国立研究開発法人
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National Cancer Center Japan

Treatment development for rare cancers: MASTER KEY Project

Invited Session 25:
Overcoming challenges in rare cancers: Leveraging registry data and innovative trial designs

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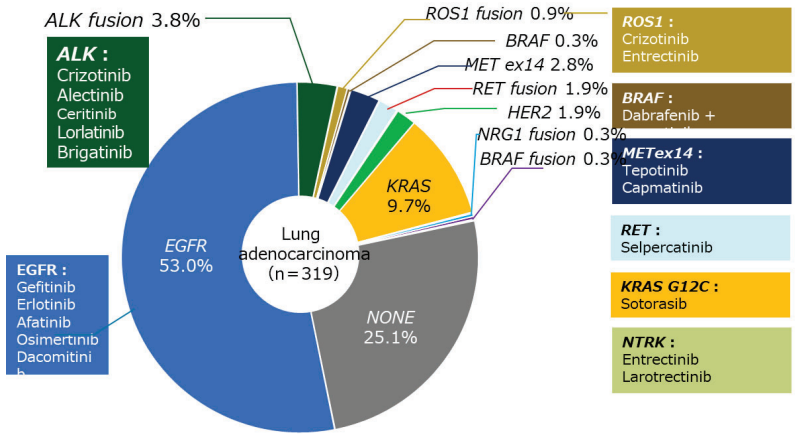
National Cancer Center Hospital, Tokyo Japan

Rare cancers and rare fractions, an underrepresented population

- Delayed treatment development
  - Difficulty in conducting a randomized trial
  - Industries are rarely interested in such a small market
  - Molecular background is not well investigated
  - Difficulty for precise diagnosis and treatment
- Rare cancers are not so rare
  - The annual incidence of all rare cancers occupy **15%** of all cancer diagnoses in Japan
- Common but rare?
  - Cancer types have been subdivided into smaller categorizations by biomarker.

✓ Each biomarker positive population is small even in lung cancer, common cancer



Stransky N, et al. Nat Commun. 2014; 5: 4846.
https://www.pmda.go.jp/PmdaSearch/iyakuSearch/
Eur J Cancer, Volume 47, Issue 17, November 2011, Pages 2493-2511

Obstacles of rare cancers from different point of view

- Academic point of view
  - Desire to increase treatment options for patients
  - Limited budget
- Pharmaceutical company point of view
  - Low cost-effectiveness with small market
  - Lack of reliable historical controls for small populations
- Regulatory authority point of view
  - Lack of evidence to confirm results for approval; limited sample size in the trial, lack of comparative control data for small populations

How could we overcome these obstacles?

MASTER KEY PROJECT since 2017

Marker Assisted Selective ThErapy in Rare cancers: Knowledge database Establishing registrY

- Aim
  - Build a comprehensive database for rare cancers
  - Establish reliable historical control data that can be used in pharmaceutical applications
  - Assign to clinical trials

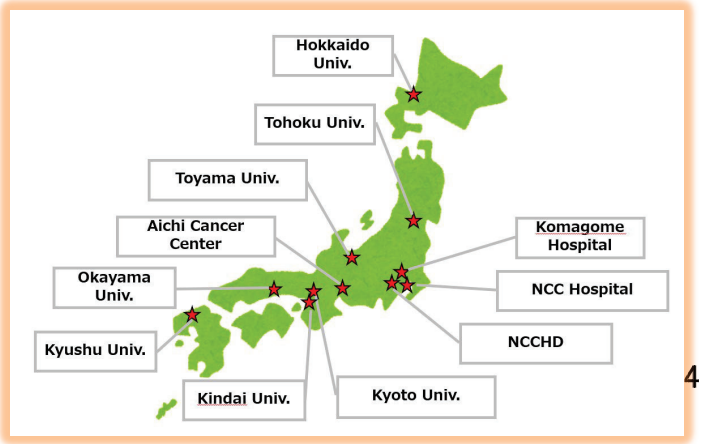
12 pharmaceutical companies

astellas
Eisai エーザイ株式会社
小野薬品工業株式会社
第一三共株式会社
大鵬薬品
Takeda
中外製薬
ロシュ グループ
Bristol Myers Squibb
Boehringer Ingelheim
SymBio シンバイオ製薬株式会社
SERVIER 日本セルヴィエ株式会社

Rare Cancer Japan
Patient advocacy group

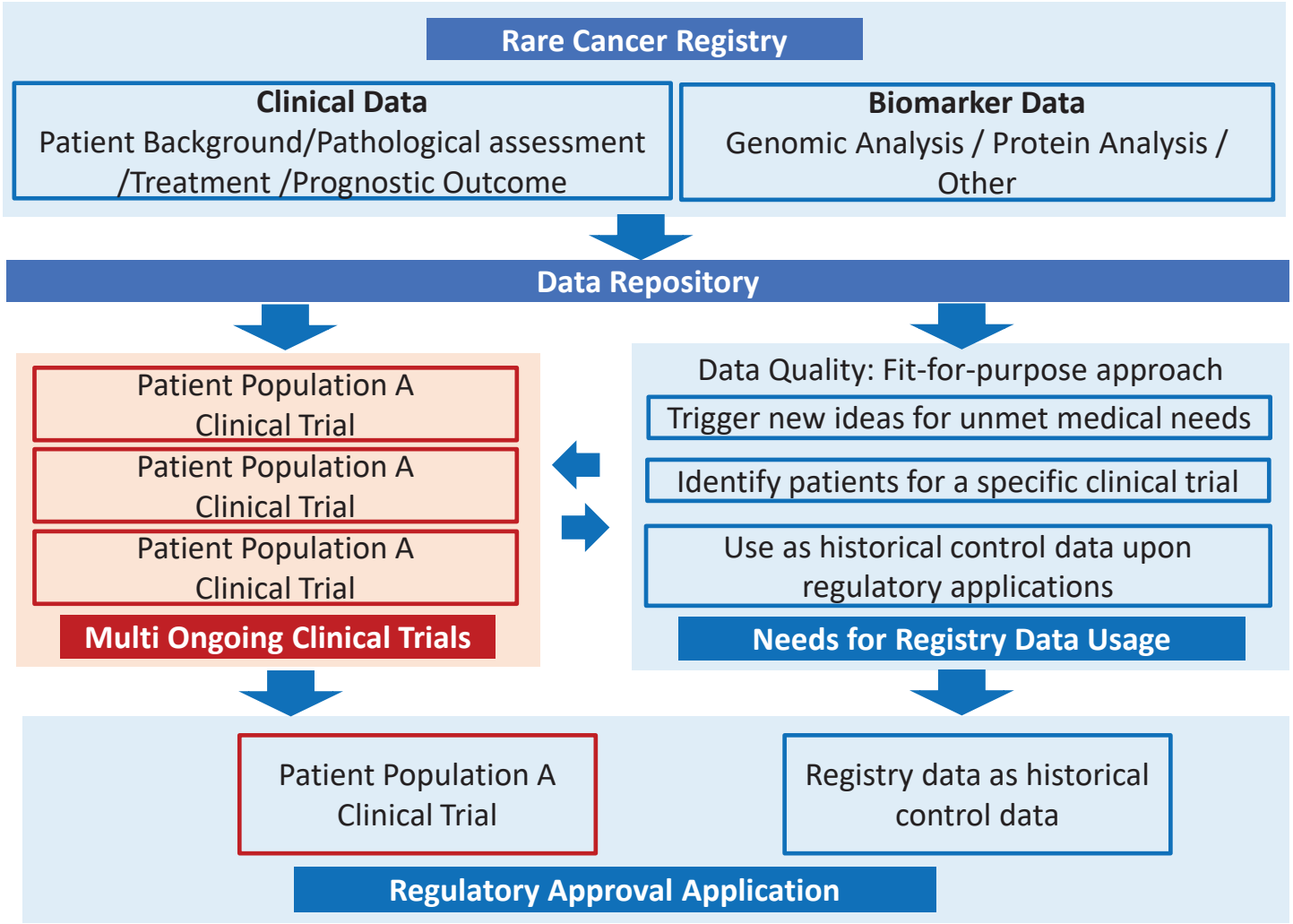
Matching the pieces!

Academic institutions



An Academia-Pharma-Patient collaborating platform

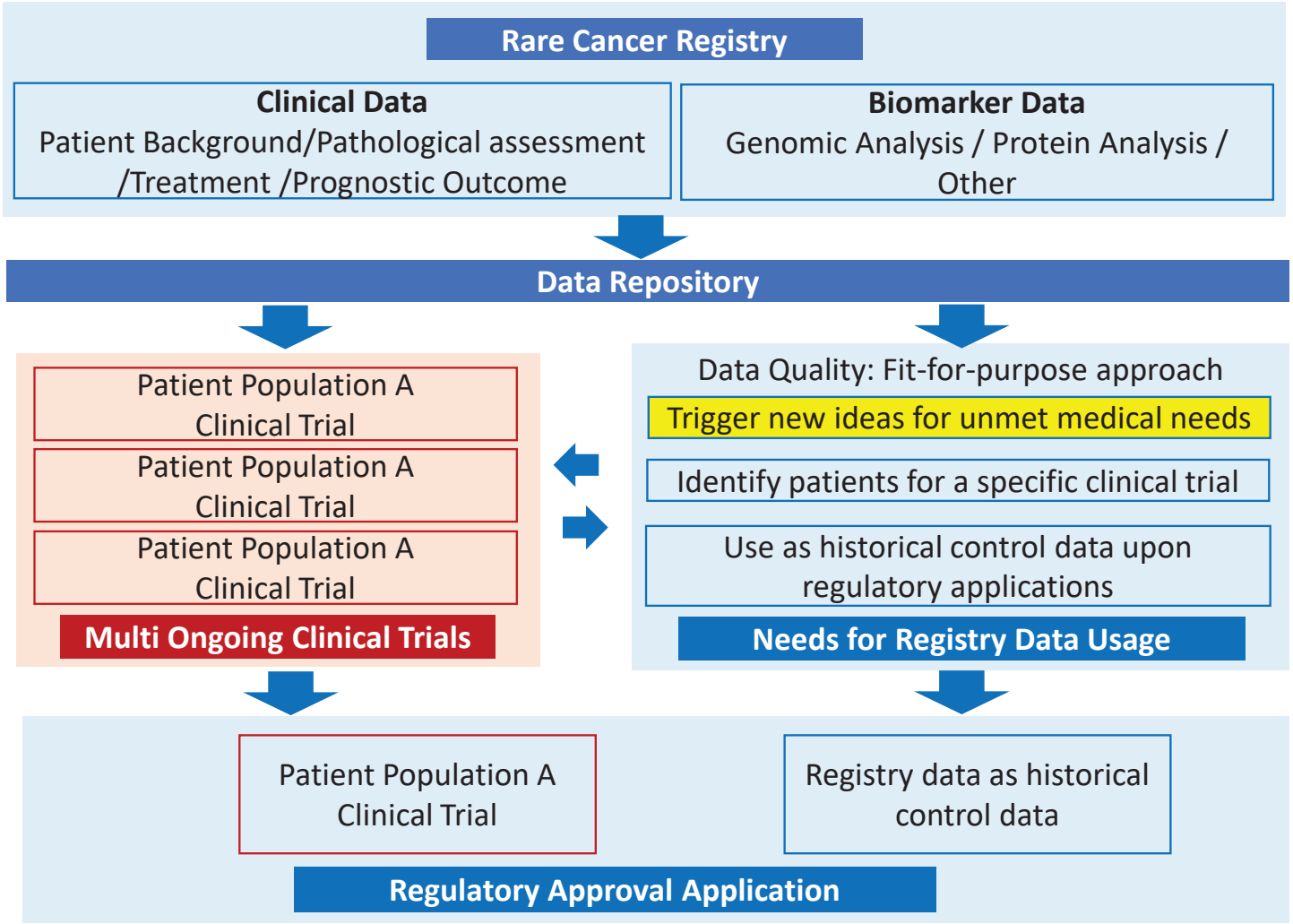
MASTER KEY study scheme



Registry part
Collect the information that is intended to use for future studies

Clinical trial part
Conduct multiple trials for rare cancer.

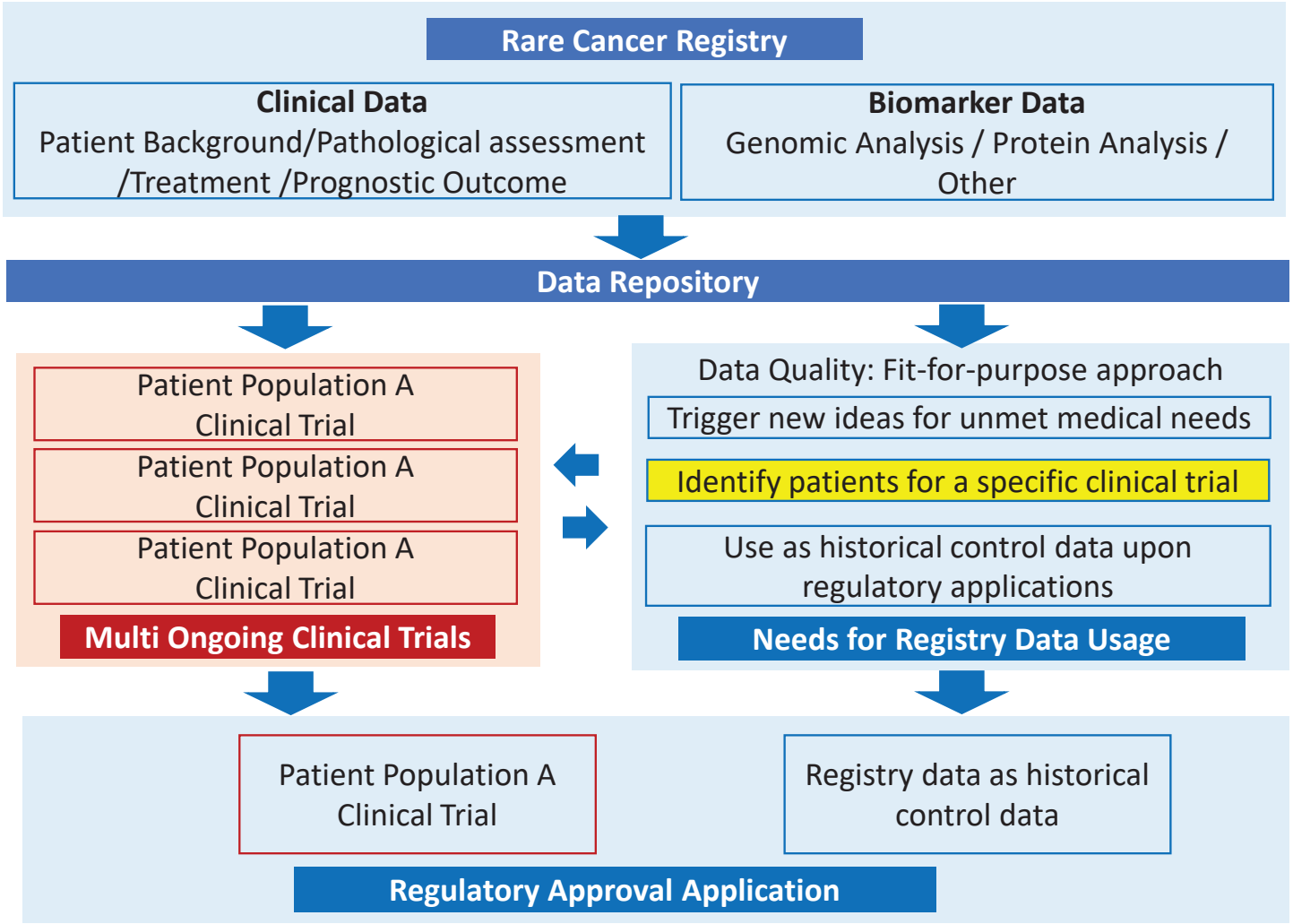
MASTER KEY study scheme



Collaboration with the National Cancer Center Research Institute

Active collaboration and joint regular meeting with researcher from NCCRI, NCCH (Oncologist and Pathologist)

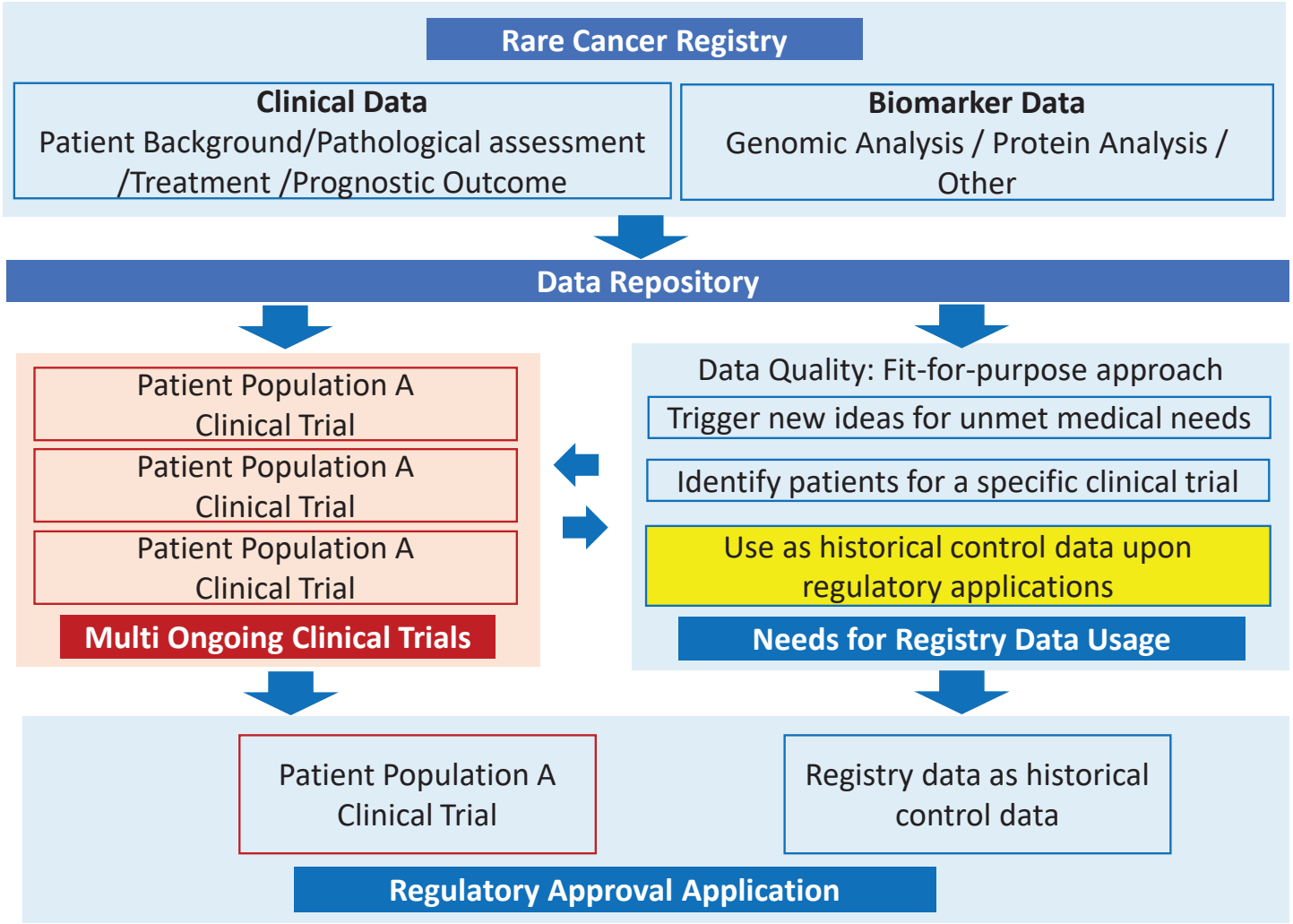
MASTER KEY study scheme



Collaboration with the physicians

Find the right patient and achieve quick enrollment

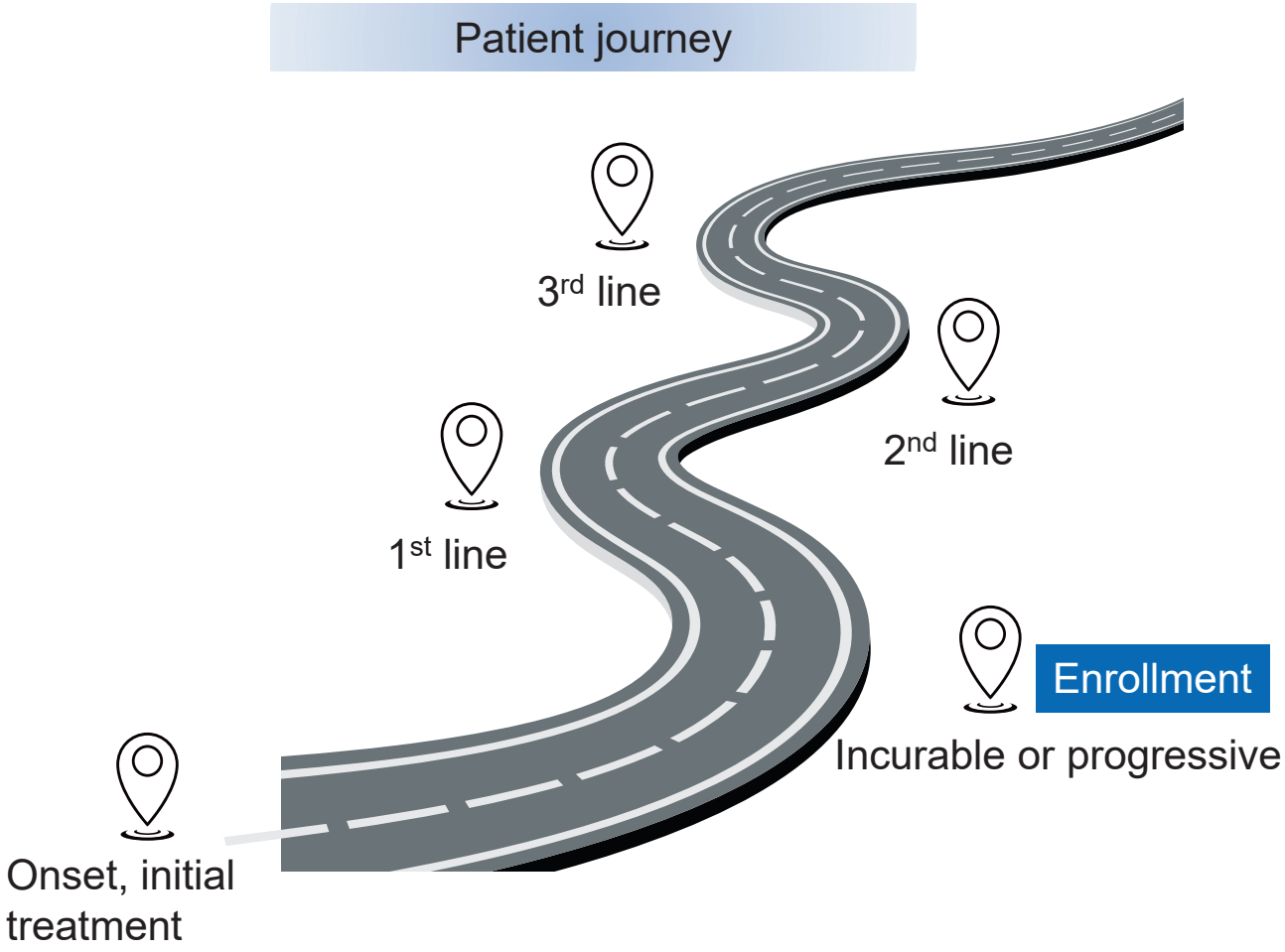
MASTER KEY study scheme



Collaboration with pharmaceutical companies

Providing quality assured data, with the fit-for purpose approach.

