towards high-quality clinical trials and
implementation of genomic medicine

ATLAS Training Program

Course ： Procedures for conducting multinational clinical trials

Speaker ： Kenichi Nakamura

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Department of International Clinical Development, National Cancer Center Hospital

EDUCATION

Medical Faculty, Kyoto University, Japan (1993–1999)

WORK EXPERIENCE

Surgical Resident/Staff, General Surgery, Kyoto University and its affiliations (1999–2006)

Research Resident, JCOG Data Center, National Cancer Center (2006–2008)

Section Head, Clinical Trial Management Section, National Cancer Center Hospital (2008–2017)

Director, JCOG Operations Office (2008–present)

Division Chief, Research Management Division, Clinical Research Support Office, National Cancer Center Hospital (2017–2020)

Chief Management Officer, Clinical Research Support Office, National Cancer Center Hospital (2017–present)

Director, Department of International Clinical Development, National Cancer Center Hospital (2020–present)

EXTRAMURAL POSITION

Board Member, Japanese Society of Clinical Trials and Research (2019–present)

Visiting Professor, Yokohama City University (2020–present)

Visiting Professor, Hiroshima University (2022–present)

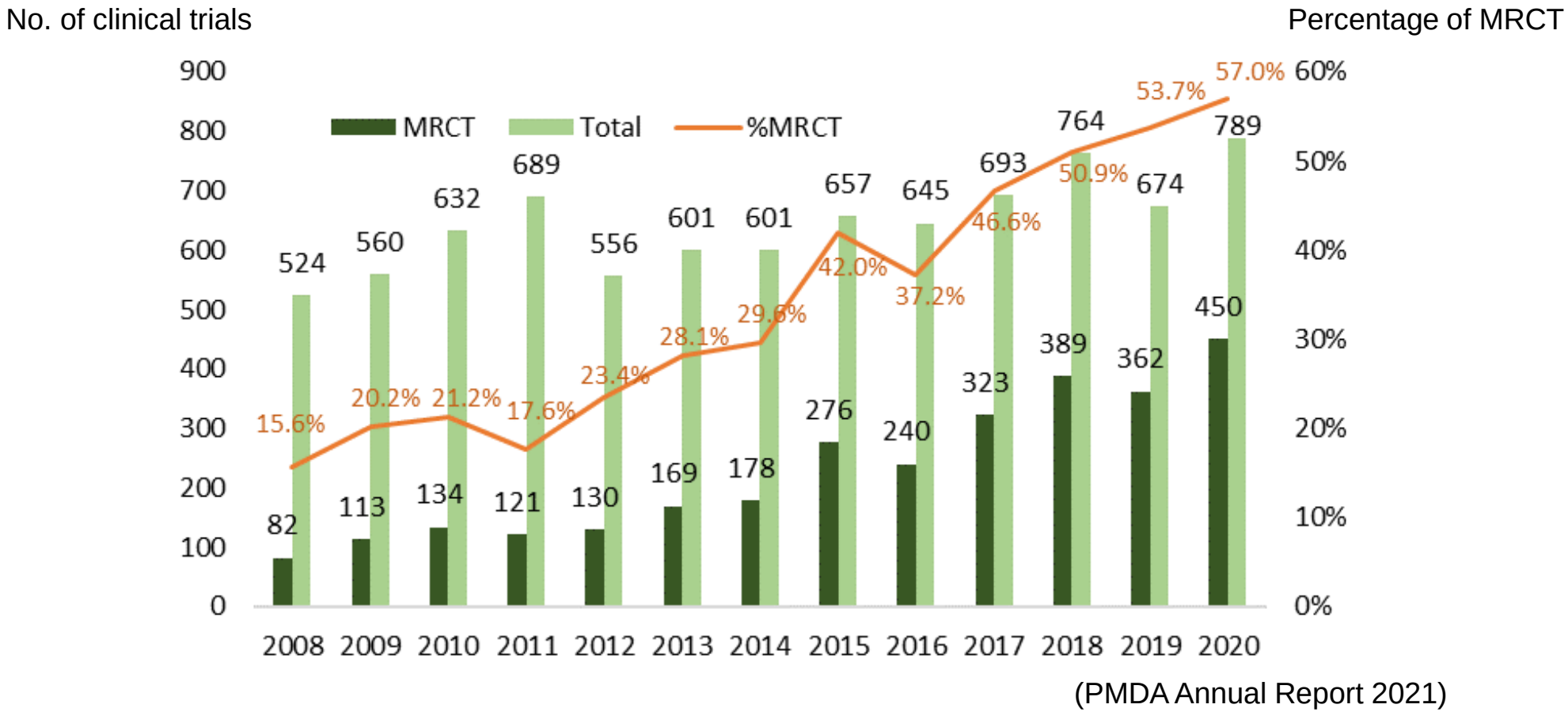
Goals

- Regulatory changes and global trends in multi-regional clinical trials
- Importance of investigator-initiated registration-directed trials (IIRDTs)
- Operational management in MRCTs

Multi-regional clinical trials (MRCTs)

Number of clinical trial notifications submitted to the PMDA

(PMDA: Pharmaceuticals and Medical Devices Agency)

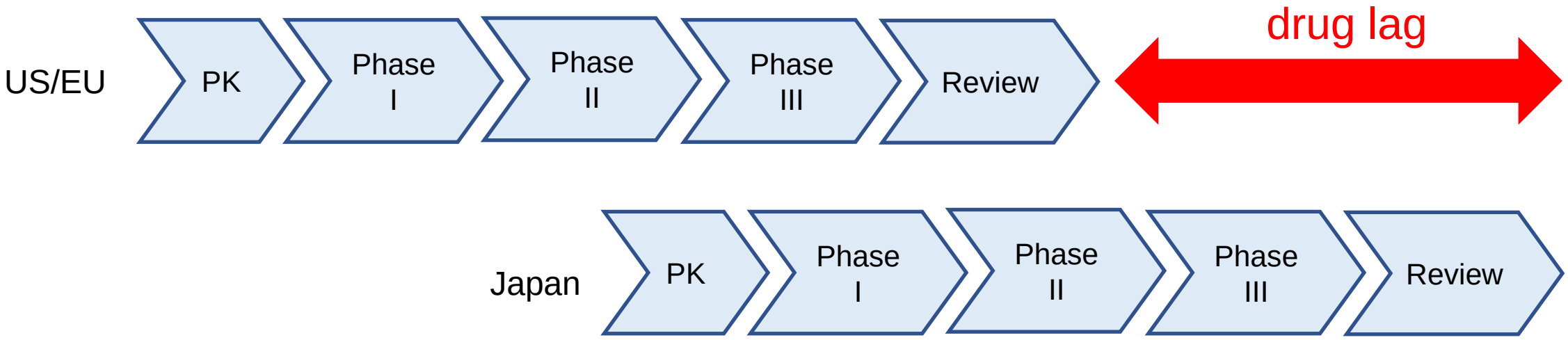


(PMDA Annual Report 2021)

