**99**
New Zealand	0	26	25	34	23	18	18	41	35	28	**248**
Peru	0	0	0	32	38	42	30	27	85	119	**373**
Saudi Arabia	0	0	0	0	0	0	0	0	2	7	**9**
Singapore	0	0	0	0	4	5	5	6	20	23	**63**
South Africa	55	44	70	72	36	10	0	0	5	9	**301**
Sweden	1	0	0	0	0	0	0	0	9	14	**24**
Switzerland	26	35	9	10	145	335	396	424	239	217	**1836**
United Kingdom	61	59	30	0	0	2	15	40	50	0	**257**
USA	23317	27742	27383	24755	25463	27333	27525	25011	25746	28143	**262418**
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Steps to international collaboration: I

- Registration of clinical trials
  - WHO, USA: clinicaltrials.gov, NCI PDQ
  - International Committee of Medical Editors
- Regular meetings of trialists at national and international forums
  - ASCO, San Antonio and St Gallen breast meetings, etc

Steps to international collaboration: III

- Harmonization of staging
  - UICC TNM
- Standardization of pathologic classification
  - WHO/IARC International Classification of Diseases-Oncology (ICD-O)
- Harmonization of data
  - Toxicity and adverse events (CTCAE 4.0), response to treatment (RECIST), common data elements (CDE), International Conference on Harmonization (ICH)

Challenges: I

- US red tape
  - FDA 1572 form, Federal-Wide Assurance (FWA), registration of ethics committees
- Non-US red tape
- Drug availability and distribution
  - Experimental agent and ‘standard’ regimen
- Synchronization of scientific and regulatory review

Challenges: II

- Adverse Event reporting
- Translation of documents
- NCI audit requirements
- Differences in infrastructure support
- Et cetera

Success stories: I

- GOG 0182/ ICON 5
  - Carboplatin/paclitaxel + topotecan or gemcitabine or liposomal doxorubicin
  - US/UK/Italy; 4312 patients; JCO 2009
- GOG 0218
  - Carboplatin/ paclitaxel +/- bevacizumab
  - US/Japan/Korea; 2000 patients; ASCO 2010

Success stories: II

- MEOC/ GOG 0241
  - 2 x 2 design; carboplatin/ paclitaxel vs oxaliplatin/ capecitabine; mucinous ovarian cancer
  - UK/ US
- JGOG 3017
  - Carboplatin/paclitaxel vs irinotecan/ cisplatin; clear cell ovarian cancer
  - Japan/Korea/France/Italy/Scotland

Backup slides

Cooperative Cancer Research Program

- Between Japan Society for the Promotion of Science and US NCI
- Began in 1974; NCI's longest standing international bilateral agreement
- Scientific seminars, exchange of scientists, exchange of materials and information
- More visiting scientists at NCI laboratories from Japan than any other country

Recent Japanese Initiatives Relevant to Cancer: I

- Third Science and Technology Basic Plan
  - Council on Science and Technology, 2006
- Basic Act for Anti-cancer Measures,
  - Japanese Diet, 2006

Recent Japanese Initiatives Relevant to Cancer: II

- Report on Promotion of the Base for Clinical Research
  - Ministry of Health, Labor, and Welfare, 2006
- New 5-year Revitalization Project for Clinical Trials, 2007
  - Ministry of Health, Labor, and Welfare
  - Ministry of Education, Culture, Sports, Science, & Technology

Expanding Japan-US partnership

- How might the US NCI partner with the the Japanese government strengthen the infrastructure for cancer clinical trials in Japan?
- How can we strengthen collaboration in cancer clinical trials between the US and Japan?

Benefits of cancer clinical trials: I

- Identification of best therapies for cancer patients
  - Children, adults, elderly
- Timely evaluation of new drugs and devices for potential licensing
- Translational research through access to specimens

Benefits of cancer clinical trials: II

- Development of guidelines for optimal cancer care
- Strengthen clinical research capability
  - Investigators: MDs, nurses, pharmacists, data managers, biostatisticians
- Foster pharmaceutical industry development of new drugs

NCI Commitment to Cancer Treatment Trials: I

- Annual accrual to treatment trials about 25,000 patients per year
- Sponsors over 900 active protocols
  - 500 new protocols per year
- Involves over 12,000 investigators at over 3300 institutions
- Sponsors over 140 Investigational New Drugs
  - Over 80 collaborative agreements with Pharmaceutical industry
- Budget: about $150 million per year

GCIG member groups

- AGO-Austria
- AGO-OVAR
- ANZGOG
- EORTC GCSG
- GEICO (Spain)
- GINECO (France)
- GOG
- JGOG
- MANGO (Italy)
- MITO (Italy)
- MRC/ NCRI (UK)
- NCI-US
- NCIC CTG (Canada)
- NSGO (Scandinavia)
- RTOG
- SGCTG (Scotland)

Japan-US collaboration in gynecologic cancer

- Atypical glandular cells on Pap smear
- Adjuvant therapy for early stage ovarian cancer
- Intraperitoneal chemotherapy for ovarian cancer
- Antiangiogenesis in ovarian cancer (GOG 218)

Who pays for cancer clinical trials?