Data that MASTER KEY posess



- **Before Registration**
- Age, sex, prior treatment history, histopathological diagnosis and biomarker test results
- **Study Period/ Follow-up**
- Treatment details, Efficacy assessment, NGS results (Asia)
- Patient survival status (If deceased, confirm date and cause of death)
- Every six months from registration until the end of the registry study

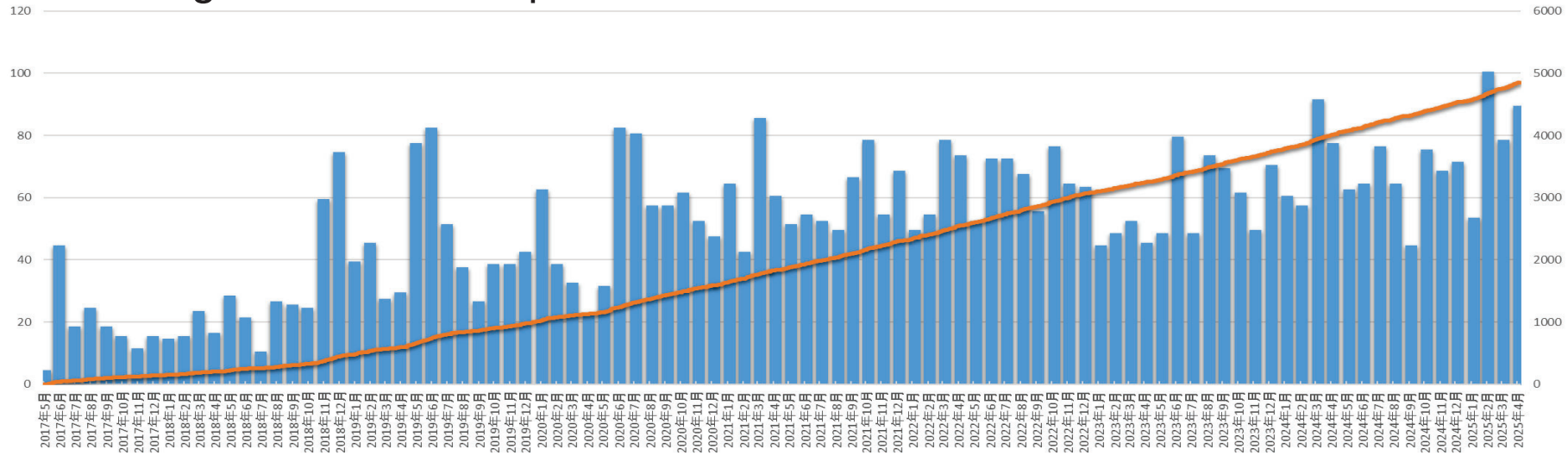
We support patients throughout their journey in terms of treatment opportunities while also collecting follow-up data.

Key eligibility criteria
1. Patients aged 0 year or older (18 for Asia)
2. Histologicaly diagnosed as rare cancer or rare tissue subtype
3. Patients with incurable or progressive lesions

MASTER KEY Registry and Clinical Trials

Number of patients in registry study（As of April 2025）

- Solid rare tumors 4290 patients
- Hematological cancer 564 patients



Number of clinical trials

- 35 clinical trials
  - ➢ 17 Investigator-initiated registration-directed trials
  - ➢ 18 industry-sponsored trials

Almost reaching 5000 rare cancer patients!

ATLAS: Asian clinical TriaLs network for cAncerS since 2020

Existing networks with Korea, Chinese-Taipei, Singapore, China (HK)

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

MASTER KEY project

MASTER KEY ASIA

Strength in Asian networks:

- Population growth, economic development, aging society - increase of cancer patients
- Little ethnic differences - genetics, physiques ...
- Reasonable cost in conducting clinical trials
- Area-specific cancers
  - head & neck, stomach etc.

ATLAS project

- Building clinical trials networks
- Educational programs
  - clinical trial procedure & genomic cancer medicine
- International clinical trials under ATLAS
  - MASTER KEY Asia, A-TRAIN study, Project CAD etc.

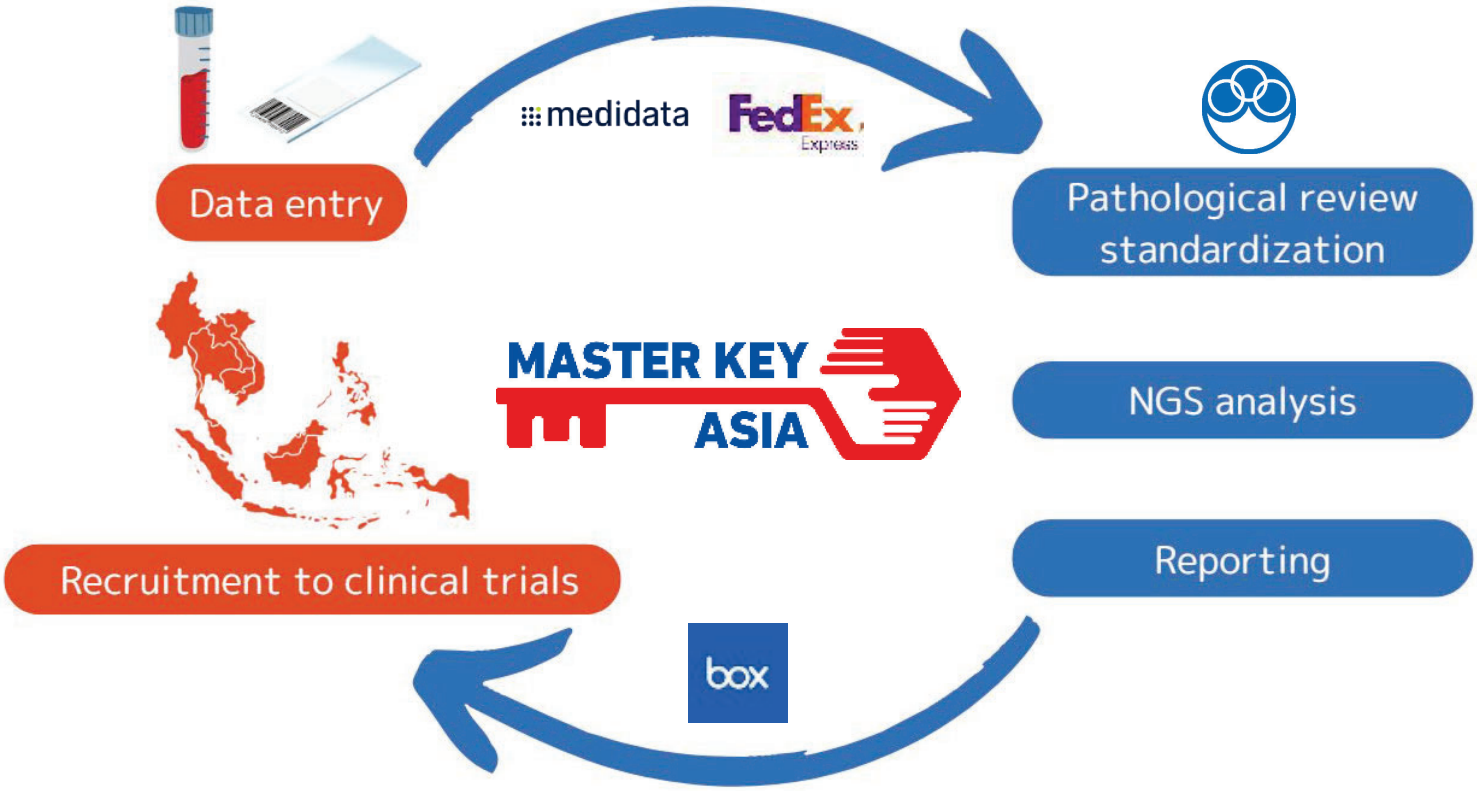
Goals of ATLAS:

- Establish the infrastructure for clinical trials in Asia
- Introduce genome-based medicine in Asia
- Obtain/expand drug indication simultaneously in Asia promoting regulatory harmonization

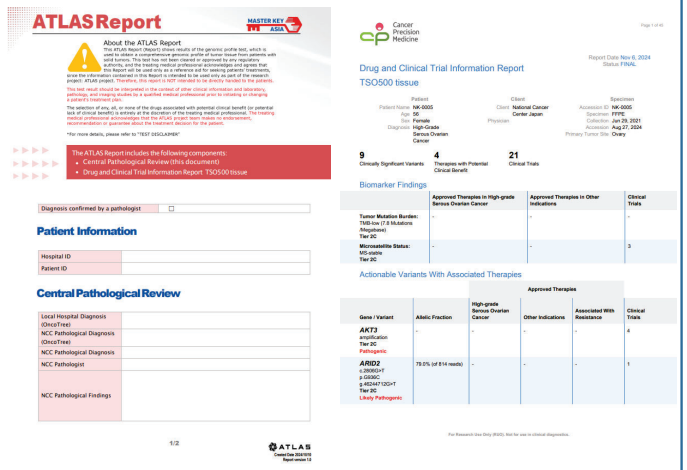
Expanded MASTER KEY to Asia, to accelerate and achieve the sustainable drug development platform.

MASTER KEY Asia scheme

- In addition to registry, we provide NGS testing for the countries where NGS testing is not reimbursed



ATLAS Report

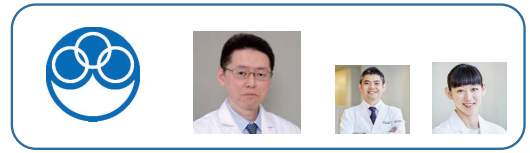


Tumor panel,
Genmine TOP, TSO-500

- Receiving and reporting blood and tumor specimens from 18 sites across 5 countries.
- Logistics, contracts are in already in place.

MASTER KEY Asia participating sites 29 sites（As of March 2025）

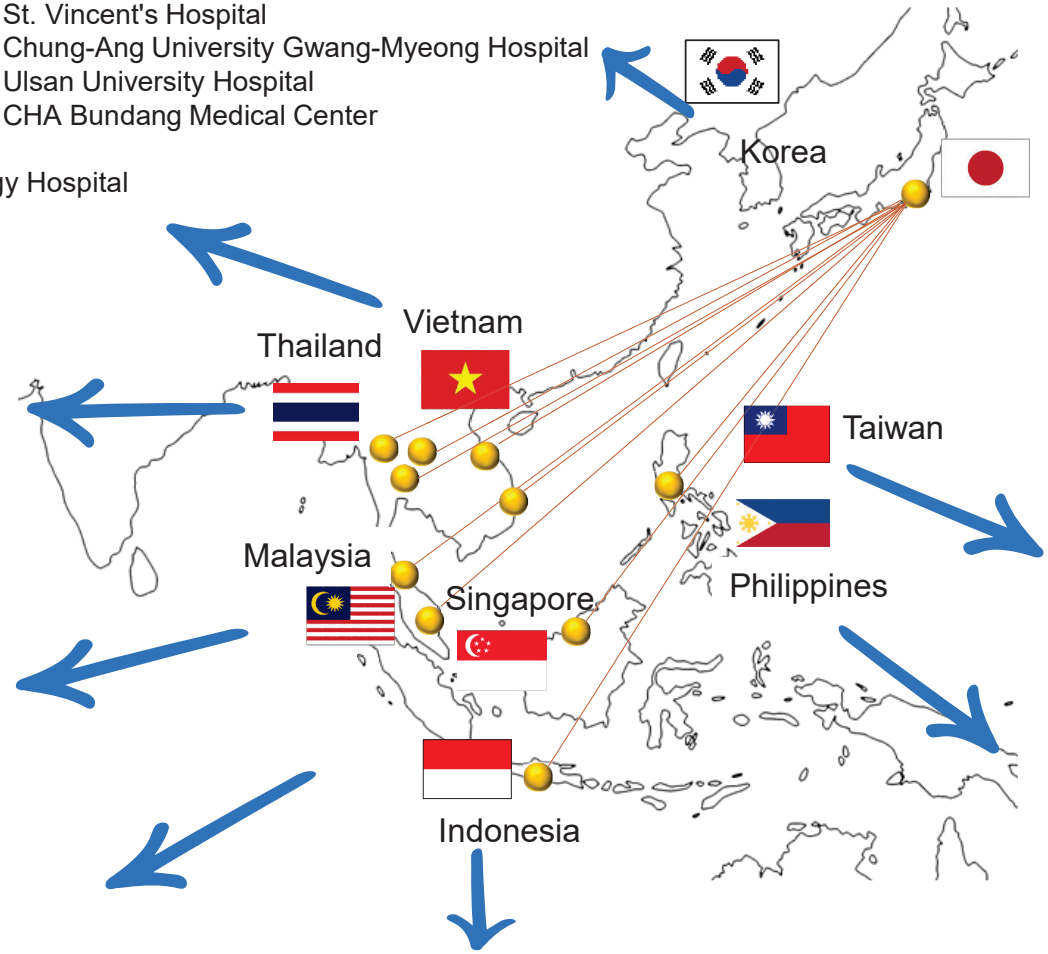
- NCC Korea
- Sanggye Paik Hospital
- St. Vincent's Hospital
- Chung-Ang University Gwang-Myeong Hospital
- Ulsan University Hospital
- CHA Bundang Medical Center



Management team

- Ho Chi Minh City Oncology Hospital
- National Cancer Institute

- Ramathibodi Hospital
- Siriraj Hospital
- Srinagarind Hospital
- Maharaj Nakorn Chiang Mai Hospital
- Prince of Songkla Hospital
- Chulalongkorn University



- National Taiwan University Hospital
- Taipei Veterans General Hospital
- Kaohsiung Medical University Chung-Ho Memorial Hospital

- Sarawak General Hospital
- Hospital Sultan Ismail
- Hospital Kuala Lumpur
- Institut Kanser Negara
- Hospital Pulau Pinang
- University Malaya Medical Center
- Hospital Raja Permaisuri Bainun

- St Lukes Medical Center

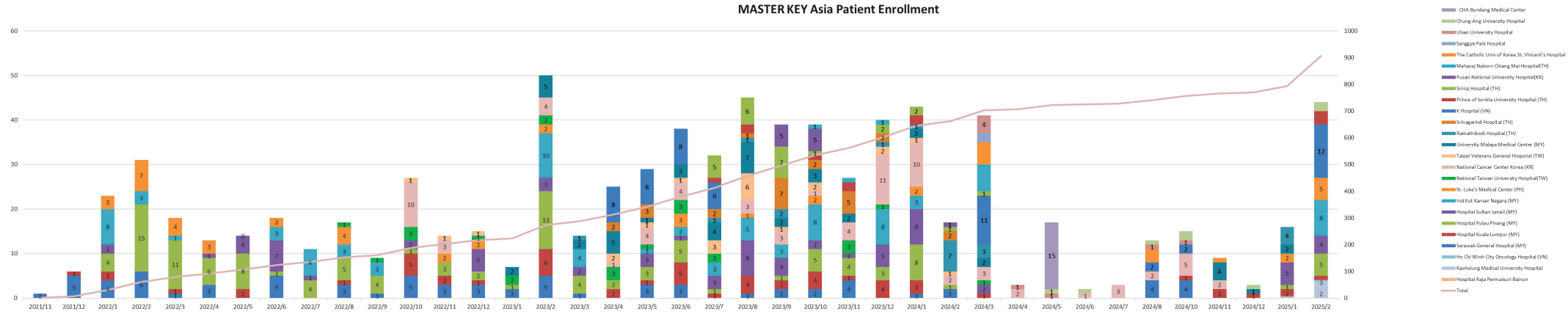
- National Cancer Center Singapore

- Siloam Hospital
- Persahabatan Hospital

MASTER KEY Asia

- 935 patients were enrolled（as of end of March , 2025）
- We hold data on nearly 6,000 patients with rare cancers in Asia, including those from within Japan.

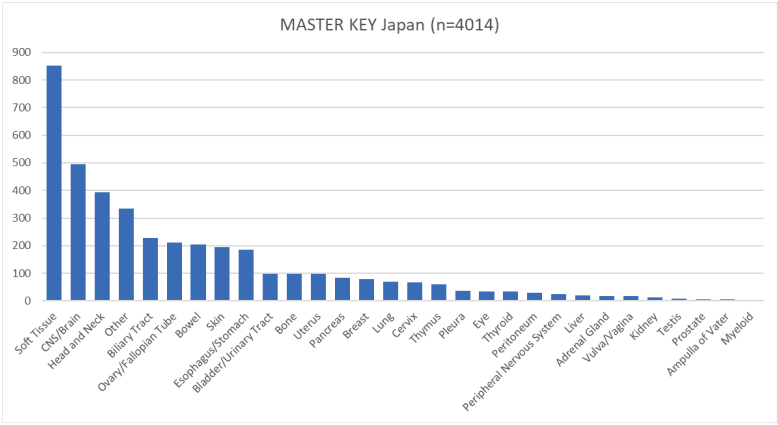
Patient registration by month

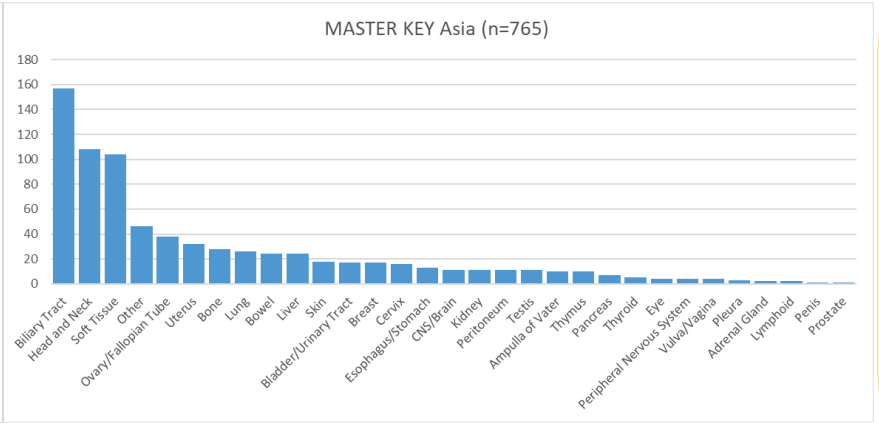


Pink line : Total enrollment

Connect the dots!
Expanding the clinical trial network

MASTER KEY Asia Cancer types

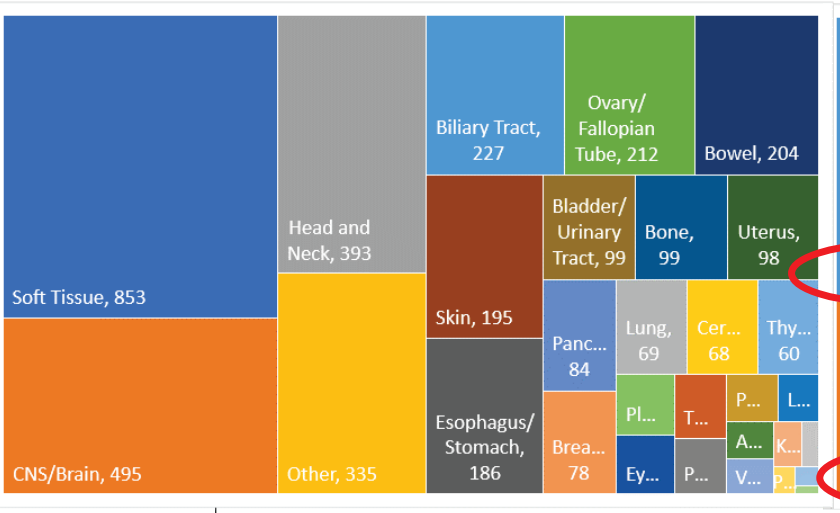




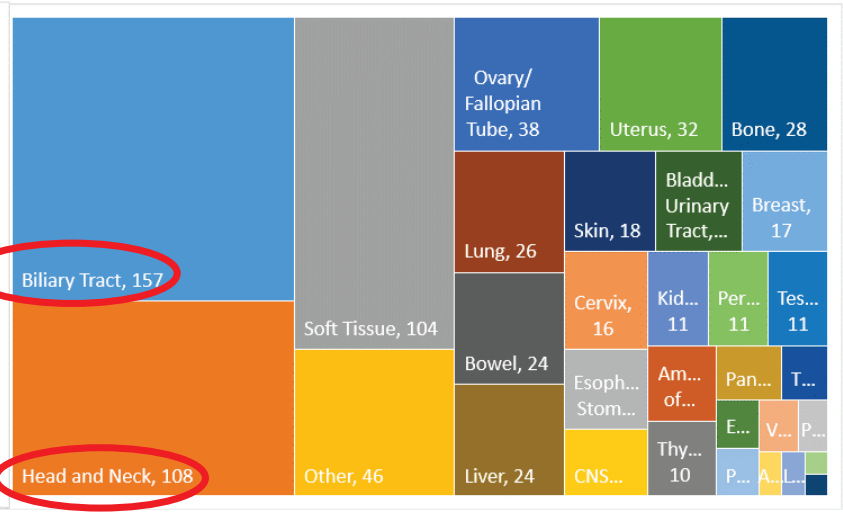
Cancer types common in Asia
（compared to Western countries）

Cervical cancer
Head and neck cancer
Biliary tract cancer

As of Jan 2025



As of Nov 2024



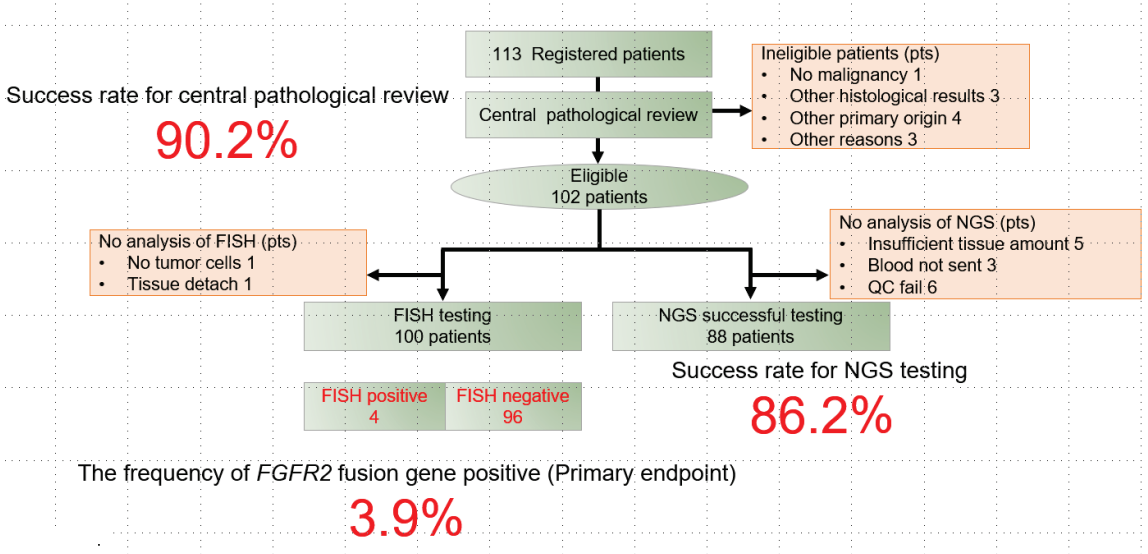
Cancer types common in Asia
（compared to Japan）

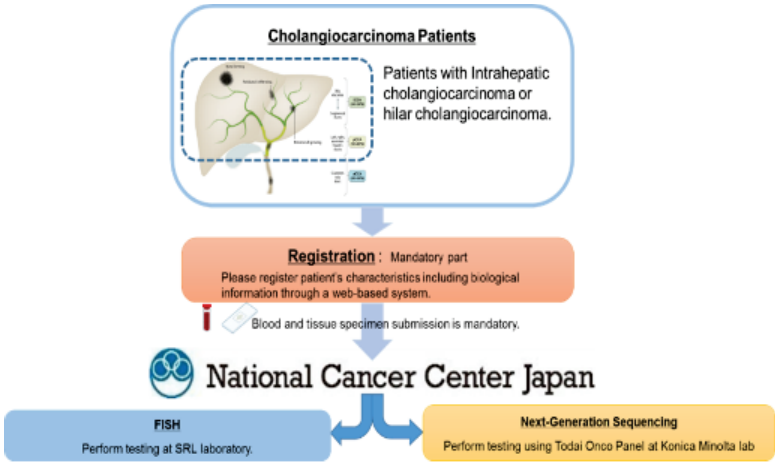
Head and neck（NPC）
Biliary tract cancer
Ovarian cancer

Which cancer types are best for treatment development in Asia?