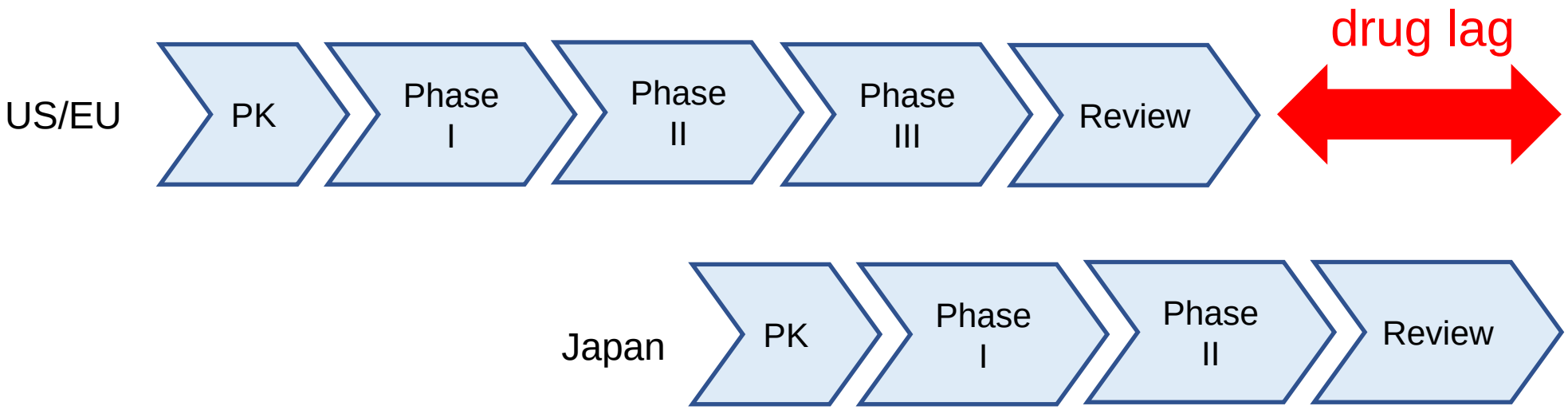
Why are MRCTs needed?

- Advantages
  - Simultaneous drug development is possible in multiple regions
  - Fast patient accrual
    - Clinical trial subjects tend to be fragmented because of the use of precision medicine
  - Reduction of total cost
  - Detection of rare adverse reactions and minor ethnic differences because of larger sample sizes
- Disadvantages
  - Insufficient number of patients in one region
  - Ethnic differences may be observed in pharmacokinetics (PK), safety, and efficacy
  - Optimal dosage may differ among regions

Traditional model (before ICH E5)



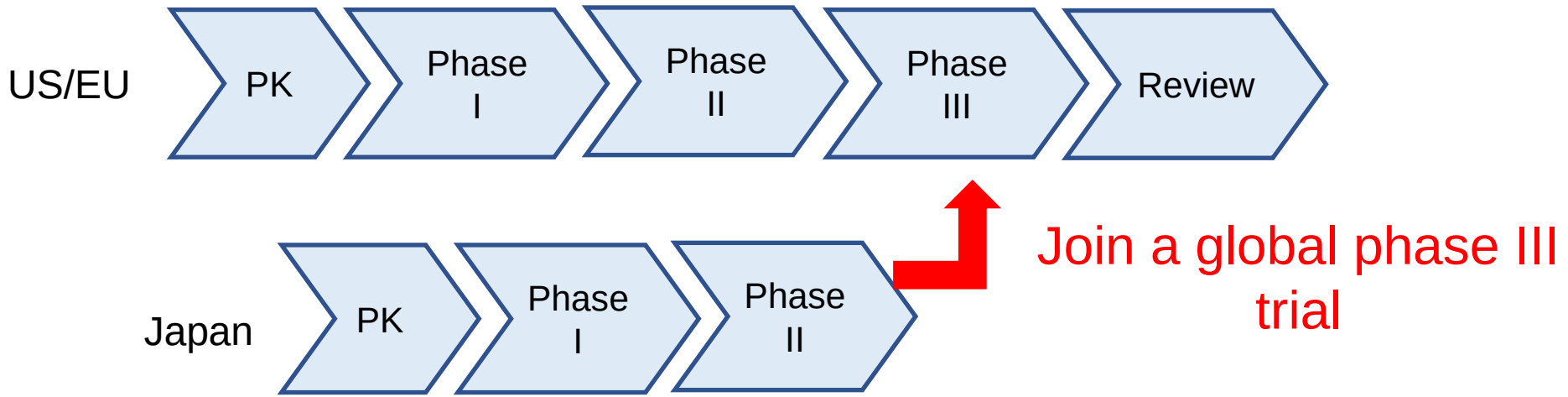
Bridging study (ICH-E5)



ICH-E5 (1998)

- Ethnic Factors in the Acceptability of Foreign Clinical Data
  - Guideline for bridging studies
    - It is not necessary to repeat the entire clinical drug development program in a new region, and strategies can be recommended for accepting foreign clinical data as full or partial support for approval of an application in a new region.
  - The need for a bridging study depends on whether the submitted clinical data are complete.
  - If the data are not complete, a local regulatory authority may require a bridging study to fill the gap, e.g., by performing:
    - clinical trials in different subsets of the population such as in patients with renal insufficiency, patients with hepatic dysfunction, etc.
    - clinical trials using different comparators based on the new region's approved dosage and dose regimen

Participation in global phase III



Governmental notification (2007)