- Government: sometimes
- Industry: sometimes for specific trials
- Charities: sometimes
- Participating institutions: always

Central costs of clinical trials: I

- Protocol design & development
  - Includes support for meetings and conference calls
- Data collection and management
- Drug supply and distribution

Central costs of clinical trials: II

- Statistical design and analysis
- Tumor and specimen banking
- Quality assurance/ quality control
- Audits of participating sites

Costs for institutions participating in clinical trials

- IRB review of proposed trials, open trials, toxicity, amendments, etc
- Time of local investigators, nurses, and data managers
- Time and resources for related studies, such as pathology and imaging

Countries with effective cancer clinical trial systems: I

- Canada: National Cancer Institute of Canada Clinical Trials Group, primarily supported by charity; some support from industry for specific trials; some support from NCI for data center
- Ireland: All-Ireland Cancer Consortium, primarily supported by governments (Republic of Ireland, and UK Northern Ireland)

Countries with effective cancer clinical trials systems: II

- UK: National Cancer Research Network, supported by government; Cancer Research UK, supported by charity; some support from industry for specific trials
- USA: Clinical trials cooperative groups, NCI Cancer Centers, SPOREs, supported by government; some support from industry for specific trials

Regional cancer clinical trials system: EORTC

- Data center partially supported by EU and NCI; minimal support for groups and participating centers
- Intermittent support from industry for specific trials
- Difficulty starting or joining new trials without substantial industry support

Accrual – EORTC Protocols

Protocol Number	Registering Institution Country	FY2000	FY2001	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007	FY2008	FY2009	Grand Total
C9581	Netherlands	29	13	0	0	0	0	0	0	0	0	**42**
	United Kingdom	47	41	7	0	0	0	0	0	0	0	**95**
	USA	366	303	181	0	0	0	0	0	0	0	**850**
	Canada	58	62	23	0	0	0	0	0	0	0	**143**
	Unknown	19	53	39	0	0	0	0	0	0	0	**111**
C9581 Total		519	472	250	0	0	0	0	0	0	0	1241
CALGB-10603	USA	0	0	0	0	0	3	0	0	0	53	**56**
	Unknown	0	0	0	0	0	7	0	0	0	175	**182**
CALGB-10603 Total		0	0	0	0	0	10	0	0	0	228	238
EORTC-30904	Belgium	4	5	9	1	0	0	0	0	0	0	**19**
	USA	1	2	0	0	0	0	0	0	0	0	**3**
	Unknown	43	32	45	8	0	0	0	0	0	0	**128**
EORTC-30904 Total		48	39	54	9	0	0	0	0	0	0	150
EORTC-30987	USA	0	0	0	14	8	0	0	0	0	0	**22**
EORTC-30987 Total		0	0	0	14	8	0	0	0	0	0	22

Accrual – EORTC Protocols (cont.)

Protocol Number	Registering Institution Country	FY2000	FY2001	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007	FY2008	FY2009	Grand Total
EORTC-62933	Belgium	1	0	0	0	0	0	0	0	0	0	**1**
	Denmark	1	0	0	0	0	0	0	0	0	0	**1**
	Germany	0	1	0	0	0	0	0	0	0	0	**1**
	Netherlands	2	0	0	0	0	0	0	0	0	0	**2**
	Sweden	1	0	0	0	0	0	0	0	0	0	**1**
	United Kingdom	2	1	0	0	0	0	0	0	0	0	**3**
	USA	1	0	0	0	0	0	0	0	0	0	**1**
EORTC-62933 Total		8	2	0	0	0	0	0	0	0	0	10
INT-0149	USA	34	21	10	0	0	0	0	0	0	0	**65**
	Canada	12	8	3	0	0	0	0	0	0	0	**23**
INT-0149 Total		46	29	13	0	0	0	0	0	0	0	88
INT-0162	USA	257	232	172	165	188	182	175	220	178	0	**1769**
	Canada	25	29	27	29	26	18	14	12	20	0	**200**
	Unknown	95	87	84	59	66	60	68	55	48	0	**622**
	South Africa	0	0	1	0	0	0	0	0	0	0	**1**
INT-0162 Total		377	348	284	253	280	260	257	287	246	0	2592

Accrual – EORTC Protocols (cont.)