MASTER KEY Asia Cholangiocarcinoma cohort

- We provided FISH analysis in addition to NGS analysis using the MASTER KEY Asia platform, .
- The study aimed to elucidate the prevalence and characteristics of FGFR2 fusion-positive biliary tract cancer.
- Total of 113 cases were enrolled between 2023 and the end of March 2024.





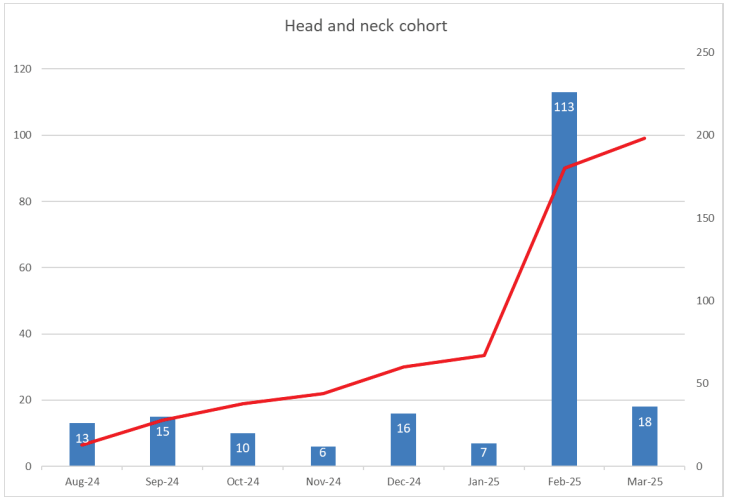
Eisai エーザイ株式会社

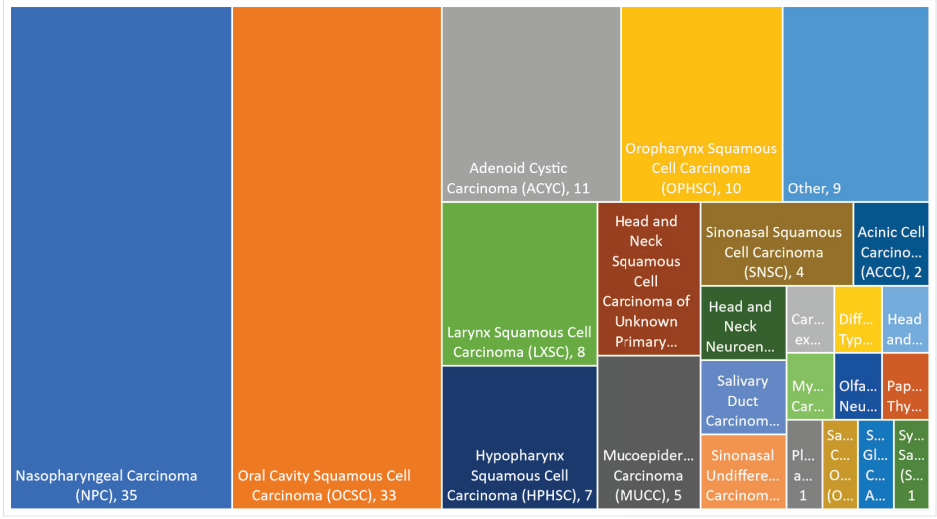
- Funded and supported by Eisai

- Using the collected data, negotiations are underway to achieve the goal of initiating a clinical trial.

MASTER KEY Asia: Head and Neck cohort

- Utilizing the MKA platform, we provide NGS analysis and viral analysis results.
- Aim: to clarify the prevalence and characteristics of head and neck cancers.
- A collaborative cohort with researchers from both overseas and NCCH within the ATLAS project.
- Over 200 patients were enrolled in 6 months, under analysis.





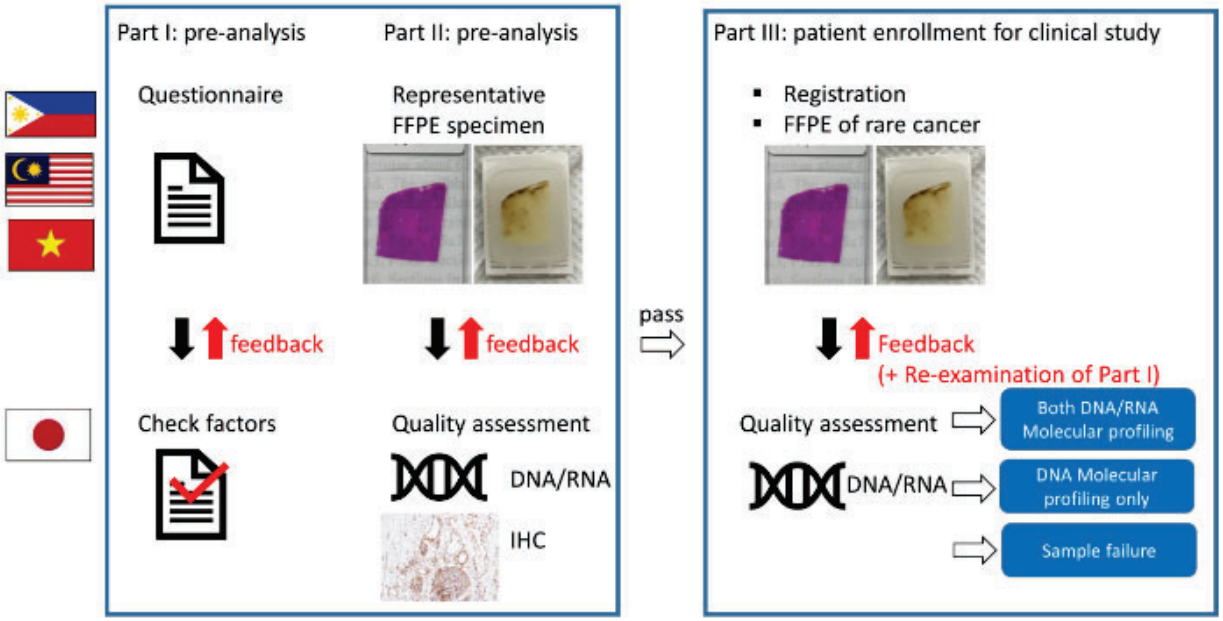
Head and Neck Cancer group Chair
Dr Darren Lim Wan Teck
(NCC Singapore)

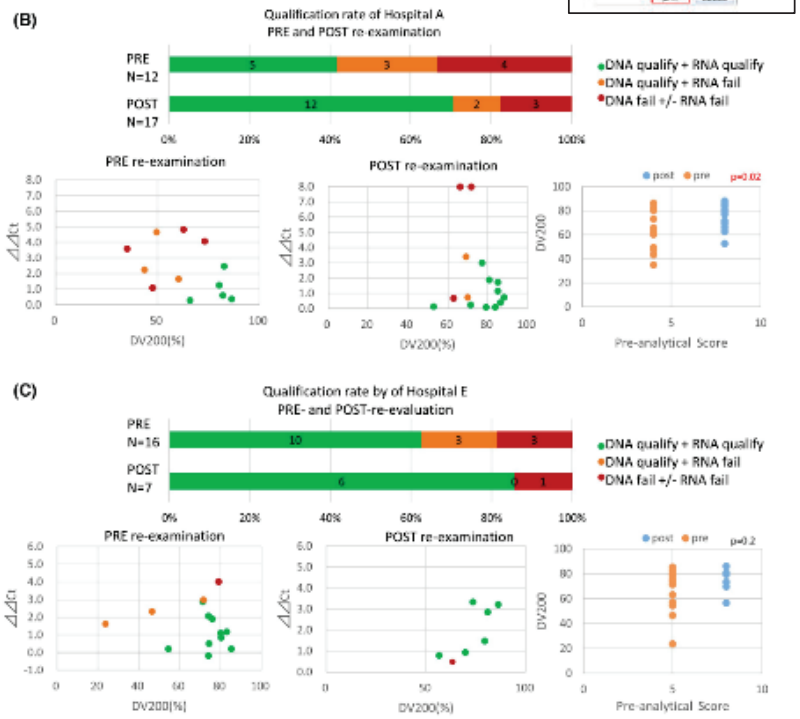
NCCH Pathologist
Dr Taisuke Mori

We hold the broad data and samples, so what about the quality?

Quality assurance of FFPE samples

- The key to successful genomic analysis lies in the quality of FFPE samples.
- We evaluated the quality of IHC, DNA, and RNA analyses and provided feedback.
- The quality of the samples has improved in some institution with this feedback, leading to introduce and improve genomic based medicine in Asia.

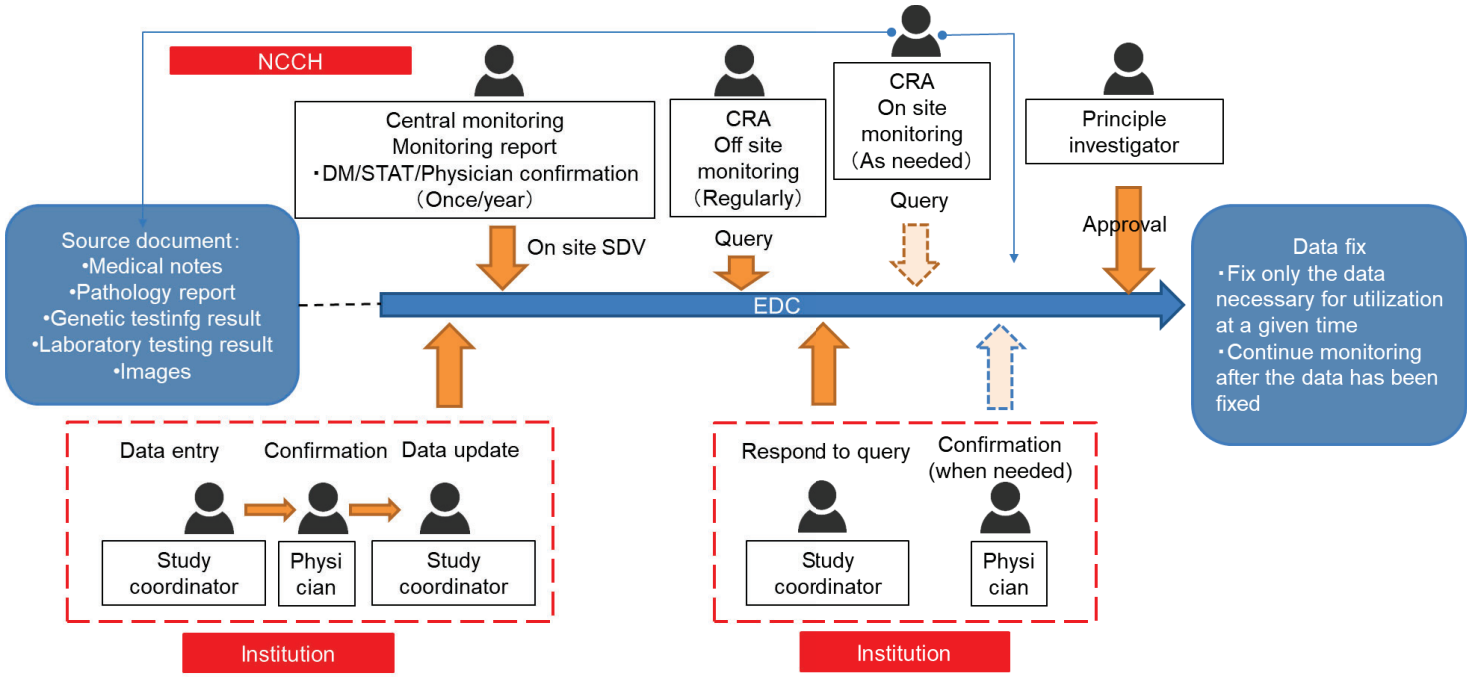




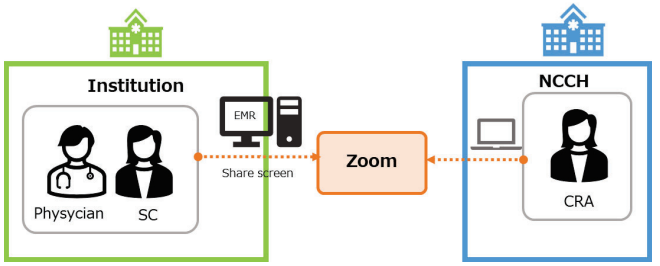
Cancer Sci . 2023 Jun;114(6):2664-2673. doi: 10.1111/cas.15790. Epub 2023 Mar 28.

Quality assurance of data

- As regular monitoring, we perform sampling SDV by CRA and central monitoring by data manager
- Once utilization has been decided, monitoring will be conducted according to individual quality purpose (Fit-for-purpose approach).
- As one of the central monitoring we perform remote access monitoring (R-SDV) for Asian sites.



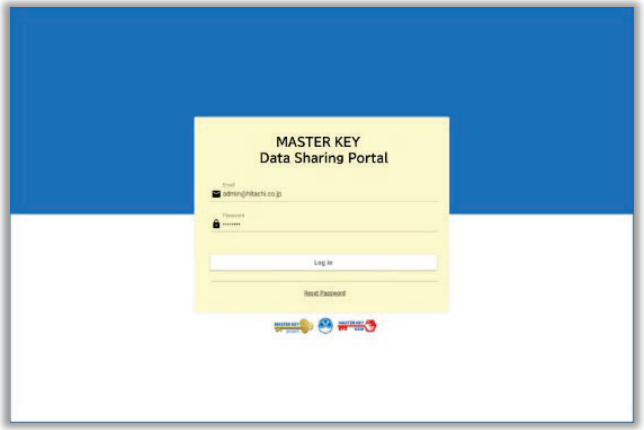
Data flow

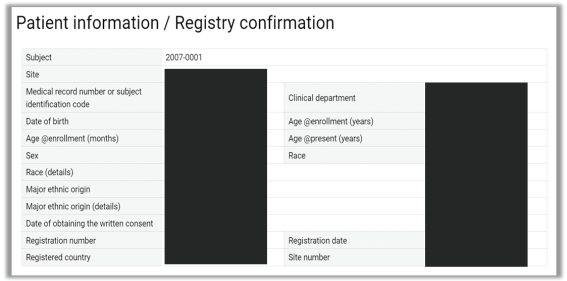


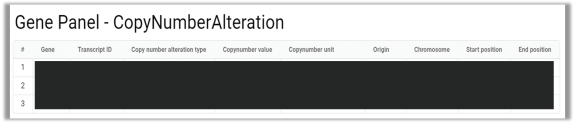
Remote access monitoring (Malaysia)

Sharing the data: MASTER KEY Data Sharing Portal

- MASTER KEY Data Sharing Portal
  - An integrated search system for Registry Data, consisting of clinical & genomic information
  - Allows searching and viewing individual patient data
  - Digitalized pathological imaging is being integrated into the database



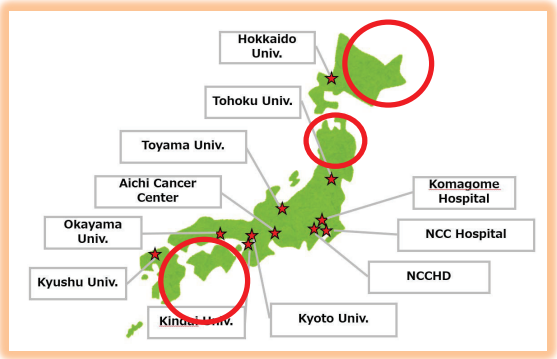




✓ Participating industries and institutions have access to all the data

Biomarker discovery, Predictive modeling, Personalized treatment, Research Opportunities….

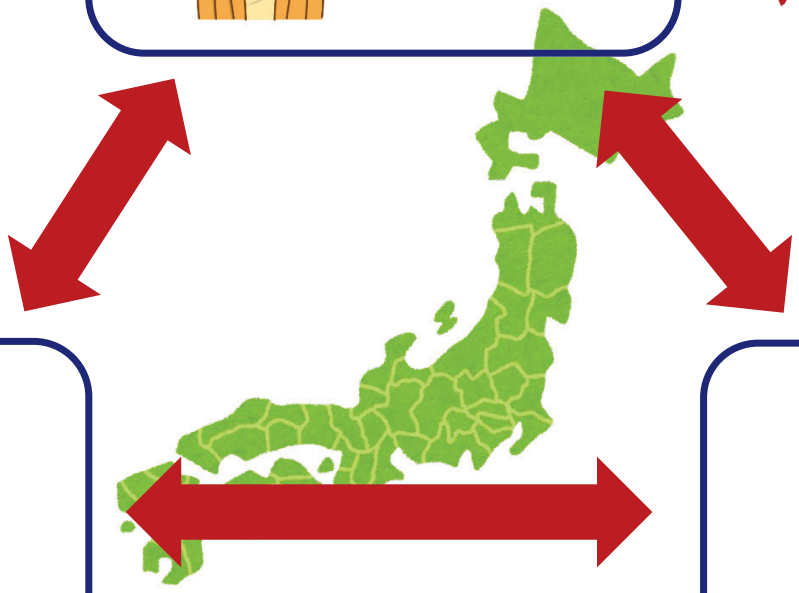
Exploration of diverse trial designs : Decentralized clinical trial



Patient living in distant area

Online visit by telemedicine

- ✓ Eligibility check
- ✓ Informed consent
- ✓ Drug shipment to patient's home
- ✓ Go/No-go decision on treatment continuation



Partner site

No IRB review
No EDC entry
Remote monitoring

See the patient collaboratively with NCC

Delegation Contract

- ✓ Research funding will be paid
- ✓ Examination results are shared

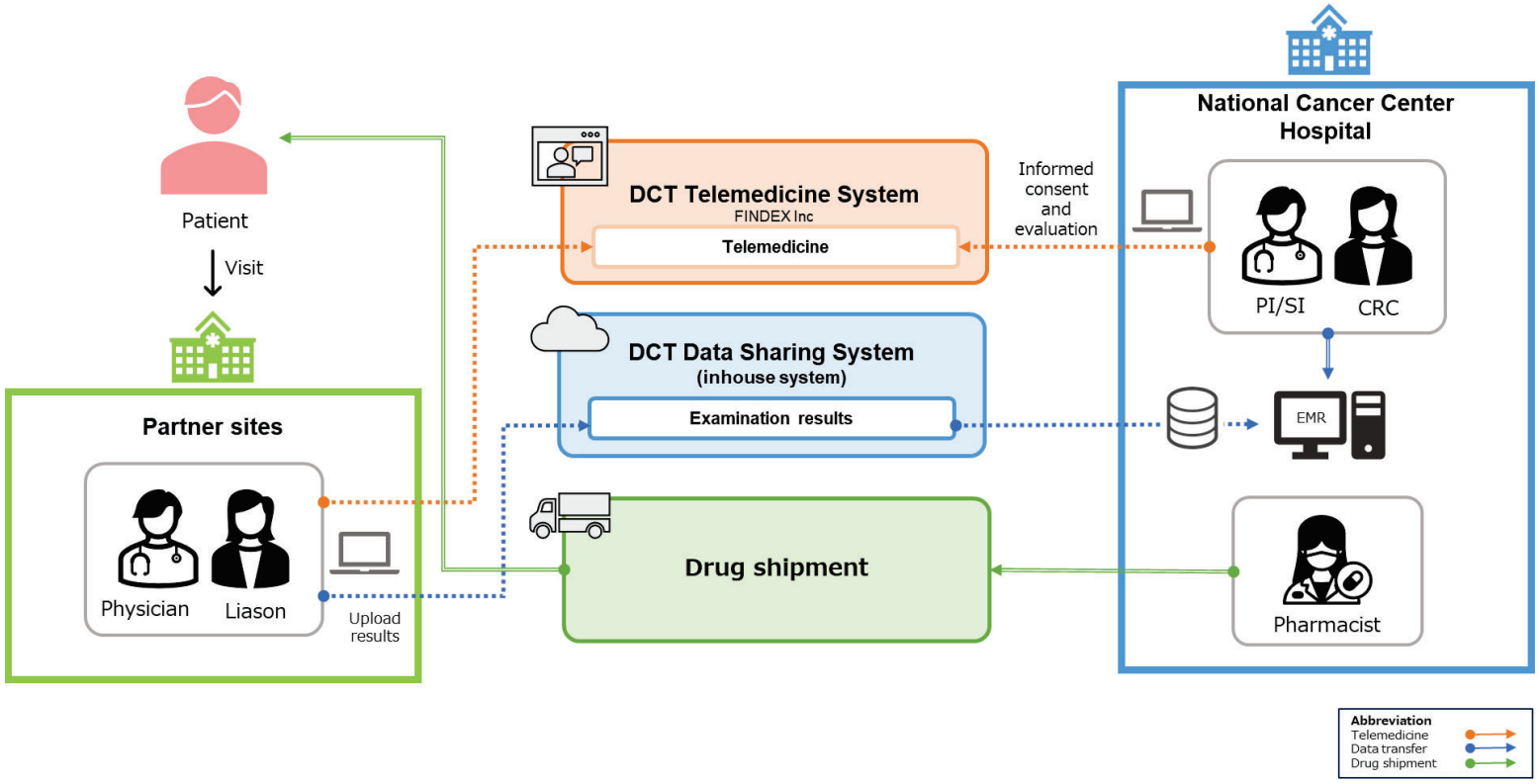
National Cancer Center (NCC)

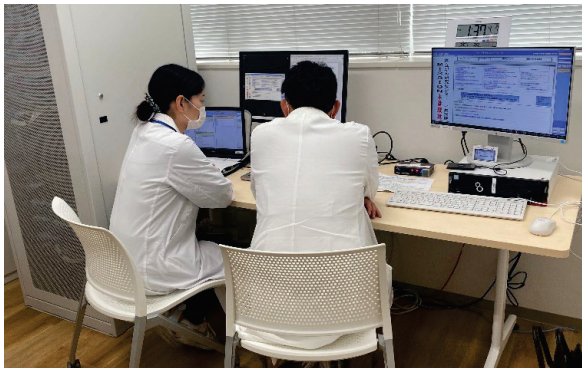
IRB review
Assign PI/SI in NCC
EDC entry
Monitoring
SAE reporting etc.