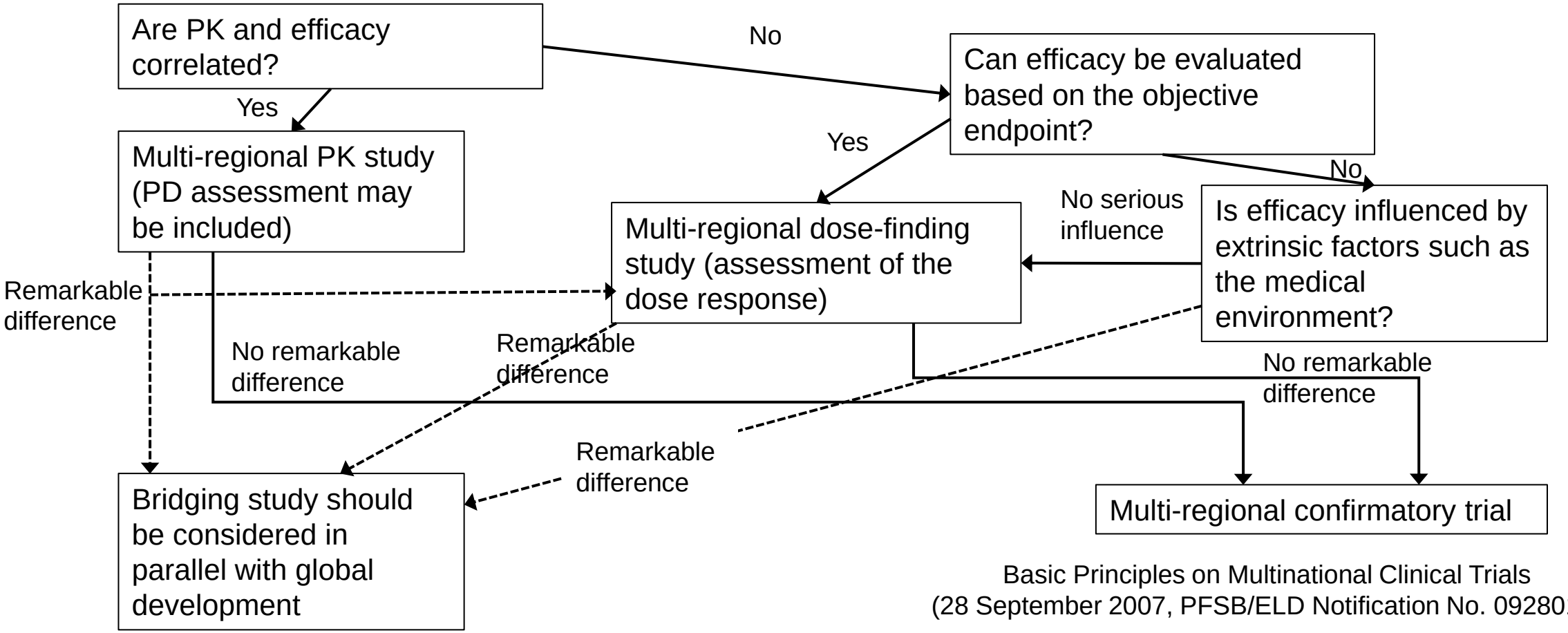
- Basic principles of multinational clinical trials for approval reviews

- Are PK assessment and/or dose optimization required for the Japanese population before a global phase III trial?
  - Basically, YES. If the sponsor can justify why these steps are unnecessary, the steps can be skipped.

- What is the method for estimating the appropriate sample size of Japanese patients in a global phase III trial?
  - It is not necessary to ensure sufficient power to detect a significant difference.
  - However, consistency between the overall and Japanese populations should be ensured so that a sufficient number of Japanese patients are included.

Basic Principles on Multinational Clinical Trials
(28 September 2007, PFSB/ELD Notification No. 0928010)

Flowchart to assess the need for an MRCT based on the government notification (2007)



Basic Principles on Multinational Clinical Trials
(28 September 2007, PFSB/ELD Notification No. 0928010)

More efficient drug development

国立がん研究センター
中央病院
National Cancer Center Hospital

NCCH Japan Department of Experimental Therapeutics
Early Phase 1 Drug Development YEAR IN REVIEW 2020

35 Global First-in-Human Phase 1 Trials in 2020-2021 (10 companies)

Number of patients enrolled on Phase 1 in FY 2020 :

243 C1D1

Established Phase 1 outpatient visits in FY 2020 :

3,800

Total number of Phase 1 trials in progress : November, 2021

65

Total new patients & consult visits in FY 2020 :

615

Number of serial tumor biopsies for biomarker research in FIH Phase I trials 2020

208
Success rate: 92.7%

Total number of NEW Phase 1 trials opened 2020

28

国立がん研究センター
中央病院
National Cancer Center Hospital

ASIA ONE

- Asian early phase I consortium

Asian Oncology Early Phase 1 Consortium

Faculty of Medicine, The Chinese University of Hong Kong
国立がん研究センター National Cancer Center Japan
National Cancer Centre Singapore SingHealth
SNUH SEOUL NATIONAL UNIVERSITY CANCER HOSPITAL

Early Phase Clinical Trials Alliance and Excellence in Asia

Transformation to Hub for Global Oncology Clinical Trials from Asia
Clinical Trial Alliance and Excellence in Asia
"Robust Asian Early Phase 1 Consortium" since Sep 2017

Allied Dedicated Phase 1 Investigators across Pan-Asia

Key Top Phase 1 Sites Collaboration Across HK, JP, KR, SIN and TW

- Chinese University of Hong Kong, Prince of Wales Hospital
- National Cancer Center Hospital Japan
- National Taiwan University Hospital
- National Cancer Center Singapore
- Seoul National University Hospital