Protocol Number	Registering Institution Country	FY2000	FY2001	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007	FY2008	FY2009	Grand Total
RTOG-0525	Belgium	0	0	0	0	0	13	8	0	0	0	**21**
	Germany	0	0	0	0	0	5	1	0	0	0	**6**
	Netherlands	0	0	0	0	0	13	0	0	0	0	**13**
	United Kingdom	0	0	0	0	0	46	31	0	0	0	**77**
	USA	0	0	0	0	0	311	346	155	0	0	**812**
	Canada	0	0	0	0	0	35	73	21	0	0	**129**
	Israel	0	0	0	0	0	29	40	2	0	0	**71**
	France	0	0	0	0	0	9	0	0	0	0	**9**
	Latvia	0	0	0	0	0	21	8	0	0	0	**29**
	Switzerland	0	0	0	0	0	3	4	0	0	0	**7**
RTOG-0525 Total		**0**	**0**	**0**	**0**	**0**	**485**	**511**	**178**	**0**	**0**	**1174**
Grand Total		**998**	**890**	**601**	**276**	**288**	**755**	**768**	**465**	**246**	**228**	**5515**

International Collaboration

Jonathan Ledermann

Why is academic international collaboration essential ?

- Globalisation of standards of care based on high quality evidence-based medicine
- Large number of new agents now available
  - Rapid evaluation and comparison
  - Benefits may be relatively small, so large trials needed
  - Answers needed fast and best achieved by international cost-sharing
- Most comparative studies will not be done by industry- eg.
  - Similar class drugs
  - Different dose, schedules and duration
- Industry prioritisation is income-led, not by clinical need

The Good and the Bad

Advantages

- Academic Networks
  - breast, gynaecological, lymphoma etc
- Design of trials is collaborative, avoiding duplication and unnecessary competition
- Common standards- harmonization in trials leads to common standards of care
  - International consensus statements
- Collaboration and sharing of data accelerates research and results

Obstacles to international trials

Disadvantages

- Increasingly stringent and different national regulations
  - Insurance/indemnity
  - Pharmacovigilance- stringent regulatory processes
  - Complex and differing legal systems- contracts (trial and drug supply etc)
- Complex and differing review processes and activation
- Design by groups dilutes individual contribution which may affect local academic standing
- Lack of infrastructural funding making academic trials prohibitively expensive

Solutions

- National investment in infrastructure
  - Eg research nurse/data management
- Simplification of regulations for academic trials
  - Risk based approached
  - Acceptance of parallel studies with agreed single analysis
- Collaborative studies with industry
  - Academic sponsorship
  - Drug supply and per patient support from industry

Moderately common tumours

- International intergroup collaboration and planning is necessary to:
  - Improve Speed
  - Maximise Opportunities
- As much about planning as doing trials together
  - Eg. Ovarian cancer
  - Eg. Renal cancer

ICON 6

International Collaboration for Ovarian Neoplasia

Novel anti-vascular targeting drug AZD2171 [cediranib; Recentin™] for relapsed ovarian cancer

- Good scientific rationale
- Company pursuing licensing of drug in colorectal cancer
- Ovarian and lung cancer studies could be used to extend indication of licensed product
- Protocol designed by GCIG
- Trial Research and Management costs met by Cancer Research UK and Astra Zeneca (AZ)
- Trial supported by UK NIHR funding and NHS, and Canadian NCI Core grant
- Drug supply AZ
- International sites receive some support costs from AZ grant