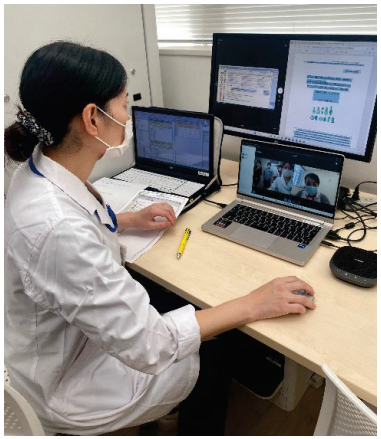
NCC is responsible for any clinical trial related activities

Reducing patient burden: Decentralized clinical trial

- DCT was Implemented to 2 clinical trials under MASTER KEY project
- Rare cancer patients face burden as small population and rare cancer patients living in distant areas face additional burdens.
- DCT can lead to better clinical trial access, faster patient accrual and reduced clinical trial cost

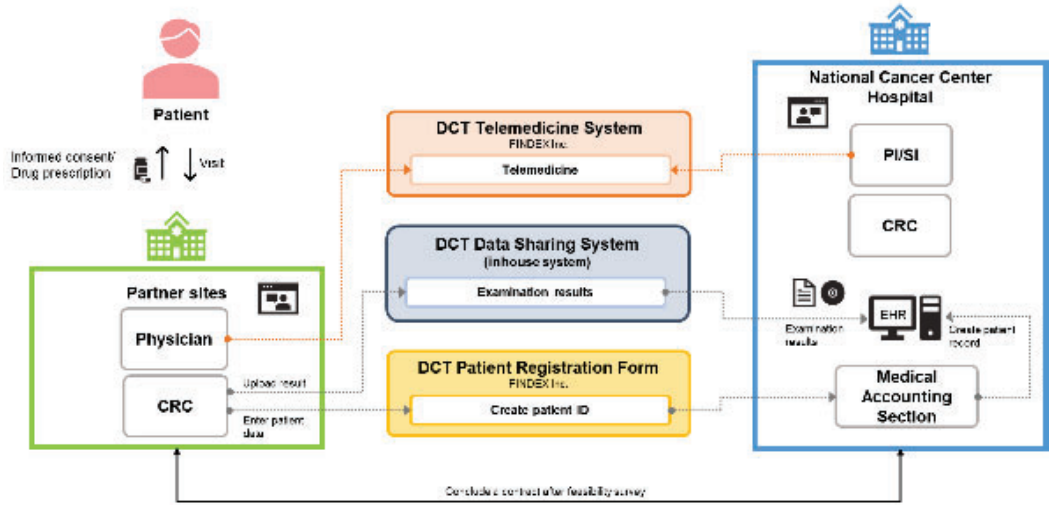


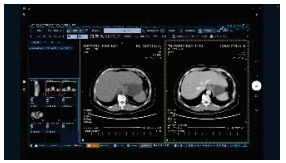


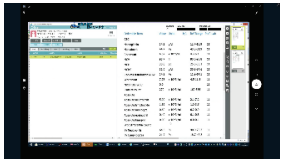


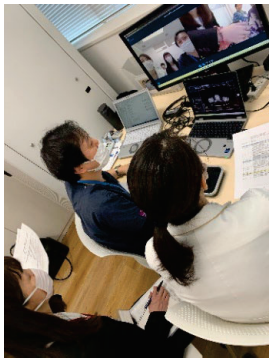
Exploration of diverse trial designs: Cross-border DCT

- With the experience in Japan, we have established a platform with one hospital in Thailand for cross-border DCT, conducted a demonstration with the institution
- No major issues were seen, except communication of medical terms.









✓ By leveraging this system, data entry can be handled in Japan, ensuring high data quality.

✓ Since the source documents are located within Japan, monitoring costs can be significantly reduced.

Take home message What MASTER KEY DO and AIM FOR

- Accelerate the treatment development for rare cancers and rare tissue subtypes through collaboration with academia, patient advocacy groups, and industries and exploration of new methods including DCT and remote access SDV.

- Developing reliable historical control data with the registry, leading to early drug approval

- With comprehensive data representing diverse populations, we could explore tailored treatment approaches that account for genetic, environmental, and cultural factors specific to Asian patients, leading to better-personalized treatments specific to Asian rare cancer patients.

Thank you for your kind attention !!

SCT 46th Annual Meeting
May 18-21, 2025@Vancouver, British Columbia, Canada

国立研究開発法人
国立がん研究センター
National Cancer Center Japan

INVITED SESSION 25: **OVERCOMING CHALLENGES IN RARE CANCERS: LEVERAGING REGISTRY DATA AND INNOVATIVE TRIAL DESIGNS**

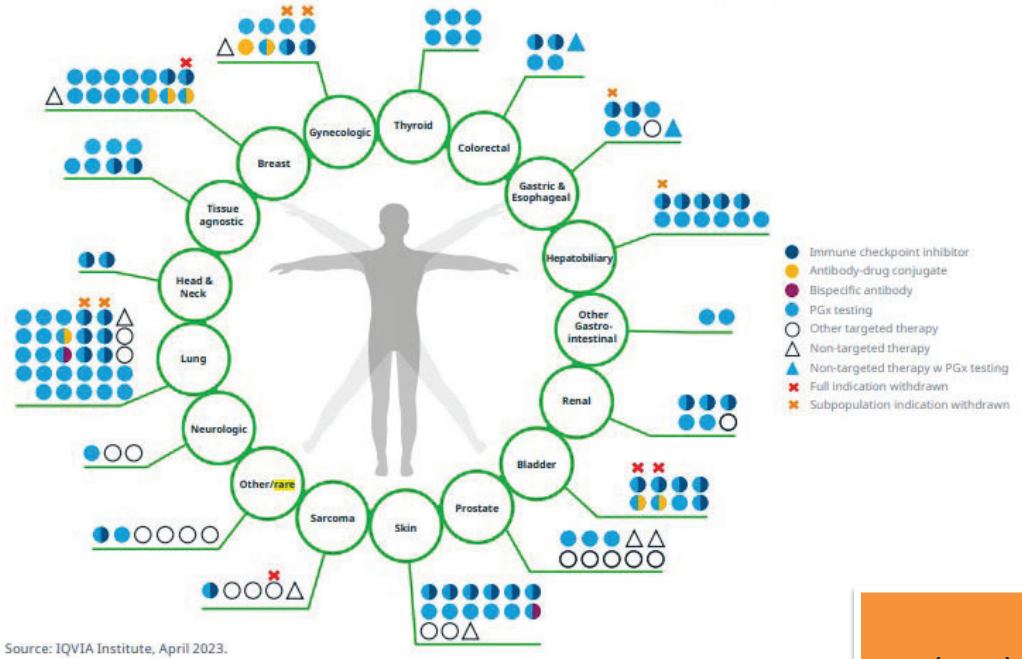
Rare Cancer Clinical Trials in MASTER KEY Project

Hitomi Okuma, MD PhD
Department of International Clinical Development
National Cancer Center Hospital, Tokyo Japan

Few approved drugs specifically for rare cancers

Since 2013, 89 NASs were launched in the U.S. to treat solid tumors with some approved for multiple indications

Exhibit 29: U.S. NASs in solid tumors launched 2013–2022 with indications, including those granted after initial launch



Source: IQVIA Institute, April 2023.

Between 2013 and 2022, 89 new anti-cancer drugs were approved by the FDA for solid tumors. Among these, 22 drugs obtained multiple indications.

Lung cancer saw the highest number of approvals, with many targeted therapies approved, including immune checkpoint inhibitors, antibody-drug conjugates (ADCs), and bispecific monoclonal antibodies.

However, approvals for rare cancers and sarcomas were limited.

Rare cancer definition:

US (NCI): about 15 cases per 100,000 individuals/year

Europe and Japan: fewer than six individuals of every 100,000/ year.

Ultrarare cancer definition:

US (FDA) : fewer than 1,000 people each year in the United States or as unique molecular variations within more common cancers

Ref : IQVIA Global Oncology Trends 2023, Copyright: IQVIA

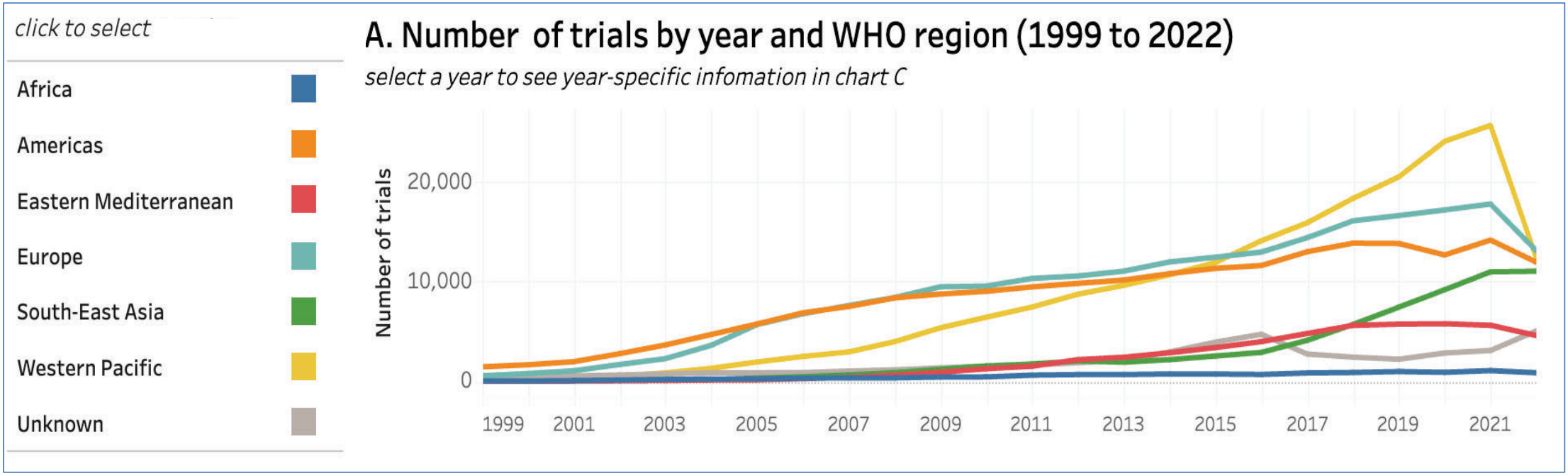
Clinical Trial Platforms for Rare Cancer Populations

	Study Name	
Prospective	ASCO TAPUR	Multiple arms show clinical benefit with many targets like BRAF, HER2, and TMB
	NCI Match	Having completed in 2023, it remains one of the largest tumor-agnostic, precision oncology trials undertaken to date
	SWOG/NCI DART	DART was the US national immunotherapy trial (nivolumab and ipilimumab) for rare cancers. It enrolled 798 patients with rare cancers on 53 cohorts and was open at >1,000 sites across the United States. Multiple cohorts reached their efficacy end points, setting the stage for several NCCN guideline changes for patients with rare cancers
	DRUP	Real-world clinical access to many off-label drugs
Retrospective	SAMBA 101	Retrospective review of prospectively enrolled patients with sarcoma on early-phase trials
	SAMBA 102	Retrospective review of prospectively enrolled patients with ultrarare sarcoma on early-phase trials
	NGS Rare Cancer Study	Retrospective review of prospectively enrolled patients with rare cancers on early-phase trials based on NGS

Rare cancer patients have significantly benefited from enrollment in clinical trials, which offer access to cutting-edge therapies and personalized treatment options

Clinical Trials in Western Pacific region

Western Pacific - the region with the highest number of trial registrations per year



Yet, **only four nations** including Australia, China, Japan, and the Republic of Korea contributed more than 90% of the clinical trials in the region during 2022—reflecting a wide disparity in levels of clinical trial development and maturity.

Source: WHO 2023 : Global observatory on health R&D

195 WHO Member States passed a resolution on clinical trials in May 2022

1) **Equitable and sustainable** capacity development
2) **Addressing major inefficiencies** in countries of all income levels in how clinical trials occur
3) **Bringing new models into the mainstream** (digitization, embedding into health systems, platform trials, decentralization and others)

Key words

- As the technology for cancer genomic sequencing advances, cancer types have subdivided to smaller categorizations by biomarker.
- New clinical trial designs are needed for such small but enriched populations to promote personalized medicine

KEY WORDS

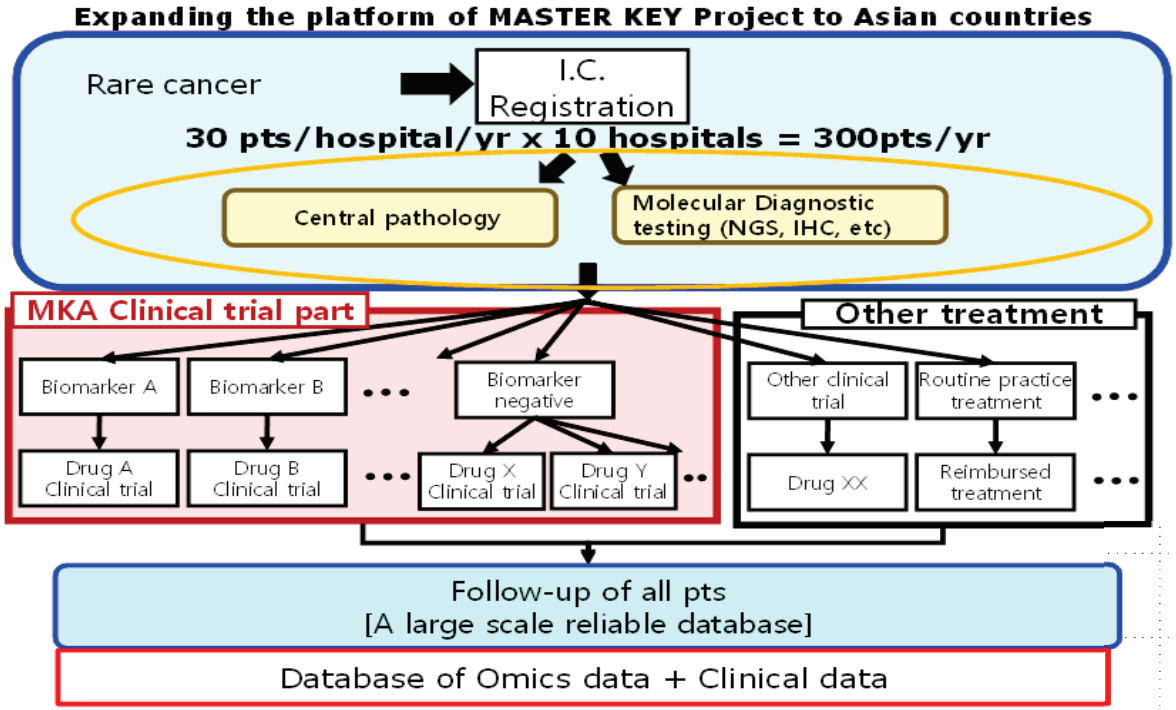
MASTER Protocol	Registry data (Real world data)	International Collaboration (Asia)	Decentralized Clinical Trial (DCT)

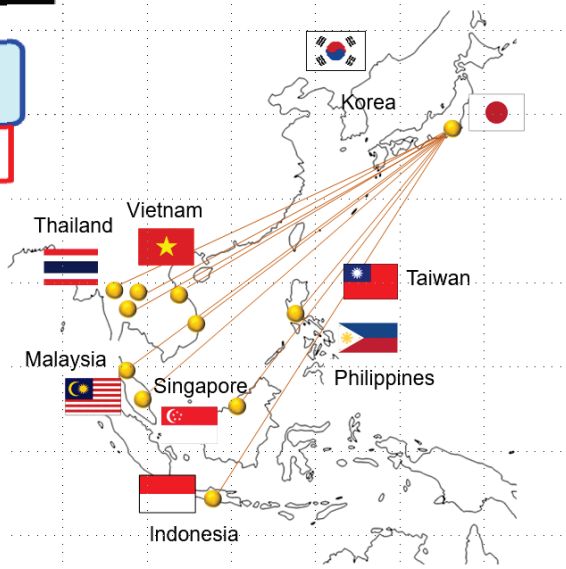
Biostatistical methods; Adaptive design

MASTER KEY: A platform trial for rare cancers

Registry part
(Ongoing Observational Study)

Clinical trial part
(Future Interventional Studies)





Patients
(Patient advocate group)

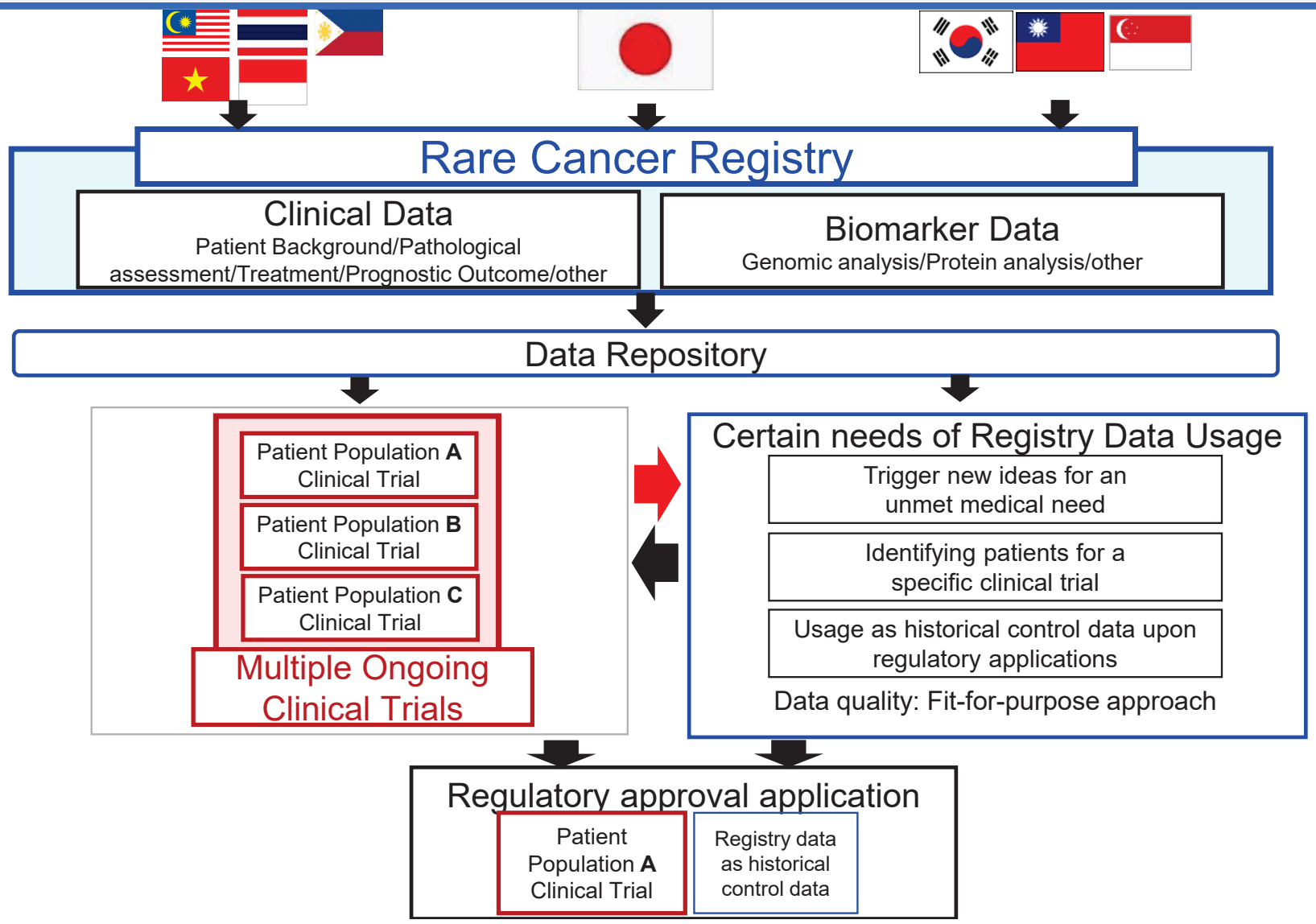
Pharmaceutical Industries

Academic Institutions

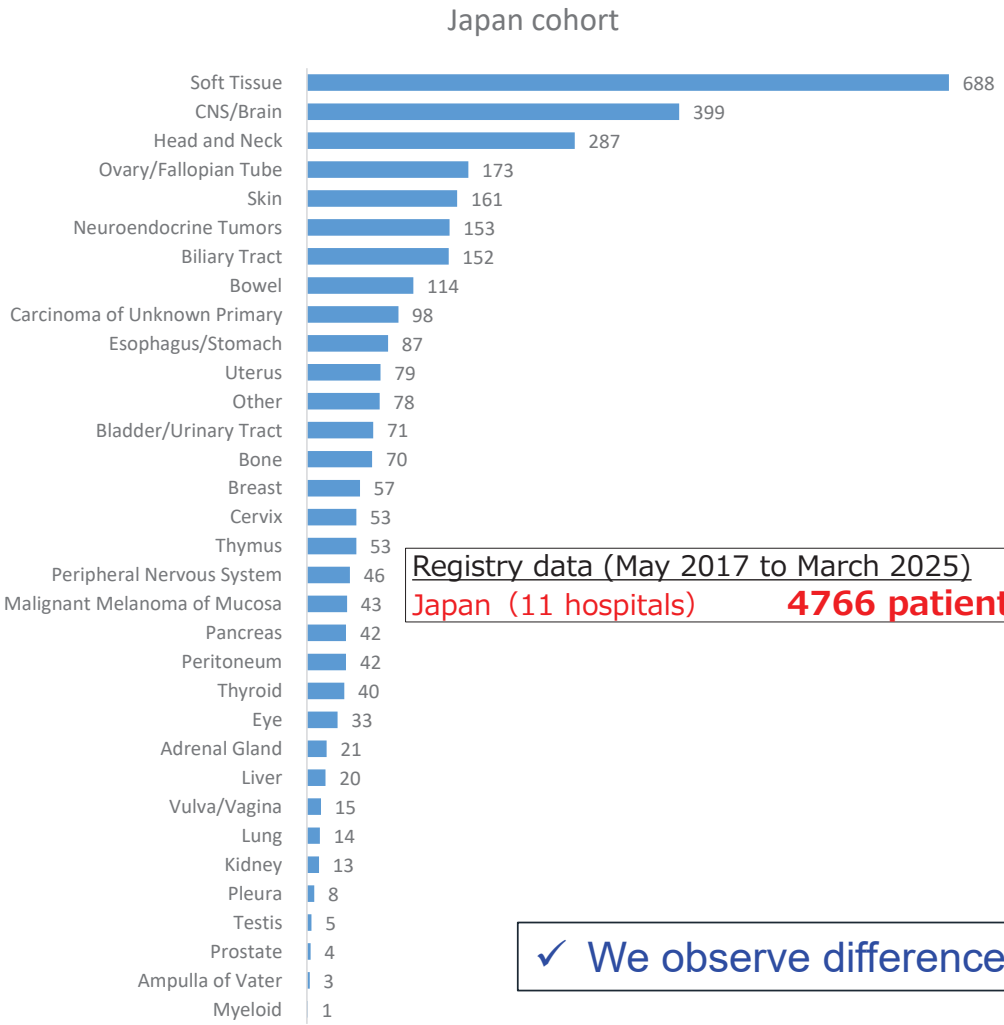
Connect the dots!