AsiaOne's Participation for Global FIH Phase 1 Trials

Phase 1 Trials Title	ClinicalTrials.gov Identifier	Companies	Asian Countries	AsiaOne Sites	Recruitment Status
A phase I dose finding study of oral LTT462 in adult patients with advanced solid tumors harboring MAPK pathway alterations.	NCT02711345 ※1	Novartis	Japan, Singapore	NCCH, NCCS	Completed
A phase I dose finding study of oral LXH254 in adult patients with advanced solid tumors harboring MAPK pathway alterations	NCT02607813 ※1	Novartis	Korea, Japan	SNUH, NCCH	Completed
A phase 1, open-label study to evaluate the safety, tolerability, and pharmacokinetics of TAK-228 (a Catalytic TORC1/2 Inhibitor) as single agent in adult East Asian patients with advanced nonhematological malignancies	NCT03370302 ※2	Takeda	Korea, Japan, Taiwan	AMC NCCH, NCCHE, NTUH	Completed
An open label, phase I Study of BI754091 monotherapy and combination therapy of BI754091 and BI754111 in Asian patients with advanced solid tumours	NCT03433898 ※2	Boheringer	Korea, Japan, Taiwan	SNUH, NCCH, NTUH	Active, not recruiting
A Phase I/Ib, open-label, multi-center dose-escalation and dose-expansion study of the safety and tolerability of intra-tumorally administered LHC165 single agent and in combination with PDR001 in patients with advanced malignancies	NCT03301896 ※1	Novartis	Korea, Japan	SNUH, NCCH	Active, not recruiting
A Phase I/Ib, Open-label, Multi-center, Study of NZV930 as a Single Agent and in Combination With PDR001 and/or NIR178 in Patients With Advanced Malignancies	NCT03549000 ※1	Novartis	Japan, Singapore	NCCH, NCCS	Recruiting
A phase I/Ib, open-label, multi-center, study of DKY709 as a single agent and in combination with PDR001 in patients with advanced solid tumors	NCT03891953 ※1	Novartis	Hong Kong, Japan, Taiwan	CUHK, NCCH, NTUH	Recruiting
Phase Ib Study of TNO155 in Combination With Spartalizumab or Ribociclib in Selected Malignancies	NCT04000529 ※1	Novartis	Hong Kong, Japan, Singapore	CUHK NCCH NCCS	Recruiting
A Phase I/Ib Study of NIZ985 Alone and in Combination With Spartalizumab	NCT04261439 ※1	Novartis	Japan, Taiwan	NCCH. NTUH	Recruiting
A Study of ABBV-927 and ABBV-181, an Immunotherapy, in Participants With Advanced Solid Tumors	NCT02988960 ※1	AbbVie	Korea, Japan	SNUH, NCCH	Recruiting
Study of LY3410738 Administered to Patients With Advanced Solid Tumors With IDH1 or IDH2 Mutations	NCT04521681 ※1	Eli Lilly/ Loxo Oncology	Japan, Korea, Hong Kong	NCCH. SNUH, CUHK	Recruiting
A Study of ASP1948, Targeting an Immune Modulatory Receptor as a Single Agent and in Combination With a PD-I Inhibitor (Nivolumab or Pembrolizumab) in Subjects With Advanced Solid Tumors	NCT03565445 ※1	Astellas	Japan, Korea, Taiwan	NCCH. SNUH, NTUH	Recruiting
Study of JDQ443 in Patients With Advanced Solid Tumors Harboring the KRAS G12C Mutation	NCT04699188 ※1	Novartis	Japan, Singapore, Hong Kong, Taiwan	NCCH. NCCS, CUHK, NTUH	Recruiting

13 global FIH phase I trials have been implemented as of Nov 2021

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

ICH-E17 (2018) From “local-first” approach to “global-first” approach

- General Principles for the Planning and Design of Multi-Regional Clinical Trials
  - Potential regional differences introduced by intrinsic and/or extrinsic factors should not preclude consideration of MRCTs.
  - Such factors should be explored in early phases so that multi-regional exploratory studies may be considered.
  - The results of primary analysis in the overall population are prioritized. Sample size calculations to detect significant differences based on region are not appropriate.
  - Ethnic differences can be mitigated by implanting measures, such as eligibility criteria, treatment plans, randomization, and statistical analyses.

Does the FDA accept overseas trial data?

- In most cases, YES, but…
- Example: ORIENT-11 trial (Sintilimab)
  - FDA rejected an application of Sintilimab
    - ORIENT-11 was a randomized, double-blinded trial conducted exclusively in China.
    - The trial met the primary endpoint of determining progression-free survival through blinded independent central review.
  - Reasons for failure
    - It was not an MRCT
    - The data were not applicable to the US population and medical practice strategies.
    - The patient characteristics in the trial differed from those of US patients with NSCLC.
    - PK data were insufficient to determine applicability to the US population.
    - Overall survival was not formally tested in ORIENT-11.
    - There were concerns related to data quality and the study was conducted at numerous clinical sites.
    - ORIENT-11 investigators did not have sufficient experience to join MRCTs.

(FDA Briefing Document, Oncologic Drugs Advisory Committee Meeting. Feb 10, 2022)

Short summary

- MRCTs are needed to accelerate drug development, and the number of MRCTs is steadily increasing.
- Drug development in Japan has seen a shift from a bridging strategy to participation to a global trial strategy.
- The timing of participation in a global trial is shifting from phase III to the PK/FIH phase.
- ICH-E17 general principles with respect to MRCTs have changed the primary approach from a local-first to a global-first approach.