Ovarian Cancer: GCIG

GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

AGO-AUST
AGO-OVAR
ANZGOG
EORTC
GEICO
GINECO
GOG
JGOG
MANGO
MITO
MRC/NCRI
NCI
NCIC CTG
NSGO
RTOG
SGCTG

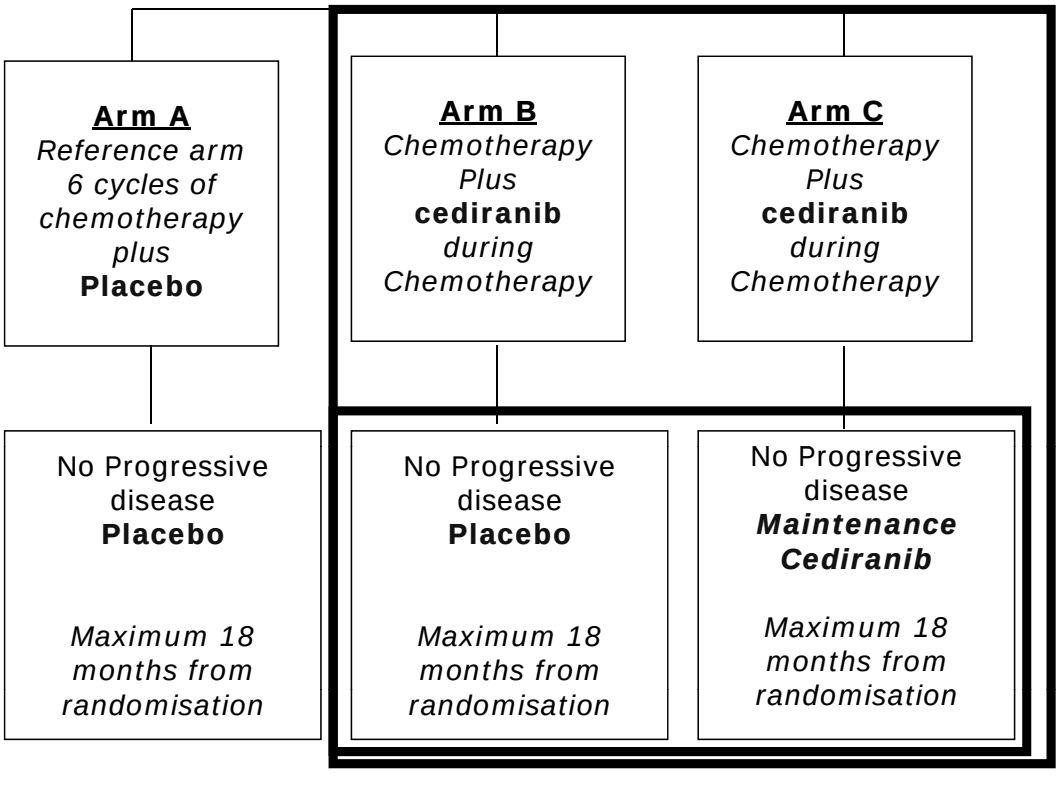
Ovarian cancer

- GCIG
  - Has already done a number of large-scale collaborative trials
  - 4000 patients in 3 years in GOG-182/ICON5
  - 5-arm trial answering 4 questions in 5 years

- Under these auspices the inter groups have planned and are undertaking:
  - at least 5 large-scale concurrent trials ovarian cancer, all asking complementary questions
    - Antibody – bevacizumab
    - Small molecule – erlotinib, cediranib
    - Timing of surgery
    - IP therapy

ICON 6 Design schema

2:3:3 RANDOMISATION



ICON 6
CEDIRANIB IN OVARIAN CANCER

Novel stage design for outcome measures

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Stage I - Safety (50 patients)

- Safety analysis after ~ 33 patients entered into Arms B &C

Stage II – Activity (600 patients/2 years)

- ~ 50 deaths, 90 events
- Progression free survival (PFS)
- Overall survival (OS)

Stage III - Confirmation of Efficacy (2000 patients/4 years)

- Overall survival (OS)
- Progression-free survival (PFS)
- Toxicity
- Quality of life, Health Economics, Translational substudies

MRC Clinical Trials Unit

ICON 6
CEDIRANIB IN OVARIAN CANCER

GYNECOLOGIC CANCER INTERGROUP
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Anticipated accrual

Country	Monthly recruitment	Annual recruitment
UK (MRC/ NCRI/SCOTROC)	15	180
Italy (ICON)	10	120
Canada (NCIC CTG)	8	96
Scandinavia (NSGO)	5	60
Australia and NZ (ANZGOG)	8	96
Spain (GEICO)	8	96
Total	**54**	**648**

MRC Clinical Trials Unit

ICON 6
CEDIRANIB IN OVARIAN CANCER

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Summary

- Academic GCIG Trial with MRC/NCRI Group as lead group
- Sponsored by MRC
- Coordinated by MRC CTU
- UK CTAAC funding (Cancer Research UK) for MRC CTU
- Administrative support from AstraZeneca for international coordination
- Grant from AstraZeneca to cover coordination by GCIG groups and some per patient support
- Drug supply AstraZeneca
- Potentialregistration trial for AstraZeneca

MRC Clinical Trials Unit