NCC

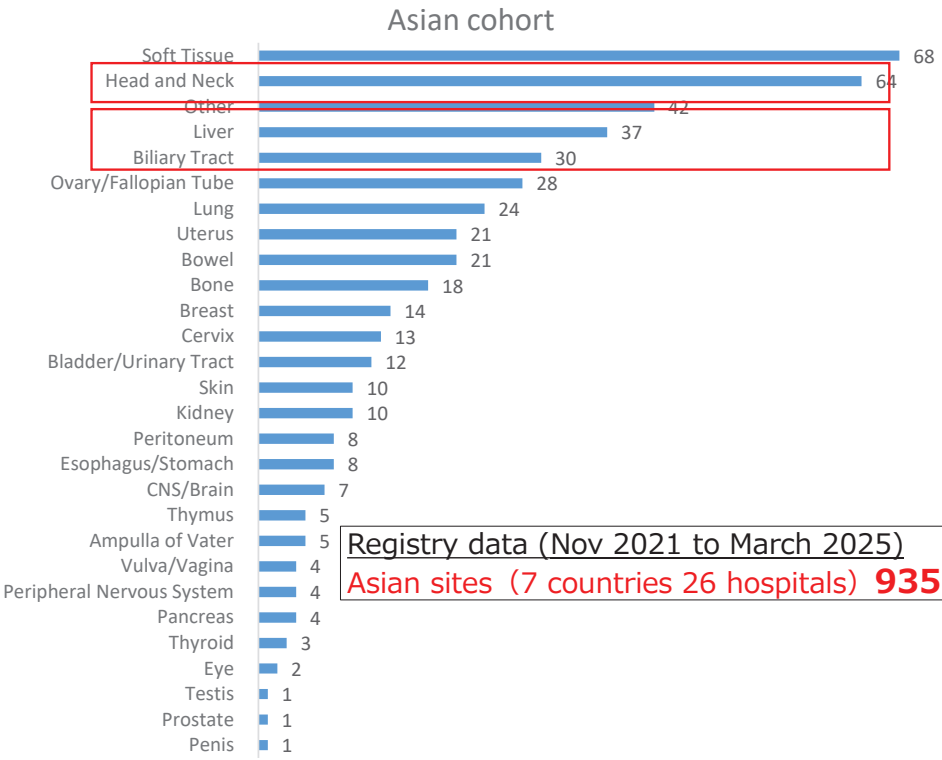
Registry data usage in MASTER KEY



Cancer types registered in MASTER KEY



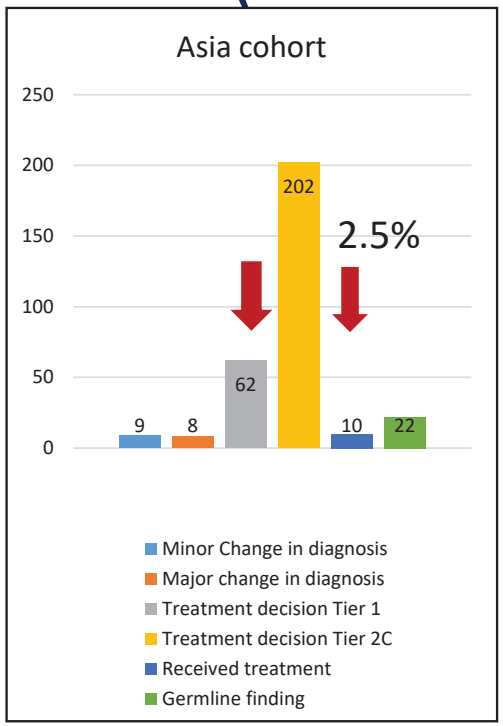
Registry data (May 2017 to March 2025)
Japan (11 hospitals) **4766 patients**



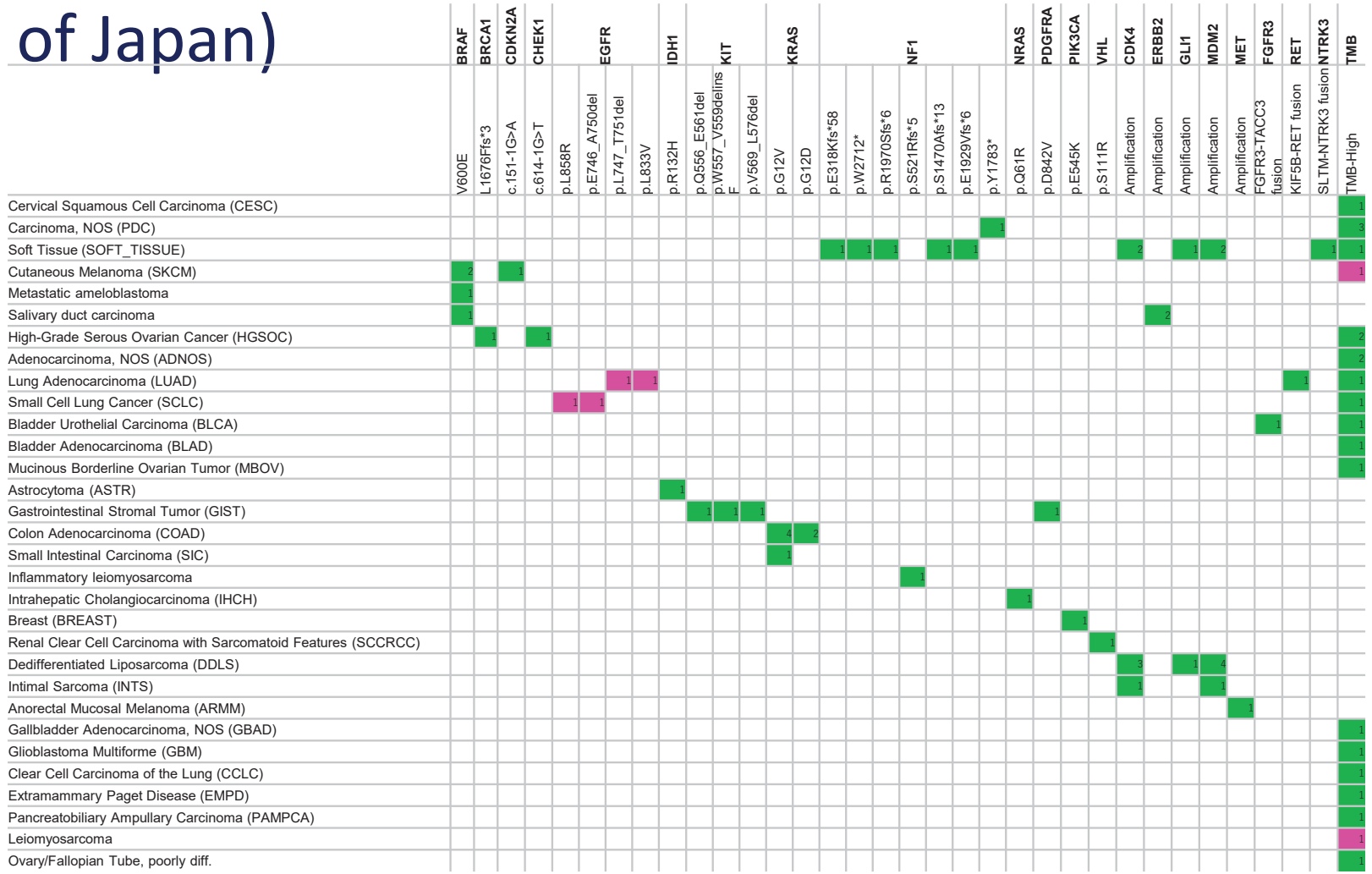
Registry data (Nov 2021 to March 2025)
Asian sites (7 countries 26 hospitals) **935 patients**

✓ We observe differences in the cancer types registered.

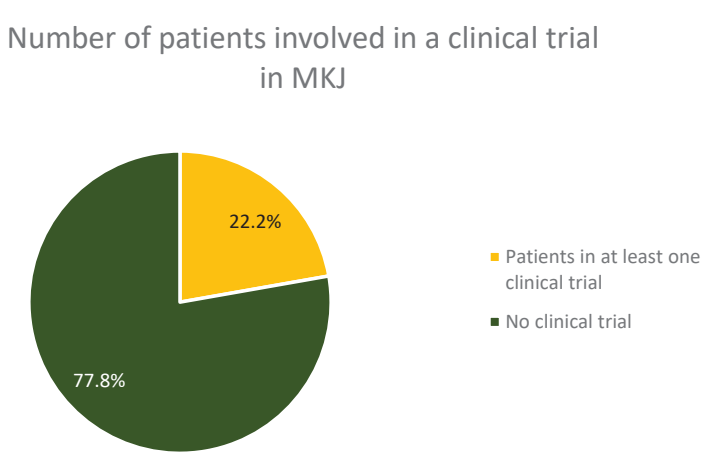
Clinical implementation after genomic findings in Asia (outside of Japan)

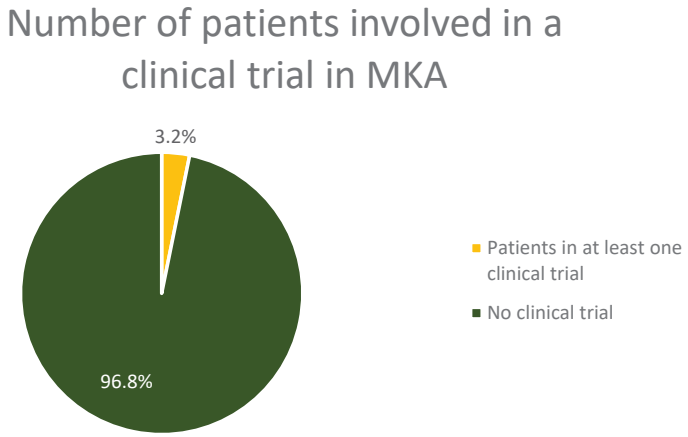


- ✓ Only 10 of the 62 patients with a Tier 1 evidence level genomic alteration gained access to a matched therapy.



Rare cancer patients involved in a clinical trial





- ✓ Since the start of MK in Japan, we have focused on initiating clinical trials for rare cancers.
- ✓ With our new Asian network, we hope to increase the clinical trial participation rate in the Asian countries.

The key is to conduct clinical trials: Trials under the MASTER KEY umbrella

	Target population
1	BRAF V600E
2	dMMR/MSI-high
3	All rare cancers
4	HER2 Carcinosarcoma
5	ALK rare cancers
6	Malignant mesothelioma
7	Adenoid cystic carcinoma
8	Intimal Sarcoma (MDM2)
9	NTRK Fusion Pediatric
10	NK/T-cell lymphoma, nasal
11	FGFR alteration solid cancers
12	Pediatric Solid tumor
13	Alveolar soft part sarcoma
14	Malignant mesothelioma (non-pleural)
15	Cancer of unknown primary
16	Advanced or recurrent solid tumor with FGFR gene alteration
17	Non-Hodgkins Lymphoma Chronic Lymphocytic Leukemia
18	Cervical cancer
19	-FGFR rearrangements solid tumor -FGFR2 amplifications gastric cancer -FGFR1 rearrangements myeloid/lymphoid neoplasms
20	HER2/Salivary gland carcinoma
21	-TP53 wt and MDM2-non-amplified/ amplified solid tumors
22	-MDM2 amplified tumors and absence of known TP53 mutation (Expansion cohorts) -TP53 wt NSCLC/ melanoma/ liposarcoma/ pleomorphic sarcoma/ HCC
23	MDM2 amplified DDLPS
24	Epithelioid sarcoma
25	Secondary central nervous system lymphoma; SCNSL
26	BRAF fusion cancer
27	PD-L1/Non-small Cell Lung Cancer ASPS, Non-small Cell Lung Cancer, gastrointestinal cancer
28	-Platinum-resistant High-grade Serous (HGS) Ovarian -Primary Peritoneal -Fallopian Tube Cancer
29	-Desmoid tumor -Solid pseudopapillary neoplasm (SPN) of pancreas -Small bowel carcinoma with mutation of CTNNB1 or APC -Adrenocortical carcinoma (ACC) with mutation of CTNNB1, APC or ZNRF3 -Solid tumors (except for CRC) with APC mutation in subjects diagnosed as familial adenomatous polyposis (FAP) -Other types of solid tumors (except for CRC and HCC) harboring one or more Wnt-related gene mutations (e.g. APC, AXIN1, CTNNB1, RNF43, etc.)
30	Relapsed or Refractory T-cell Lymphoma
31	TP53 wt and MDM2 amplified DDLPS
32	Conventional chondrosarcoma IDH1 mutation
33	Relapsed or Refractory Lymphoma Relapsed or Refractory Extranodal Natural Killer/T-cell Lymphoma

For details:
https://www.ncc.go.jp/jp/ncch/masterkeyproject/substudy/index.html

Driving clinical trials for even ultra-rare cancers are one of our priorities.

Red: Biomarker driven drugs.
*Some trials have finished enrollment
*Detailed eligibility criteria apply.

Rare cancer trials under MK(Japan) that led to drug approval

- Investigator-initiated Phase 2 clinical trial (VIOLA trial: HCM-002) of nivolumab in patients with malignant mesothelioma (excluding malignant pleural mesothelioma)

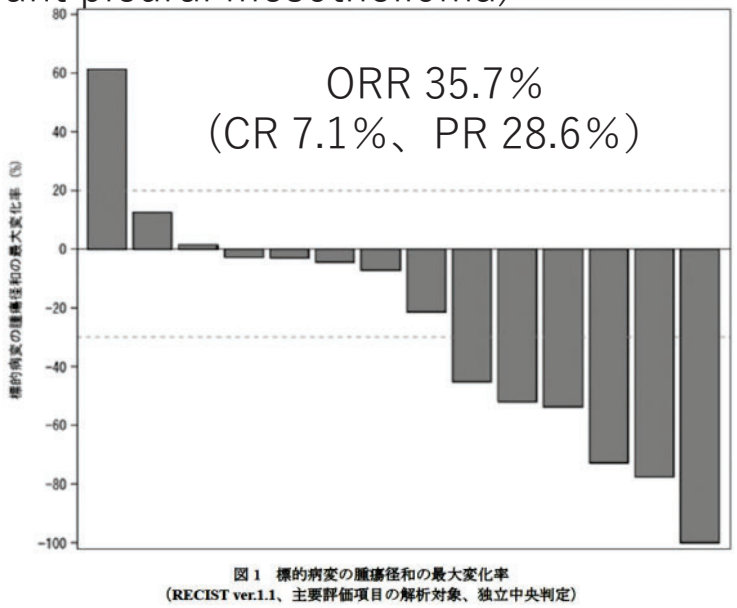
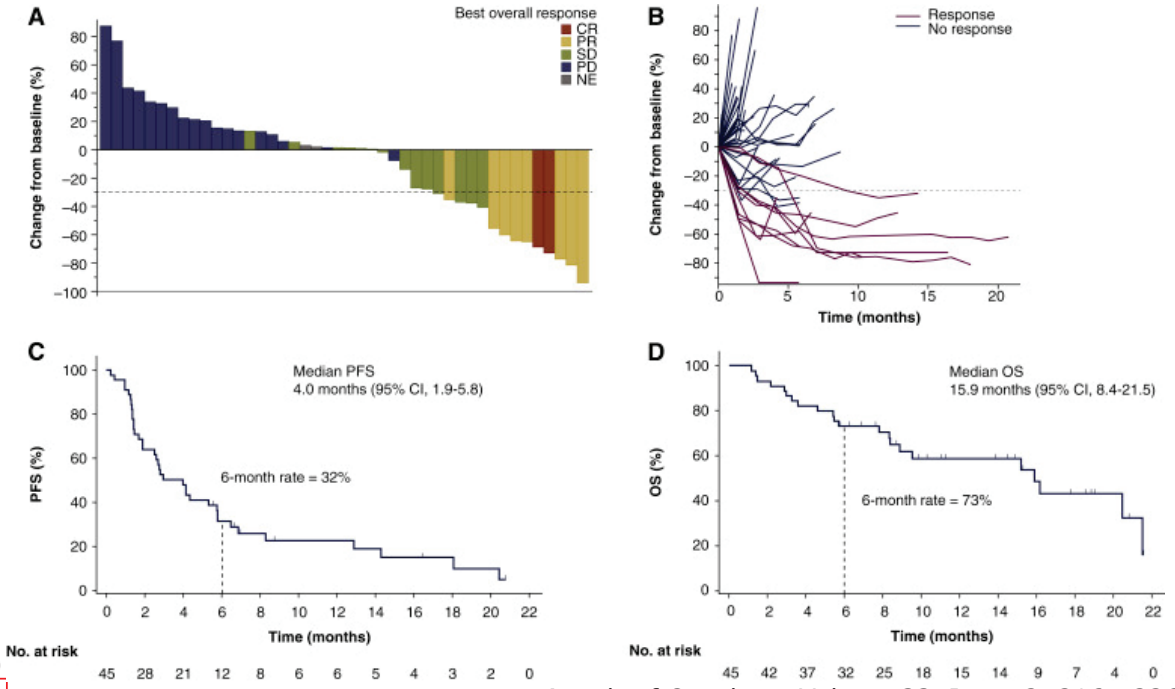


図 1　標的病変の腫瘍径和の最大変化率
（RECIST ver.1.1、主要評価項目の解析対象、独立中央判定）

(from PMDA Review Reports)

2023/11/24
Approval of Opdivo® in Japan to Expand its Use for the Treatment of Malignant Mesothelioma (Excluding Malignant Pleural Mesothelioma)

- Investigator-initiated Phase 2 clinical trial (NIVOCUP trial) of nivolumab in patients with carcinoma of unknown primary



Annals of Oncology, Volume 33, Issue 2, 216 - 226

2021/12/24
Approval of Opdivo® in Japan to Expand its Use for the Treatment of CUP

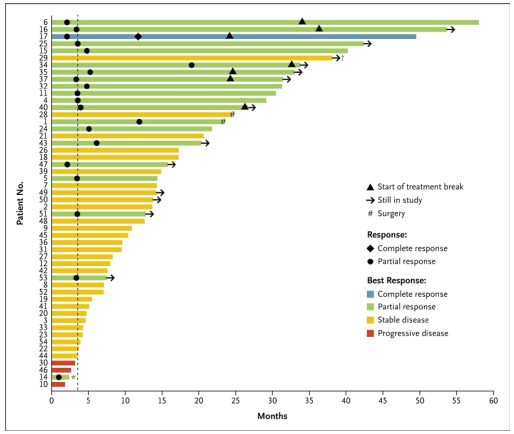
Rare cancer trials under MK(Japan) that led to drug approval **Alveolar soft part sarcoma**

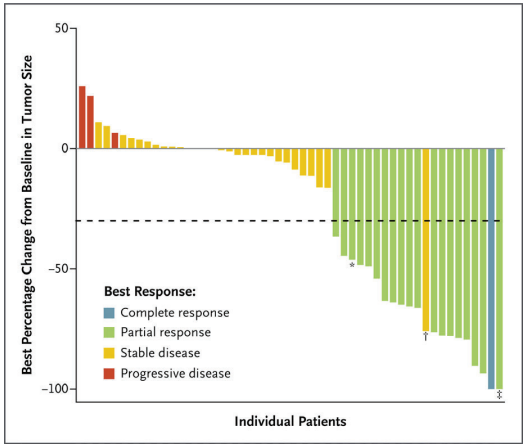
US NCI trial

ORIGINAL ARTICLE

Atezolizumab for Advanced Alveolar Soft Part Sarcoma

Alice P. Chen, M.D., Elad Sharon, M.D., M.P.H., Geraldine O'Sullivan-Coyne, M.D., Ph.D., Nancy Moore, R.N., Jared C. Foster, Ph.D., James S. Hu, M.D., Brian A. Van Tine, M.D., Ph.D., Anthony P. Conley, M.D., William L. Read, M.D., Richard F. Riedel, M.D., Melissa A. Burgess, M.D., John Glod, M.D., Ph.D., et al.