Academic international trials and operational procedures

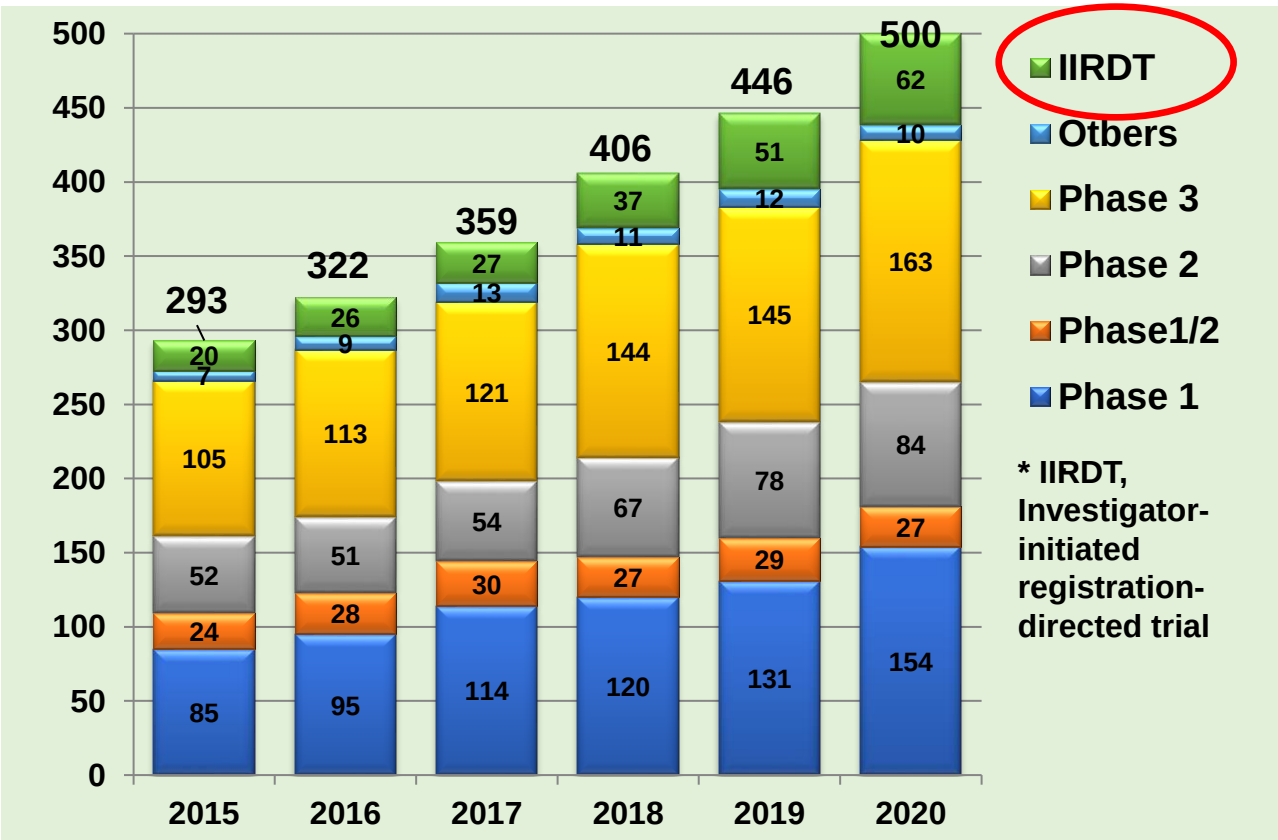
Terminology

Clinical Study
Research involving patients/human volunteers

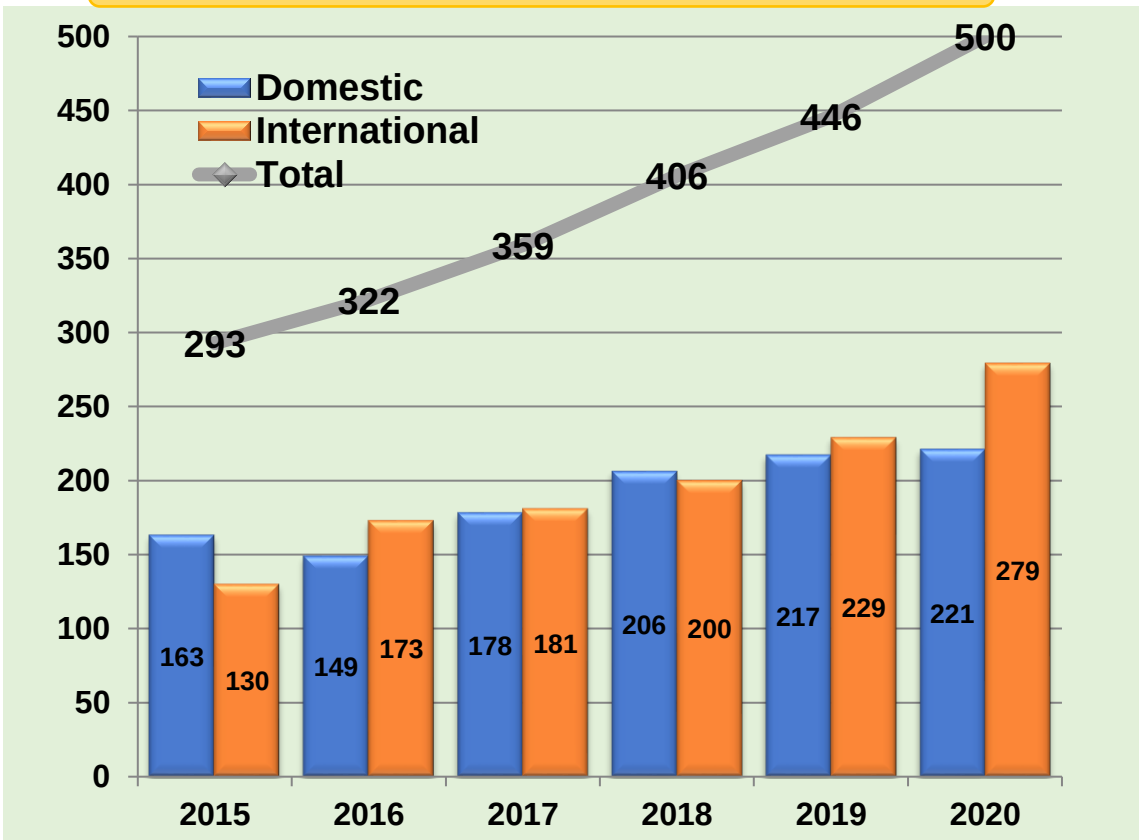
- **Observational studies**
  Investigators assess health outcomes in groups of participants receiving routine medical care
- **Interventional studies (also called “Clinical trials”)**
  Participants receive specific interventions according to the study protocol created by the investigators
  - **Clinical trials for clinical evidence**
    Practically named as “academic clinical trials”
  - **Registration-directed trials (also known as “Chiken” in Japanese)**
    Clinical trials aiming at regulatory application
    - **Industry-sponsored [registration-directed] trials**
      Most industry-sponsored trials are conducted with regulatory applications as a goal
    - **Investigator-initiated registration-directed trials (IIRDT)**
      Study sponsors are not industries but academic institution/investigators

Registration-directed trials at NCCH

N of trials by phase



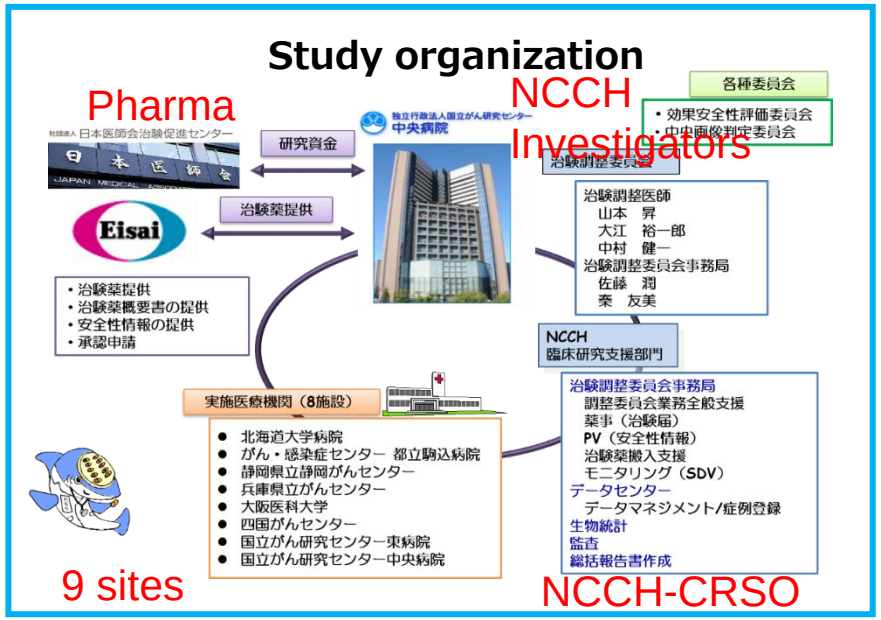
N of international trials

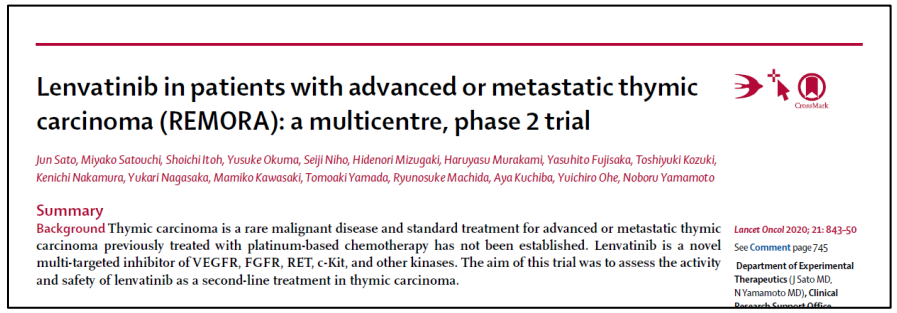


ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Expansion of the indication of lenvatinib for thymic cancer and results of IIRDT

REMORA trial : Phase II trial of lenvatinib in patients with metastatic or recurrent thymic carcinoma





Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial

Jun Sato, Miyako Satouchi, Shoichi Itoh, Yusuke Okuma, Seiji Niho, Hidenori Mizugaki, Haruyasu Murakami, Yasuhito Fujisaka, Toshiyuki Kozuki, Kenichi Nakamura, Yukari Nagasaka, Mamiko Kawasaki, Tomoaki Yamada, Ryunosuke Machida, Aya Kuchiba, Yuichiro Ohe, Noboru Yamamoto

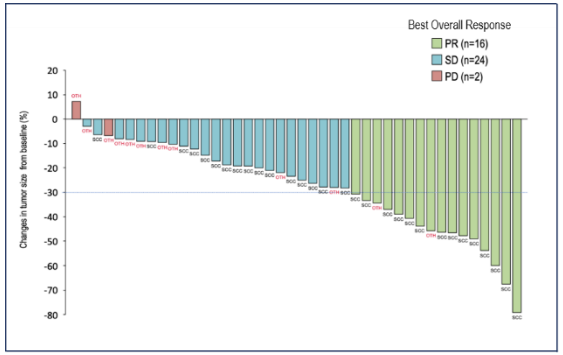
Summary

Background Thymic carcinoma is a rare malignant disease and standard treatment for advanced or metastatic thymic carcinoma previously treated with platinum-based chemotherapy has not been established. Lenvatinib is a novel multi-targeted inhibitor of VEGFR, FGFR, RET, c-Kit, and other kinases. The aim of this trial was to assess the activity and safety of lenvatinib as a second-line treatment in thymic carcinoma.

Lancet Oncol 2020; 21: 843-50
See Comment page 745
Department of Experimental Therapeutics (J Sato MD, N Yamamoto MD), Clinical

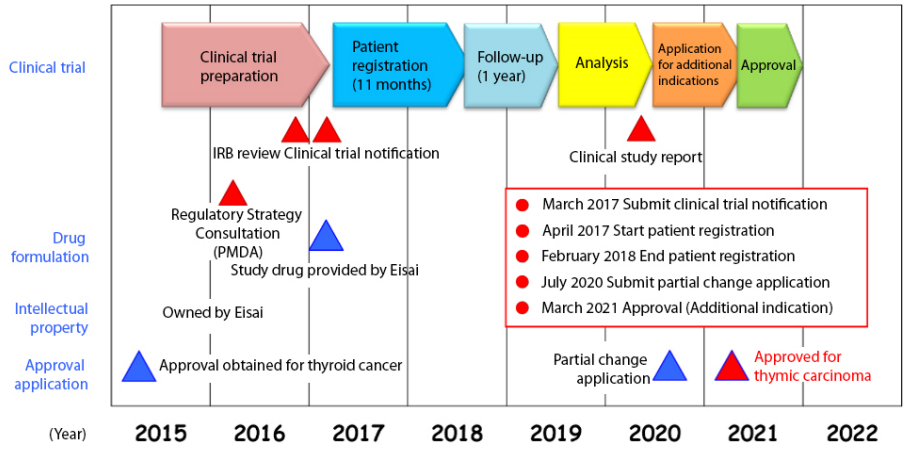
(Sato, et al. Lancet Oncol 2020;21:843-50)