U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / Development & Approval Process | Drugs / Drug Approvals and Databases / Resources for Information | Approved Drugs / FDA grants approval to atezolizumab for alveolar soft part sarcoma

FDA grants approval to atezolizumab for alveolar soft part sarcoma

2022/12/9 FDA grants approval

Resources for Information | Approved Drugs

On December 9, 2022, the Food and Drug Administration (FDA) approved atezolizumab (Tecentriq, Genentech, Inc.) for adult and pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS).

Content current as of: 12/09/2022

Chen et al. N Engl J Med 2023; 389:911-92

Japan MASTER KEY trial

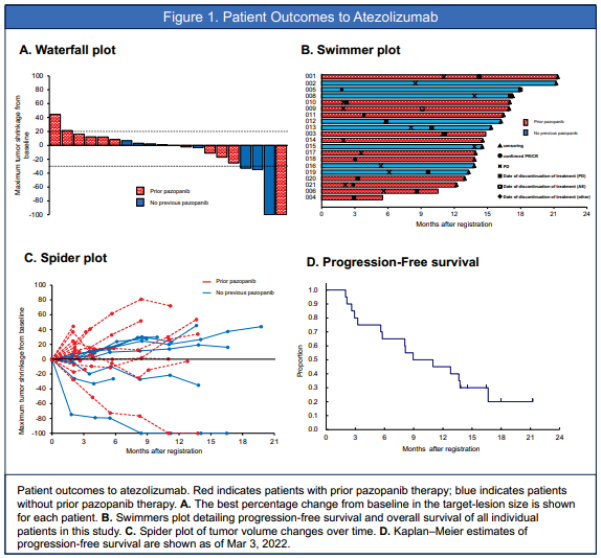
#1571824

Atezolizumab in Japanese patients with advanced alveolar soft part sarcoma: a multi-center, single-arm, investigator-initiated phase 2 trial (NCCH1907)

Makoto Endo[1)], Yuki Kojima[2)], Motoko Arakaki[2)], Tadaaki Nishikawa[2)], Yukari Hoshina[2)], Kenta Anjo[2)], Ryunosuke Machida[2)], Akihiro Hirakawa[3)], Masahiko Ichimura[2)], Hitomi S. Okuma[2)], Kenichi Nakamura[2)], Ikuo Kudawara[4)], Masanobu Takahashi[5)], Kan Yonemori[2)]

1) Kyushu University, Japan, 2) National Cancer Center Hospital, Tokyo, Japan, 3) Tokyo Medical and Dental University, Japan, 4) National Hospital Organization Osaka National Hospital, Japan, 5) Tohoku University Hospital, Japan

Figure 1. Patient Outcomes to Atezolizumab



Patient outcomes to atezolizumab. Red indicates patients with prior pazopanib therapy; blue indicates patients without prior pazopanib therapy. **A.** The best percentage change from baseline in the target-lesion size is shown for each patient. **B.** Swimmers plot detailing progression-free survival and overall survival of all individual patients in this study. **C.** Spider plot of tumor volume changes over time. **D.** Kaplan–Meier estimates of progression-free survival are shown as of Mar 3, 2022.

CTOS 2023. Abstract #1571824

CHUGAI Roche Group

News Release

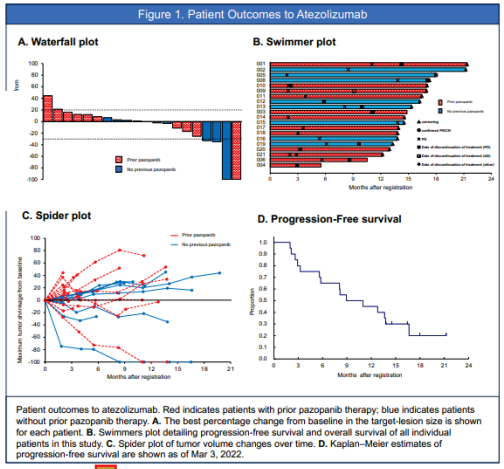
Chugai Obtains Regulatory Approval for Tecentriq for the Additional Indication of Alveolar Soft Part Sarcoma, an Ultra-rare Disease

- Tecentriq is the first immune checkpoint inhibitor in Japan for unresectable alveolar soft part sarcoma, a disease with no standard treatment established
- Approval for unresectable alveolar soft part sarcoma in adults and children over 2 years, which is a type of alveolar soft part sarcoma of high incidence in the AYA (Adolescent and Young Adult) generation
- The approval is based on the results from an investigator-initiated Japanese phase II clinical study and a U.S. NCI-initiated overseas phase II clinical study

2025/2/20
PMDA grants approval of atezolizumab for ASPS

Rare cancer trials under MK(Japan) that led to drug approval **Alveolar soft part sarcoma**

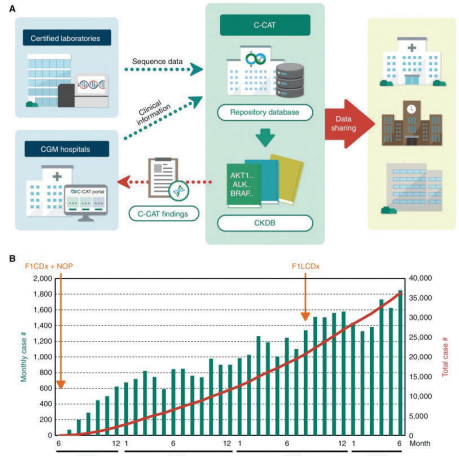
Single arm phase 2 clinical trial
Conducted under MASTER KEY

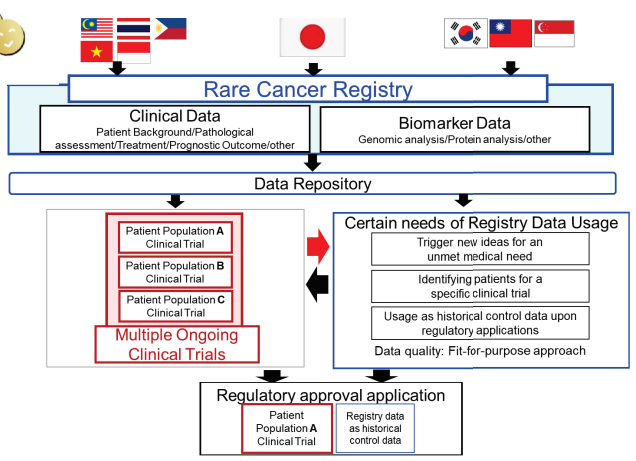


PMDA regulatory approval filing

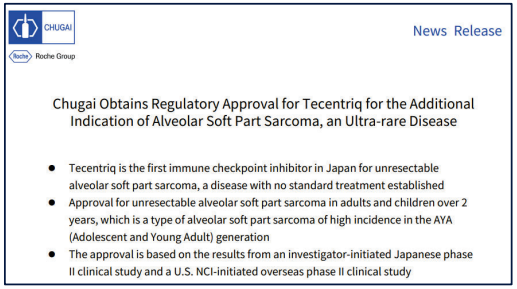
MASTER KEY and C-CAT database RWD used as supporting data

C-CAT
Center for Cancer Genomics and Advanced Therapeutics





Cancer Discov. 2022 Nov 2;12(11):2509–2515.



2025/2/20
PMDA grants approval of atezolizumab for ASPS

Other ultra-rare clinical trials (Investigator initiated)① Intimal sarcoma

CANCER DISCOVERY

ABOUT ARTICLES FOR AUTHORS ALERTS NEWS COVID-19 WEBINARS 10TH ANNIVERSARY

（＊本邦未承認）

Article Contents

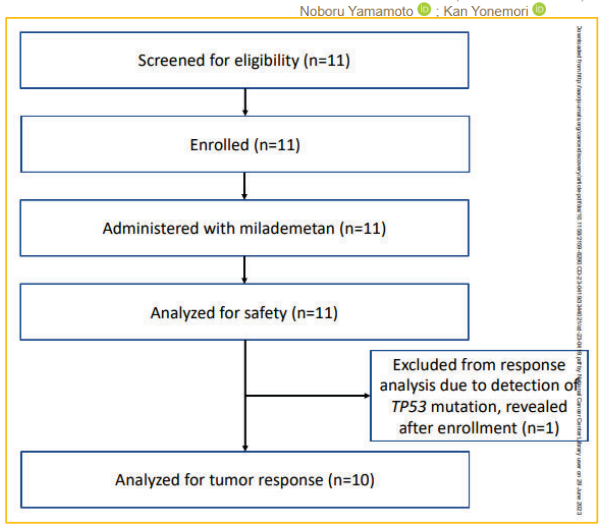
Abstract

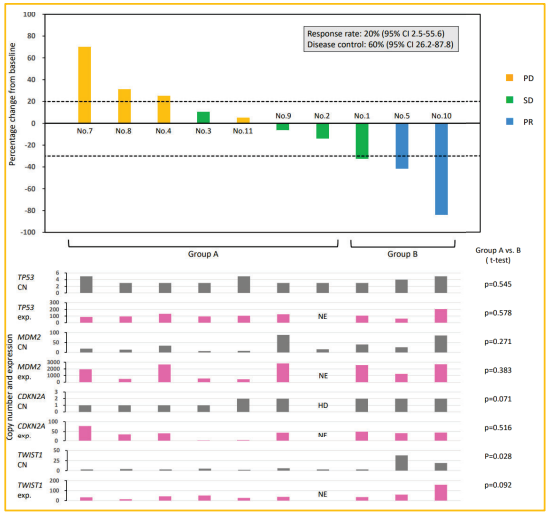
Supplementary data

RESEARCH ARTICLE | JUNE 27 2023

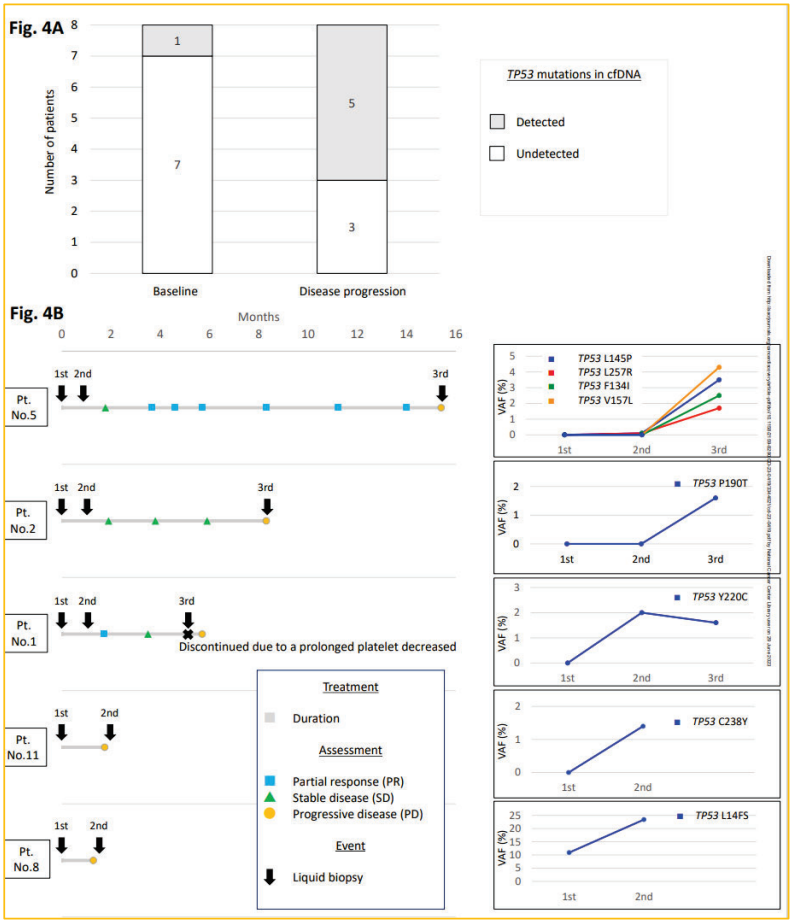
Clinical activity and exploratory resistance mechanism of milademetan, an MDM2 inhibitor, in intimal sarcoma with MDM2 amplification: an open-label phase 1b/2 study

Takafumi Koyama ; Toshio Shimizu ; Yuki Kojima ; Kazuki Sudo ; Hitomi Sumiyoshi. Okuma ; Tatsunori Shimoi ; Hitoshi Ichikawa ; Shinji Kohsaka ; Ryo Sadachi ; Akihiro Hirakawa ; Akihiko Yoshida ; Reiko Makihara. Ando ; Toshihide Ueno ; Mitsuru Yanagaki ; Naoko Matsui ; Kenichi Nakamura ; Noboru Yamamoto ; Kan Yonemori





A sarcoma inside the cardiovascular system is an extremely rare type of sarcoma. While it is said that there are no effective treatments, a clinical trial has been realized. The anti-tumor effect of the drug is suggested to have a positive correlation with TWIST1 amplification abnormality (P = 0.028) and a negative correlation with CDKN2A deletion (P = 0.071)



Abnormalities in the TP53 gene were detected during treatment in multiple cases using liquid biopsy, suggesting the possibility of acquired resistance abnormalities

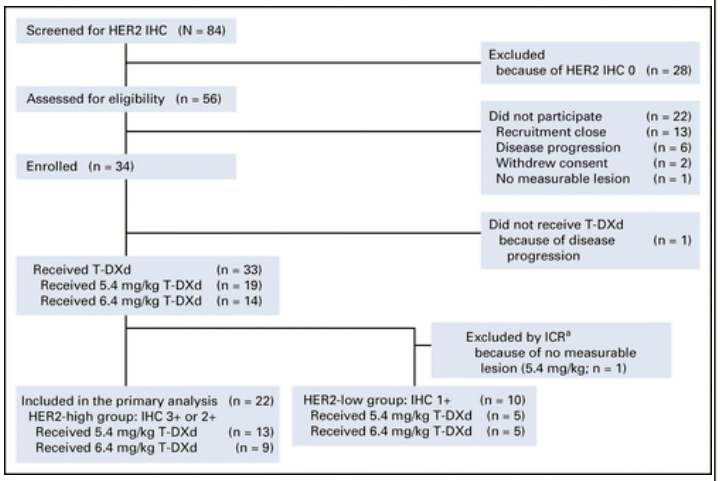
Cancer Discov 2023:13:1814-1825

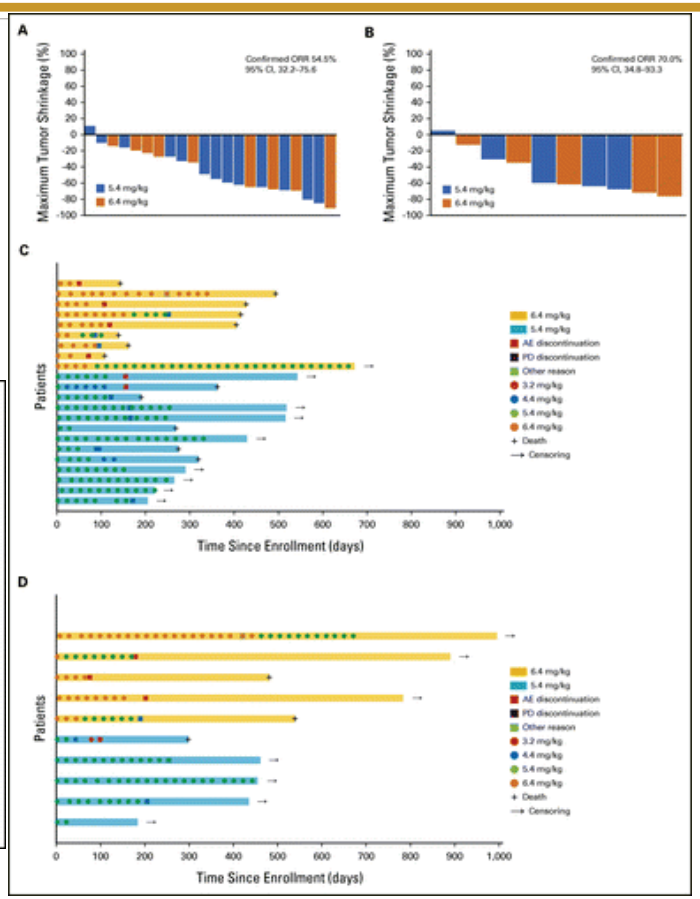
Other ultra-rare clinical trials (Investigator initiated)② Uterine Carcinosarcoma

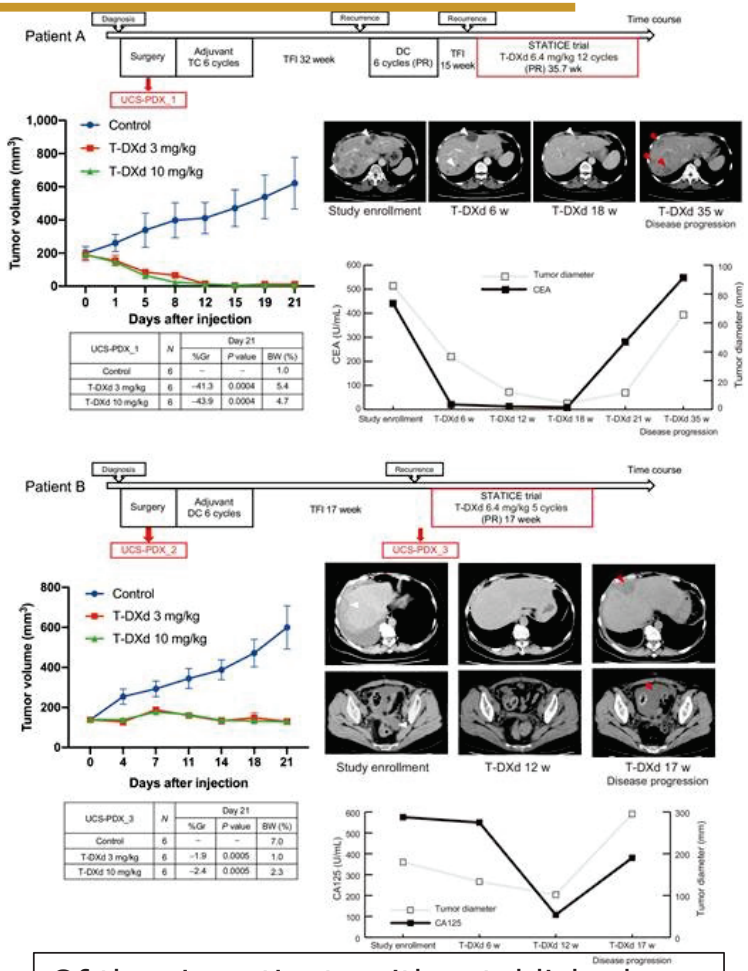
original reports

Trastuzumab Deruxtecan for Human Epidermal Growth Factor Receptor 2–Expressing Advanced or Recurrent Uterine Carcinosarcoma (NCCH1615): The STATICE Trial

Tadaaki Nishikawa, MD, PhD[1]; Kosei Hasegawa, MD, PhD[2]; Koji Matsumoto, MD[3]; Masahiko Mori, MD, PhD[4]; Yasuyuki Hirashima, MD, PhD[5]; Kazuhiro Takehara, MD, PhD[6]; Kazuya Ariyoshi, MD, PhD[7]; Tomoyasu Kato, MD, PhD[8]; Shigehiro Yagishita, MD, PhD[9]; Akinobu Hamada, PhD[9]; Mamiko Kawasaki, MS[10]; Satoshi Kawashima, PhD[10]; Sawako Tomatsuri, MS[10]; Yukari Nagasaka, BS[10]; Hiroshi Yoshida, MD, PhD[11]; Ryunosuke Machida, ME[12]; Akihiro Hirakawa, PhD[13]; Kenichi Nakamura, MD, PhD[10]; and Kan Yonemori, MD, PhD[1]







Response rates at central review:
54.5% and 70% in the HER2-high (IHC score ≥2+; n = 22) and HER2-low (IHC score of 1+; n = 10) groups

Clin Cancer Res 2023. ahead of print. doi: 10.1158/1078-0432.CCR-22-3861.
J Clin Oncol. 2023 Mar 28:JCO2202558.
https://www.ncc.go.jp/jp/information/pr_release/2023/0410/index.html

Of the six patients with established PDX, patients A and B participated in an investigator-initiated trial of T-DXd for treating HER2-expressing UCS

The key is to conduct clinical trials: Trials under the MASTER KEY umbrella

	Target population
1	BRAF V600E
2	dMMR/MSI-high
3	All rare cancers
4	HER2 Carcinosarcoma
5	ALK rare cancers
6	Malignant mesothelioma
7	Adenoid cystic carcinoma
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30	Relapsed or Refractory T-cell Lymphoma
31	TP53 wt and MDM2 amplified DDLPS
32	Conventional chondrosarcoma IDH1 mutation
33	Relapsed or Refractory Lymphoma Relapsed or Refractory Extranodal Natural Killer/T-cell Lymphoma

For details:
https://www.ncc.go.jp/jp/ncch/masterkeyproject/substudy/index.html

Tumor-agnostic approach for rare cancers are one of our priorities.

Red: Biomarker driven drugs.
*Some trials have finished enrollment
*Detailed eligibility criteria apply.

Tumor agnostic approaches for Rare genomic fractions

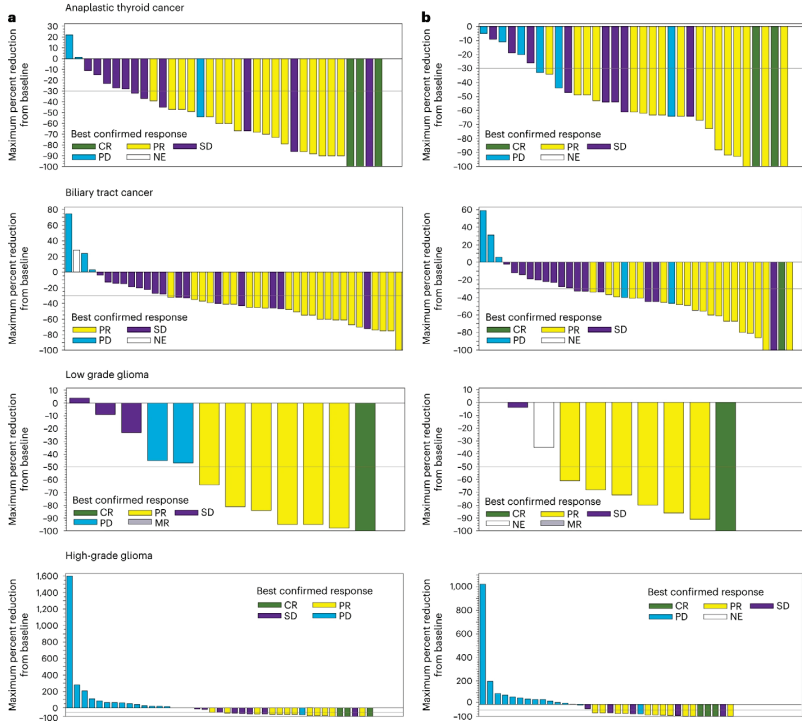
- Industry sponsored: Dabrafenib plus trametinib in BRAF V600E-mutated rare cancers: the phase 2 ROAR trial

Dabrafenib plus trametinib in *BRAFV600E*-mutated rare cancers: the phase 2 ROAR trial

Vivek Subbiah ✉, Robert J. Kreitman, Zev A. Wainberg, Anas Gazzah, Ulrik Lassen, Alexander Stein, Patrick Y. Wen, Sascha Dietrich, Maja J. A. de Jonge, Jean-Yves Blay, Antoine Italiano, Kan Yonemori, Daniel C. Cho, Filip Y. F. L. de Vos, Philippe Moreau, Elena Elez Fernandez, Jan H. M. Schellens, Christoph C. Zielinski, Suman Redhu, Aislyn Boran, Vanessa Q. Passos, Palanichamy Ilankumaran & Yung-Jue Bang

Nature Medicine (2023) | Cite this article

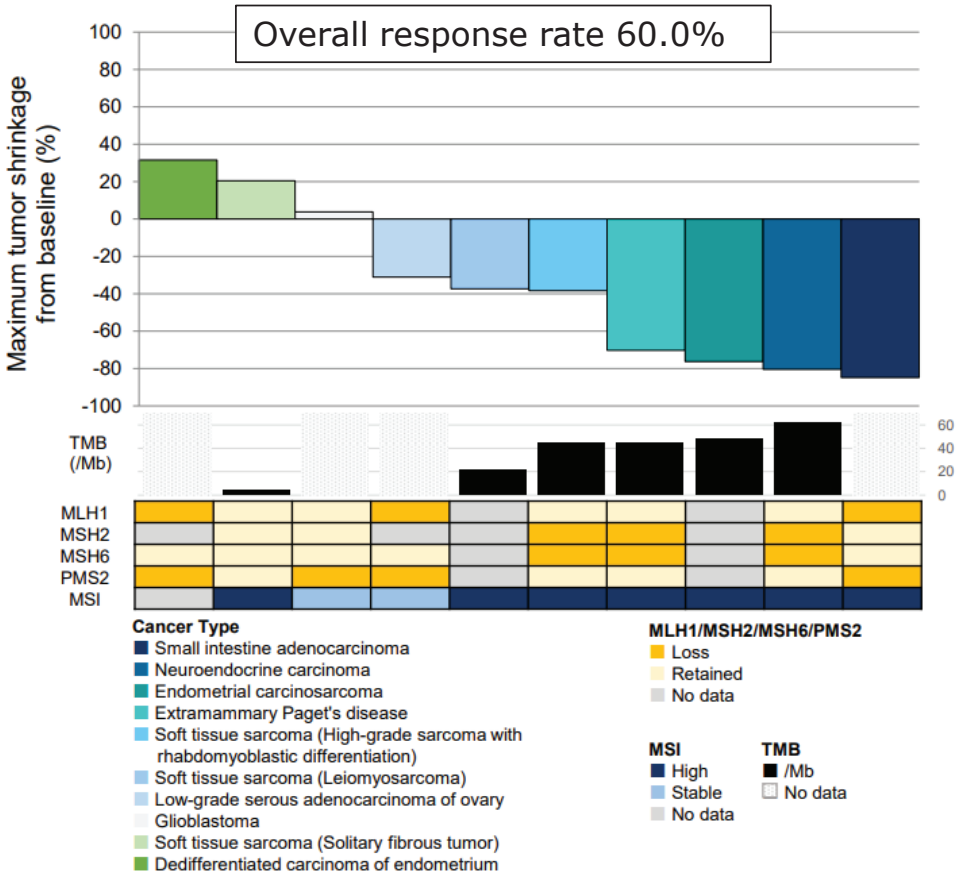
2023/11/24
Approval of Tafinlar® (dabrafenib) and Mekinist® (trametinib), in Japan, for the treatment of solid tumors with the BRAF V600E mutation



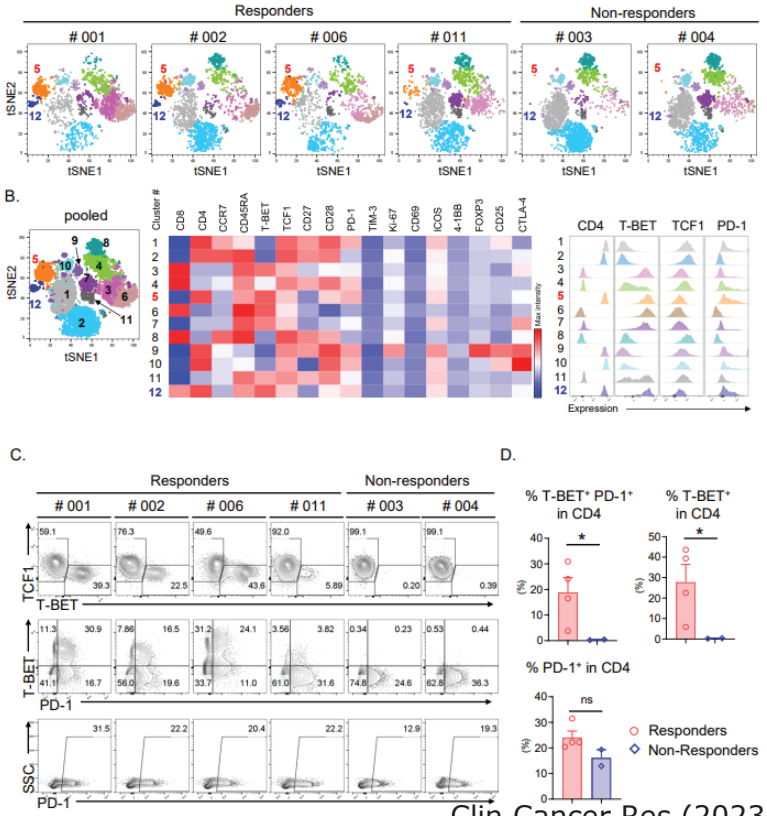
(Nat Med 2023;29:1103–1112)

Tumor agnostic approaches for Rare genomic fractions

Phase 2 trial of nivolumab in metastatic rare cancer with dMMR or MSI-H and relation with immune phenotypic analysis (the ROCK trial)



Immune phenotyping of PBMC showed a increase inT-BET+ or T-BET+ PD-1+ cells in responders compared to non-responders



Clin Cancer Res (2023) 29 (24): 5079–5086

Tumor agnostic FDA/PMDA approvals

	Biomarker	FDA approval	PMDA approval	n	Overall Response
Pembrolizumab	MSI-H, dMMR	2017 2022 (Full approval)	○	149 (updated 504)	39.6% (CR 7.4%) 33.3% (CR 10.3%)
Pembrolizumab	TMB-H	2020	○	102	29% (CR 4%)
Dostarlimab	MSI-H, dMMR	2021	-	209	41.6% (CR 9.1%)
Larotrectinib	NTRK fusion	2018	○	55 (updated 140)	75% (CR 22%)
Entrectinib	NTRK fusion	2019	○	54	57%
Repotrectinib	NTRK fusion	2024	-	TKI naïve 40 TKI pretreated 48	58% 50%
Selpercatinib	RET fusion	2022	-	41	44% (CR 4.9%)
Dabrafenib + Tramatinib	BRAF V600E	2022	-	131	41%
Trastuzumab deruxtecan	HER2 protein	2024	-	267	37.1%

However, challenges for clinical development remain

Challenge 1: Time taken for clinical trials on rare cancers and rare fractions.

- Promote patient enrollment from non-clinical trial facilities.
- An international perspective

Challenge 2: Barriers after clinical trial until market approval

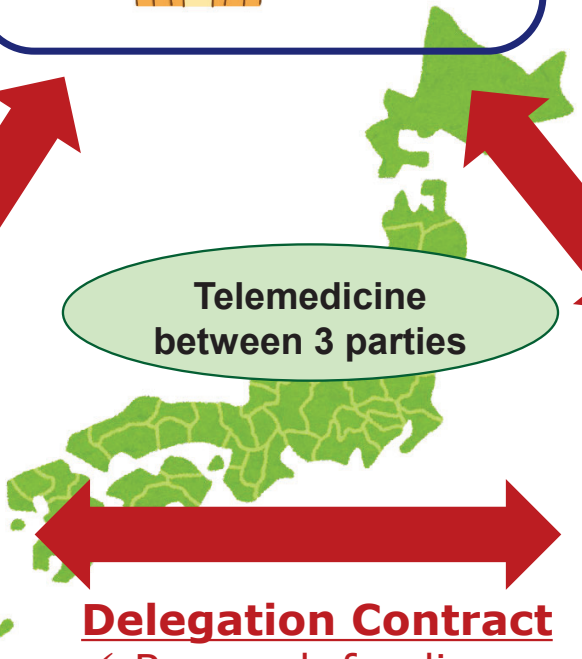
- Companion diagnostic test regulations
- Post-marketing requirements

Decentralized clinical trials (Remote clinical trials)

Patients in local hospitals

Online visit by telemedicine
- ✓ Eligibility check
- ✓ Informed consent
- ✓ Go/No-go decision on treatment continuation
- ✓ Efficacy/Safety evaluation

Delegation of medical care and lab tests/exams
- ✓ Regular visits and exams
- ✓ Appointments according to trial schedule



Telemedicine between 3 parties

Partner hospital

Delegation of lab tests
Test results shared with NCC

Delegation Contract
- ✓ Research funding
- ✓ Test results sharing

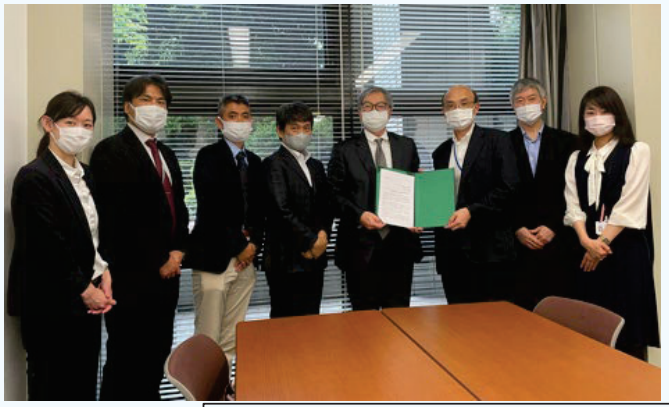
National Cancer Center Hospital

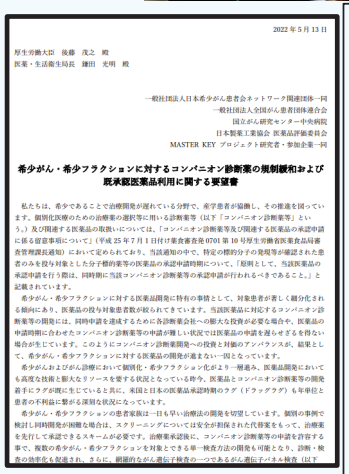
IRB submission/approval
PI/Sub-I assigned
EDC entry
Monitaoring
SAE reporting etc.

NCCH is responsible for all clinical trial related activities

Seeking Regulatory assistance from PMDA: CDx issue

May 13, 2022





2022 年 5 月 13 日

厚生労働大臣　後藤　茂之　殿
医薬・生活衛生局長　鎌田　光明　殿

一般社団法人日本希少がん患者会ネットワーク関連団体一同
一般社団法人全国がん患者団体連合会
国立がん研究センター中央病院
日本製薬工業協会 医薬品評価委員会
MASTER KEY プロジェクト研究者・参加企業一同

希少がん・希少フラクションに対するコンパニオン診断薬の規制緩和および既承認医薬品利用に関する要望書

私たちは、希少であることで治療開発が遅れている分野で、希望患者が協働し、その推進を図っています。個別化医療のための治療薬の選択等に用いる診断薬等（以下「コンパニオン診断薬等」という。）及び関連する医薬品の取扱いについては、「コンパニオン診断薬等及び関連する医薬品の承認申請に係る留意事項について」（平成 25 年 7 月 1 日付け薬食審査発 0701 第 10 号厚生労働省医薬食品局審査管理課長通知）において定められており、当該通知の中で、特定の標的分子の発現等が確認された患者のみを投与対象とした分子標的薬等の医薬品の承認申請時期について、「原則として、当該医薬品の承認申請を行う際は、同時期に当該コンパニオン診断薬等の承認申請が行われるべきであること。」と記載されています。

希少がん・希少フラクションに対する医薬品開発に特有の事情として、対象患者が著しく細分化される傾向にあり、医薬品の投与対象患者数が絞られてきています。当該医薬品に対応するコンパニオン診断薬等の開発には、同時申請を達成するために各診断薬会社への膨大な投資が必要な場合や、医薬品の申請時期に合わせたコンパニオン診断薬等の申請が難しい状況では医薬品の申請を遅らせざるを得ない場合が生じています。このようなコンパニオン診断薬開発への投資と対価のアンバランスが、結果として、希少がん・希少フラクションに対する医薬品の開発が進まない一因となっています。

希少がんおよびがん診療において個別化・希少フラクション化がより一層進み、医薬品開発においても高度な技術と膨大なリソースを要する状況となっている昨今、医薬品とコンパニオン診断薬等の開発着手にラグが現に生じていると共に、米国と日本の医薬品承認時期のラグ（ドラッグラグ）も年単位と患者の不利益に繋がる深刻な状況になっています。

希少がん・希少フラクションの患者家族は一日も早い治療法の開発を切望しています。個別の事例で検討し同時開発が困難な場合は、スクリーニングについては安全が担保された代替案をもって、治療薬を先行して承認できるスキームが必要です。治療薬承認後に、コンパニオン診断薬等の申請を許容する事で、複数の希少がん・希少フラクションを対象とできる単一検査方法の開発も可能となり、診断・検査の効率化も促進され、さらに、網羅的ながん遺伝子検査の一つであるがん遺伝子パネル検査（以下

Together with the Rare Cancer Japan Patient advocacy group and MASTER KEY team, a petition letter regarding the relaxation of regulations on companion diagnostics for rare cancers/rare fractions and the use of approved diagnostics was submitted.

NCCH Homepage
https://www.ncc.go.jp/jp/ncch/information/2022/0606/index.html

Feb 24, 2023

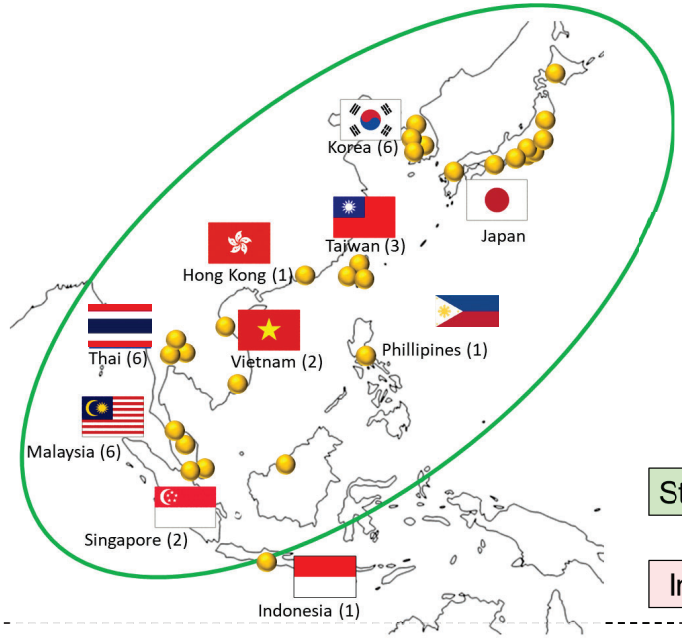
1．対象範囲
本通知の対象範囲は、以下の（1）～（3）のいずれにも該当する医薬品とする。本通知に基づいて承認申請できるかどうかについては、別添の申込書に必要事項を記入の上、事前に医薬品審査管理課に相談すること。

（1）希少がんを対象として医師主導治験によって得られた臨床試験成績に基づき医薬品製造販売業者が医薬品の一部変更承認申請を予定する医薬品
（2）医薬品の承認申請と同時期に体外診断用医薬品又は医療機器の製造販売業者が、当該 CDx の承認申請を行えない場合
（3）薬事承認されている遺伝子変異解析プログラム等を用いたがんゲノムプロファイリング検査（以下、「CGP 検査」という。）の結果に基づき当該医薬品を使用した場合に、臨床試験の被験者と同等の有効性及び安全性が期待できることが説明可能な医薬品

2．承認申請に係る取扱い
上記 1．を満たす医薬品であって、当該医薬品の一部変更承認申請と同時期に当該医薬品に関する CDx の承認申請が行えない場合は、当該医薬品の一部変更承認申請を先行して行っても差し支えないこと。
なお、本通知の対象となった場合も、CDx を開発することが基本であり、本通知に基づき一部変更承認申請がなされた医薬品は、承認にあたっては承認のあった日から一定の期限までに当該医薬品の CDx の承認申請を行うことを承認条件として付されることに留意すること。

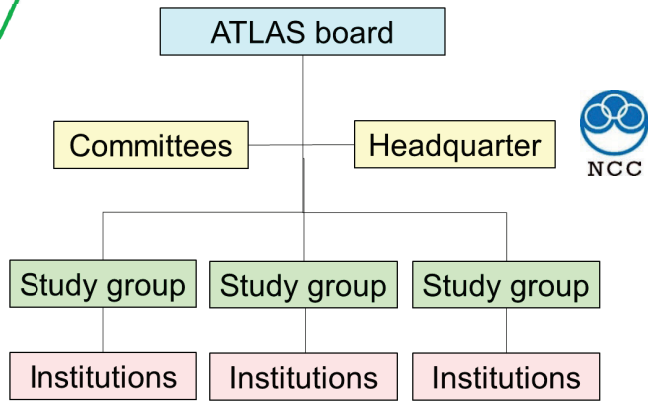
Not long after, a new notification from the Ministry of Health, Labour and Welfare was issued, notifying some relaxation of regulation regarding companion diagnostics upon drug approval for drugs targeting genomic biomarkers.
This was an outcome based on the petition in May 2022.

Expanding clinical trials through international collaborations



ATLAS
ASIAN CLINICAL TRIALS NETWORK FOR CANCERS PROJECT

ATLAS Clinical Trial Network



NCC

Study drug Funding

Proposal

Regulatory authorities in Asia

Pharma

CRO

ATLAS Clinical Trial Network

- ✓ One-stop service for cancer drug development in Asia
- ✓ The network will conduct 5-10 clinical trials constantly (academic or industrial)
- ✓ All participating sites join semi-annual meeting
- ✓ ATLAS board has been established with participating sites serving as a board member
- ✓ We are expanding the ATLAS network to other countries

Study Groups

- ✓ Head and Neck Cancer Group
- ✓ Soft Tissue and Rare Cancer Group

Others coming soon

Essence of Clinical Trial Networks

NETWORKING:

With the network between cancer advocate groups and academic institutions, rapidly recruit patients into clinical trials whether it's pharma sponsored or academic sponsored.

INNOVATION:

Collaborate with pharmas and research institutions to find new targets for new trial ideas to focus on trial development

CLINICAL TRIAL DESIGNING:

Novel approaches such as Decentralized Clinical Trial designs to focus specifically on research delivery.

REGULATORY ASSISTANCE:

Advice/guide pharma companies toward regulatory approval

Thank you for your kind attention !!

Statistical consideration for rare cancer/fraction: examples from Japanese-led clinical trials

Junki MIZUSAWA, ME PhD MBA

Head, Biostatistics section, Biostatistics Division,
Center for Research Administration and Support, National Cancer Center
Head, Biostatistics section, Research Management Division,
Clinical Research Support Office, National Cancer Center Hospital
Head, Data Management section, Data Management Division,
Clinical Research Support Office, National Cancer Center Hospital
Coordinating Statistician, Statistics Section, JCOG Data Center

May 21, 2025
46th Annual meeting of Society for Clinical Trials @ Vancouver, Canada

Disclosures

- No disclosures to declare

Clinical trial design for rare cancer

- Conventional clinical trial designs with separate protocols for each subject are not realistic for rare cancers.
  - Limited population size
  - Heterogeneity among rare cancer types
  - Less financial support and/or pharma may be reluctant to invest
  - Low power or precision of treatment effect

More efficient clinical trial led by academia is necessary to advance rare cancer research

Subbiah V, Othus M, Palma J, Cuglievan B, Kurzrock R. Designing Clinical Trials for Patients With Rare Cancers: Connecting the Zebras. Am Soc Clin Oncol Educ Book. 2025 Jun;45(3):e100051.

Master protocol

a protocol designed with multiple substudies, which may have different objectives and involve coordinated efforts to evaluate one or more medical products in one or more diseases or conditions within the overall study structure.