Waterfall plot (Independent radiological review)



	n=42
PR	16 (38.1%)
SD	24 (57.1%)
PD	2 (4.8%)
ORR (%)	38.1%
90% CI	25.6 - 52.0
DCR (%)	95.2%
95%CI	83.8 - 99.4

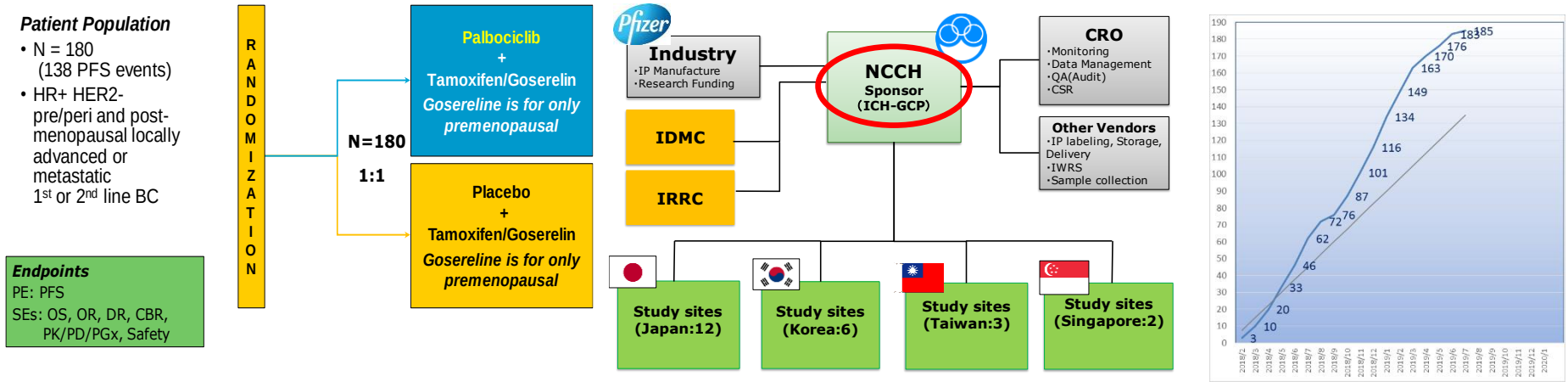
ORR; objective response rate, DCR; disease control rate, CI; confidence interval



The indication of lenvatinib was expanded to thymic cancer based on the data from the REMORA trial (evaluation data for the PMDA)

PATHWAY trial

Asian Collaborative Investigator-initiated Registration-Directed Trial (Chiken) for Advanced Breast Cancer



- ✓ Japanese Academia-initiated, GCP-compliant, placebo, double-blind, randomized phase III trial
- ✓ Participating sites: Japan (12), Korea (6), Taiwan (3), Singapore (2)
- ✓ Aimed at simultaneous regulatory application for expanding drug indication
- ✓ National Cancer Center Hospital was the Sponsor under ICH-GCP
  (NCCH has been certified as an AMED Global Clinical Research Core Center)
- ✓ Pfizer provides study drug and research funding (~$25M USD)

Planned accrual, 24 months

↓↓↓

Competed in 18 months

Actual accrual
Japan 118
Korea 31
Taiwan 25
Singapore 11

Difficulties: Document management

- Document management at multiple levels
  - Study level
    - Single English protocol at study level
  - Country level
    - Translated protocol in each region
    - Translated IC forms with multi-languages
      - i.e., Malaysia requires English, Malay, Chinese, and Tamil versions
  - Site level
    - Each site or each IRB may require additional explanations

Essential IND dossier and its language

	Japan	South Korea	Taiwan	Singapore
Protocol	Yes (in Japanese)	Yes (in Korean)	Yes (in Chinese or English)	Yes (in English)
ICF	Yes (in Japanese)	Yes (in Korean)	Yes (in Chinese)	Yes (in English)
IB	Yes (in Japanese)	Yes (in Korean)	Yes (in Chinese or English)	Yes (in English)
Investigator's CV	No	No	Yes	Yes
CRF	No	No	Yes	Yes
Study subject compensation documents	No	Yes (Subject Compensation Letter and Insurance Certificate)	Yes (Insurance Certificate)	Yes (Insurance Certificate)
CMC documents	No	Yes (in Korean)	Yes	Yes
GMP certificate of the investigational drug	No	Yes	Yes (in Chinese or English)	Yes
DSUR	Yes	Yes	Yes	Yes

(Hata, et al. Clin Transl Sci. 2021;13:1015-25)

Investigational product management

	Japan	South Korea	Taiwan	Singapore
Procedure for IP import/export	Drug import license or Yakkan certificate is **not required**. Only CTN is needed for customs clearance.	Drug import license is **not required.** Standard customs clearance schedules report form must be issued by the official.	IP import license is **required**. The license specifies the valid period and upper quantity limit.	IP import license is **not required.** Clinical Research Material Notification must be submitted to the Health Science Authority.
Items to be listed on the IP label	・For clinical trial use (protocol number) ・Title and address of the sponsor-investigator ・Chemical name/laboratory code ・Lot or batch number identifying content and packaging operation of the product ・Storage conditions ・Expiration date (if necessary) ・Quantity per IP bottle (if necessary)	・For clinical trial use (protocol number) ・Study sponsor (local IND holder) ・Chemical name/laboratory code ・Quantity per IP bottle ・Storage conditions ・Dosage and administration ・Lot or batch number identifying content and packaging operation of the product ・Expiry date	・For clinical trial use (protocol number) ・Study sponsor ・Chemical name/ laboratory code ・Quantity per IP bottle ・Storage conditions ・Dosage and administration ・Lot or batch number identifying content and packaging operation of the product ・Expiry date	・For clinical trial use (protocol number) ・Study sponsor ・IP manufacturer ・Chemical or name of substance, strength or potency, quantity of units ・Name/laboratory code ・Quantity per IP bottle ・Storage conditions ・Pharmaceutical form, dosage and route of administration ・Lot or batch number identifying content and packaging operation of the product ・manufacturing date ・Expiry date

(Hata, et al. Clin Transl Sci. 2021;13:1015-25)

Safety reporting requirements

	Japan	South Korea	Taiwan	Singapore
Safety Reporting Regulations	・Clinical Safety Data Management: Definitions and Standards for Expedited Reporting ・Reporting of Adverse Drug Reactions Occurring in Clinical Trials to PMDA	・Korean-GCP ・Korea MFDS guidelines on SUSAR reporting	・Taiwan-GCP ・Taiwan National Adverse Drug Reactions Reporting system Q&A	・ICH-GCP ・Expedited Safety Reporting Requirements for Therapeutic Products and Medicinal Products used in Clinical Trials
Safety Reporting to regulatory authority (in case drug is approved)	・Death or life-threatening cases (only SUSARs); within 7 calendar days from the investigator's awareness ・Non-death or non–life threatening cases (only SUSARs), death, or life-threatening cases (non-SUSARs); within 15 calendar days from the investigator's awareness ・Research Reports ・Reports of Safety Measures ・Annual safety update (DSUR)	・Death Fatal or life-threatening cases (only SUSARs); within 7 calendar days from the investigator's awareness ・Non-death or non–life threatening cases (only SUSARs); within 15 calendar days from the investigator's awareness ・Annual safety update (DSUR)	・Death or life-threatening cases (only SUSARs); within 7 calendar days from the investigator's awareness ・Non-death or non–life threatening cases (only SUSARs); within 15 calendar days from the investigator's awareness ・Annual safety update (DSUR)	・Death or life-threatening cases (only SUSARs); within 7 calendar days from the investigator's awareness ・Non-death or non–life threatening cases (only SUSARs); within 15 calendar days from the investigator's awareness ・Annual safety update (DSUR)

(Hata, et al. Clin Transl Sci. 2021;13:1015-25)

Study site procedures

	Japan	South Korea	Taiwan	Singapore
Certification of study site by the government	No	**Yes**: Certified by MFDS according to Ordinances for Institution Designation	**Yes**: Available only at government-certified medical sites	No
IRB	Central IRB is applicable (not mandatory)	Central IRB is applicable (not mandatory)	Central IRB is applicable	Central IRB is applicable
Renewal of IRB approval	Required (annually)	Required (annually)	Required (annually)	Required (annually)
ICF language	Japanese	Korean **If gene-/embryonic cell–related testing is included, additional ICF is required**	Chinese	English, Chinese, Tamil, and Malay
Language of clinical trial agreement	Japanese in principle	English available	Chinese in principle	English
Accessibility to source data documents during monitoring/ audit	No restriction	No restriction	No restriction	Certified copy check. Occasional spot-checks of electronic health records by CRAs allowed with site supervision and over-the-shoulder access.

(Hata, et al. Clin Transl Sci. 2021;13:1015-25)

Difficulties: Site costs

[Subject reimbursement (actual expense)]

Difference in reimbursement rule:

- ✓ In Korea, Taiwan, and Singapore, examination fees (e.g., laboratory tests, CT, & MRI) and concomitant drug fees should be covered by the sponsor in a registration trial.
- ✓ In Japanese IIRDTs, these costs are covered by national health insurance.
- ✓ Rules for IIRDTs are not well-established in countries other than Japan.

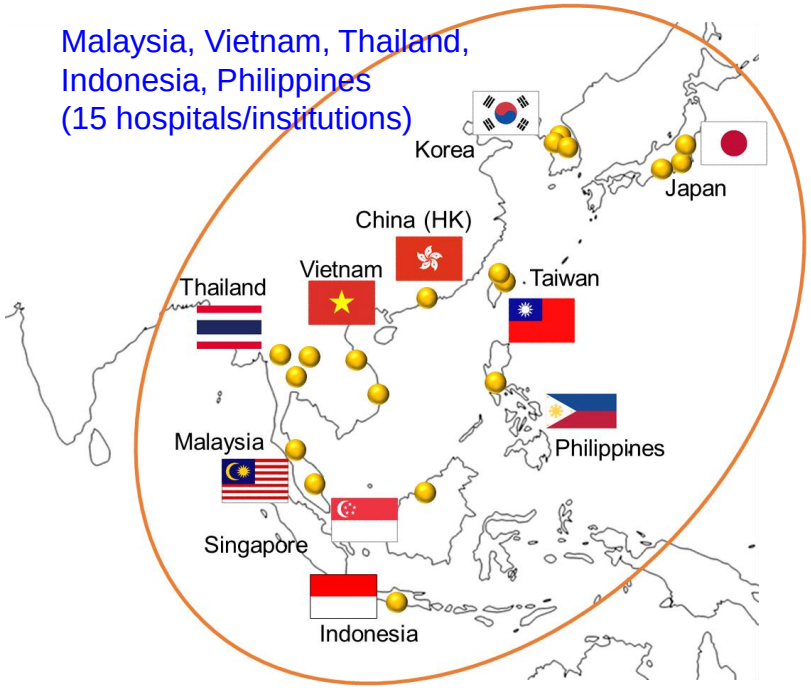
	Estimated reimbursement per subject (Study treatment duration: 13 months)
Japan	0 USD Special or specified medical care coverage (Partial expenses such as infectious disease test, pregnancy test, image copying fee, etc. are borne by each hospital)
South Korea	20,000 USD
Taiwan	10,000 USD
Singapore	15,000 USD

ATLAS: Asian clinical TriaLs network for cAncerS

Existing networks with highly advanced Asian countries（Korea, Taiwan, Singapore, China (HK)

Establish and expand the Asian Cancer Trials Network and facilitate early drug development and genomic medicine together with ASEAN countries

Malaysia, Vietnam, Thailand, Indonesia, Philippines
(15 hospitals/institutions)



Strength in Asian networks:

- Population growth, economic development, aging society - increase in the number of patients with cancer, more patients require high-level treatment
- Little ethnic differences - genetics, physiques ...
- Reasonable cost in conducting clinical trials
- Area-specific cancers
  - liver, heat & neck, stomach etc.

ATLAS project

- Building infrastructure & clinical trial networks
- Capacity for building programs
  - clinical trial procedure & genomic cancer medicine
- International clinical trials under ATLAS
  - MASTER KEY Asia, A-TRAIN study, TEAL trial

Goals of ATLAS:

- Establish infrastructure for conducting clinical trials in Asia
- Introduce genome-based medicine in Asian
- Obtain/expand drug indication simultaneously in Asia, thereby promoting regulatory harmonization with the PMDA

Summary

- IIRDTs are important for meeting a patient's unmet needs, especially in the context of disease types not covered by the industry.

- Multi-regional IIRDTs under the ATLAS project will facilitate simultaneous drug development across Asia.

- Academic institutions serving as study sponsors should reinforce the research support capability for MRCTs.