Basket trial

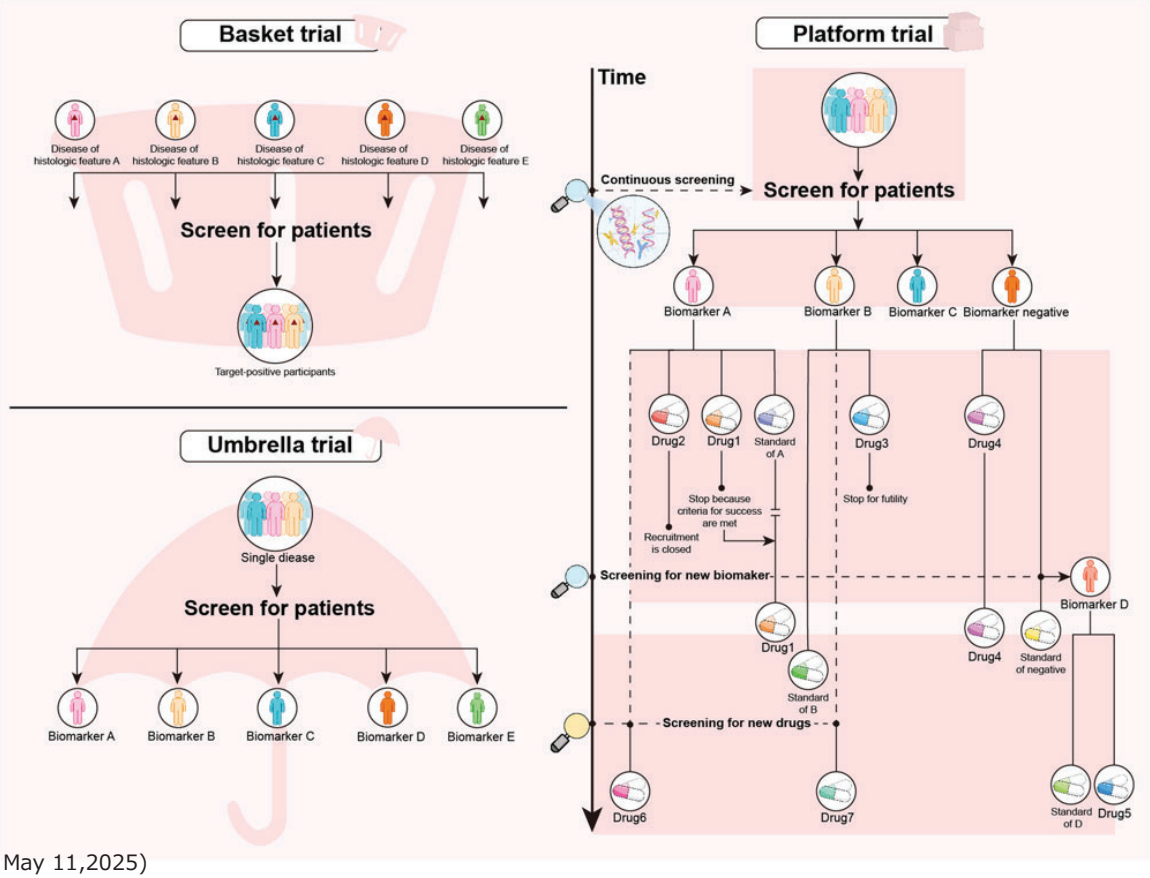
A single drug × multiple disease or subtypes

designed to evaluate a medical product for multiple diseases, conditions, or disease subtypes.

Umbrella trial

multiple drugs × a single disease

designed to evaluate multiple medical products concurrently for a single disease or condition



Platform trial

designed to evaluate multiple medical products for a disease or condition in an ongoing manner, with medical products entering or leaving the platform

www.fda.gov/media/174976/download (Access: May 11,2025)

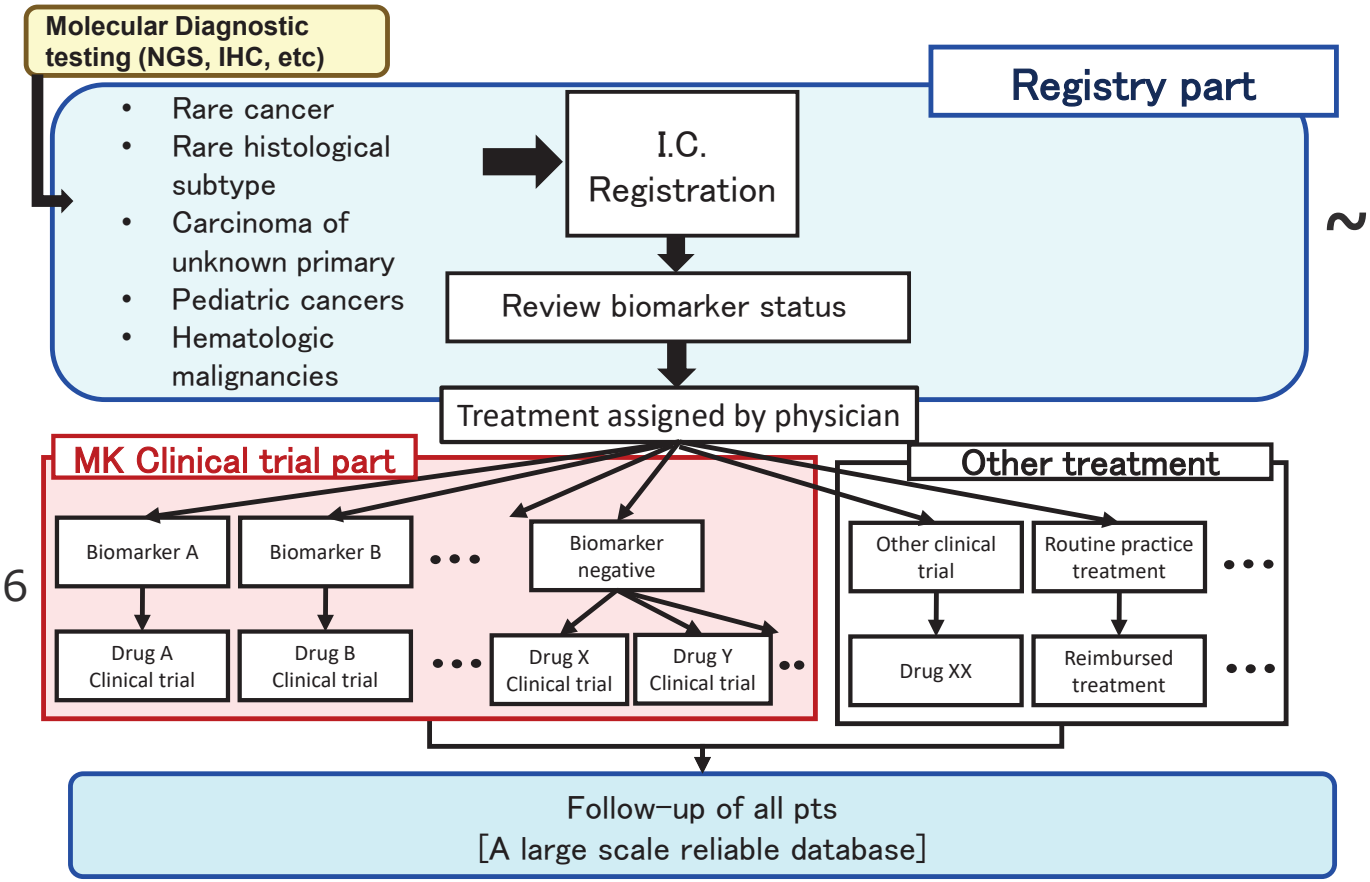
Duan, XP., Qin, BD., Jiao, XD. et al. New clinical trial design in precision medicine: discovery, development and direction. Sig Transduct Target Ther 9, 57 (2024).

Other types of trial design

Trial design	Definition
Registry-based trials /master observational trials (MOT)	• Registry-based trials or MOTs leverage existing patient registries to identify eligible participants and collect data. • These trials can be particularly efficient for rare cancers as they use pre-existing infrastructure and patient cohorts. • The use of registries can facilitate rapid patient recruitment and real world data collection
Multi-arm, multi-stage (MAMS) trials	• MAMS trials are designed to evaluate multiple treatments simultaneously and can progress through different stages based on interim analyses. • This design allows for the efficient comparison of several therapies and the early discontinuation of ineffective treatments
Hybrid designs	• Uses external control data sets and random assignment to experimental and control groups to effectively assess the impact of the experimental treatment

Subbiah V, Othus M, Palma J, Cuglievan B, Kurzrock R. Designing Clinical Trials for Patients With Rare Cancers: Connecting the Zebras. Am Soc Clin Oncol Educ Book. 2025 Jun;45(3):e100051.

MASTER KEY project



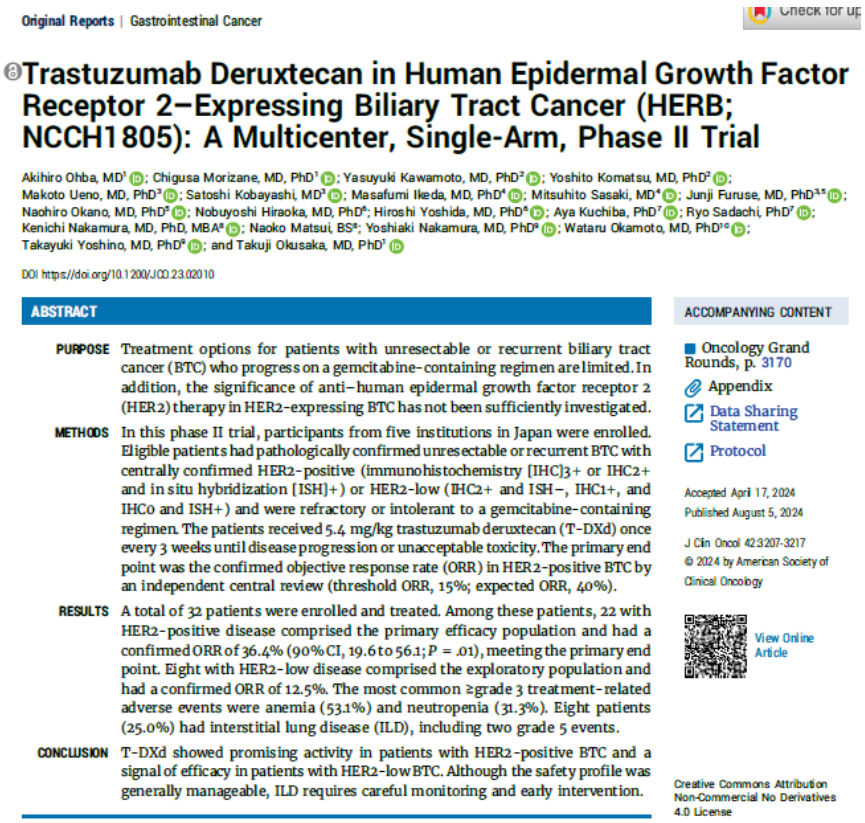
~4,500 pts

33 trials

Investigator 16
Industry17

- MASTER KEY is a platform trial in that it allows drugs to leave or enter, and Registry-based trials to identify eligible participants and collect data
- The protocol is modular (master protocol + MK Clinical trial part sub-document).
- Each trial can be a simple cancer-specific trial or a basket trial for a specific biomarker.

Traditional phase II design in oncology



Original Reports | Gastrointestinal Cancer

Trastuzumab Deruxtecan in Human Epidermal Growth Factor Receptor 2–Expressing Biliary Tract Cancer (HERB; NCCH1805): A Multicenter, Single-Arm, Phase II Trial

Akihiro Ohba, MD[1]; Chigusa Morizane, MD, PhD[1]; Yasuyuki Kawamoto, MD, PhD[2]; Yoshito Komatsu, MD, PhD[2]; Makoto Ueno, MD, PhD[3]; Satoshi Kobayashi, MD[3]; Masafumi Ikeda, MD, PhD[4]; Mitsuhito Sasaki, MD[4]; Junji Furuse, MD, PhD[4,5]; Naohiro Okano, MD, PhD[5]; Nobuyoshi Hiraoka, MD, PhD[6]; Hiroshi Yoshida, MD, PhD[6]; Aya Kuchiba, PhD[7]; Ryo Sadachi, PhD[7]; Kenichi Nakamura, MD, PhD, MBA[8]; Naoko Matsui, BS[8]; Yoshiaki Nakamura, MD, PhD[9]; Wataru Okamoto, MD, PhD[10]; Takayuki Yoshino, MD, PhD[9]; and Takuji Okusaka, MD, PhD[1]

DOI https://doi.org/10.1200/JCO.23.02010

ABSTRACT

PURPOSE Treatment options for patients with unresectable or recurrent biliary tract cancer (BTC) who progress on a gemcitabine-containing regimen are limited. In addition, the significance of anti–human epidermal growth factor receptor 2 (HER2) therapy in HER2-expressing BTC has not been sufficiently investigated.

METHODS In this phase II trial, participants from five institutions in Japan were enrolled. Eligible patients had pathologically confirmed unresectable or recurrent BTC with centrally confirmed HER2-positive (immunohistochemistry [IHC]3+ or IHC2+ and in situ hybridization [ISH]+) or HER2-low (IHC2+ and ISH−, IHC1+, and IHC0 and ISH+) and were refractory or intolerant to a gemcitabine-containing regimen. The patients received 5.4 mg/kg trastuzumab deruxtecan (T-DXd) once every 3 weeks until disease progression or unacceptable toxicity. The primary end point was the confirmed objective response rate (ORR) in HER2-positive BTC by an independent central review (threshold ORR, 15%; expected ORR, 40%).

RESULTS A total of 32 patients were enrolled and treated. Among these patients, 22 with HER2-positive disease comprised the primary efficacy population and had a confirmed ORR of 36.4% (90% CI, 19.6 to 56.1; $P = .01$), meeting the primary end point. Eight with HER2-low disease comprised the exploratory population and had a confirmed ORR of 12.5%. The most common ≥grade 3 treatment-related adverse events were anemia (53.1%) and neutropenia (31.3%). Eight patients (25.0%) had interstitial lung disease (ILD), including two grade 5 events.

CONCLUSION T-DXd showed promising activity in patients with HER2-positive BTC and a signal of efficacy in patients with HER2-low BTC. Although the safety profile was generally manageable, ILD requires careful monitoring and early intervention.

ACCOMPANYING CONTENT

Oncology Grand Rounds, p. 3170

Appendix

Data Sharing Statement

Protocol

Accepted April 17, 2024
Published August 5, 2024

J Clin Oncol 42:3207-3217

View Online Article

- Primary endpoint : ORR
- A typical single arm, single stage phase II
  - Frequentist approach
- Required sample size of 22 patients
  - Considering two ineligible patients, 24 patients are planned to enroll
  - Minimum number of patients with response of 7
  - Threshold ORR = 15%, Expected ORR = 40%
  - One-sided alpha = 5%, power = 80%
- Result: ORR was 36.4% (90% CI, 19.6-56.1, p=0.01)

- This is a typical single-arm phase 2 trials in cancer based on frequentist approach.
- Simple and straightforward.
- Good if this design is feasible, but other more efficient methods including Bayesian method may be preferred for rare cancers that is difficult to enroll subjects

Regulatory issues to use Bayesian approach in Japan

- **Specifications of prior information**
  - The final decision strongly depends on the pre-specified decision thresholds and the prior distribution assumed for the response rate (the primary endpoint).
  - A non-informative prior may be a reasonable choice when reliable prior information is unavailable
- **Thereshold for detecting therapeutic effect and target posterior probability of the exceeding the threshold**
  - Those a threshold is often based on historical data on the therapeutic effect of the standard treatment or placebo effect
  - Generally, target posterior probability value to conclude the treatment is promising is $\geq$ 90%
- **Evaluation of operating characteristics**
  - Clinical trial simulation studies are needed to investigate the trade-off relationship between type I and II error rates and the sample size of the Bayesian design under various scenarios

- Bayesian approach is useful in some cases of registration trials with a limited sample size, however, those issues should be discussed before trial initiation

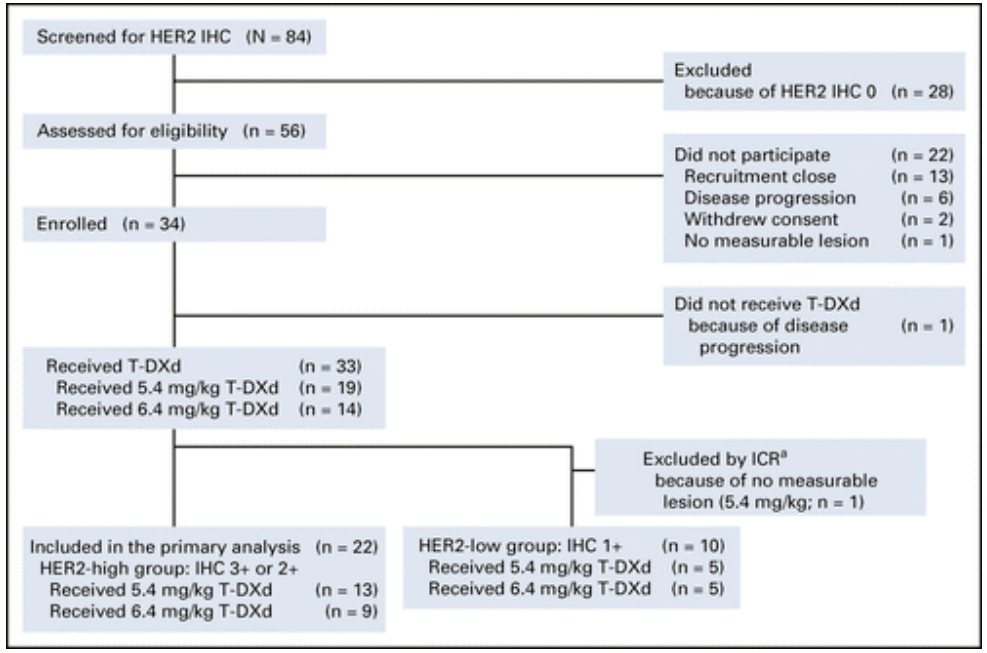
Hirakawa A, Sato H, Igeta M, Fujikawa K, Daimon T, Teramukai S. Regulatory issues and the potential use of Bayesian approaches for early drug approval systems in Japan. Pharmaceutical Statistics. 2022; 21(3): 691-695.

NCCH1615/STATICE trial

original reports

Trastuzumab Deruxtecan for Human Epidermal Growth Factor Receptor 2–Expressing Advanced or Recurrent Uterine Carcinosarcoma (NCCH1615): The STATICE Trial

Tadaaki Nishikawa, MD, PhD[1]; Kosei Hasegawa, MD, PhD[2]; Koji Matsumoto, MD[3]; Masahiko Mori, MD, PhD[4]; Yasuyuki Hirashima, MD, PhD[5]; Kazuhiro Takehara, MD, PhD[6]; Kazuya Ariyoshi, MD, PhD[7]; Tomoyasu Kato, MD, PhD[8]; Shigehiro Yagishita, MD, PhD[9]; Akinobu Hamada, PhD[9]; Mamiko Kawasaki, MS[10]; Satoshi Kawashima, PhD[10]; Sawako Tomatsuri, MS[10]; Yukari Nagasaka, BS[10]; Hiroshi Yoshida, MD, PhD[11]; Ryunosuke Machida, ME[12]; Akihiro Hirakawa, PhD[13]; Kenichi Nakamura, MD, PhD[10]; and Kan Yonemori, MD, PhD[1]



- **Primary endpoint**: Objective Response rates (ORR) at central review in the HER2-high group
- **Design**: Bayesian design (Thall & Simon)
  - Threshold ORR:5%
    - Prior distribution: Beta (10, 190)
  - Expected ORR :30%
    - Prior distribution: Beta (0.6, 1.4)
  - Target posterior probability of the exceeding the threshold ORR: >95%
- **Sample size**: 15-25 patients
  - If 15 patients are enrolled, efficacy analysis is performed

Required number of patients to exceed threshold											
Number of doses analyzed	15	16	17	18	19	20	21	22	23	24	25
Required number of responders	3	3	3	3	3	3	3	4	4	4	4

Results: ORRs at central review in the HER2-high group 54.5% (12/22)

Nishikawa T, et al., J Clin Oncol. 2023 May 20;41(15):2789-2799.

NCCH1709/ROCK trial (Basket trial)

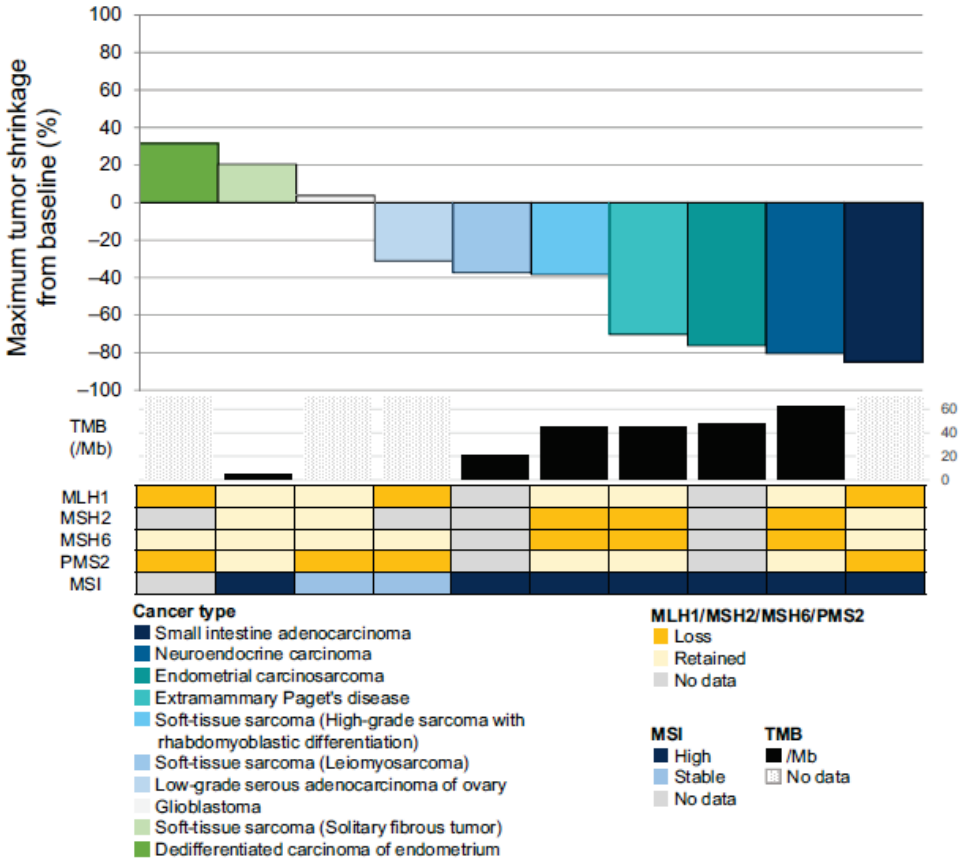
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Phase II Trial of Nivolumab in Metastatic Rare Cancer with dMMR or MSI-H and Relation with Immune Phenotypic Analysis (the ROCK Trial)

Hitomi S. Okuma[1,2], Keisuke Watanabe[3], Kenji Tsuchihashi[4], Ryunosuke Machida[2], Ryo Sadachi[2], Akihiro Hirakawa[5], Hiroshi Ariyama[4], Masashi Kanai[6], Masahisa Kamikura[2], Kenta Anjo[2], Akari Hiramitsu[2], Shigeki Sekine[7], Natsuko Okita[2], Hiroyuki Mano[8], Hiroyoshi Nishikawa[9], Kenichi Nakamura[2], and Kan Yonemori[1]

- **Primary endpoint**: ORR at central review
- **Design**: Bayesian design (Thall & Simon)
  - Threshold ORR:5%
    - Prior distribution: Beta (10, 190)
  - Expected ORR :30%
    - Prior distribution: Beta (0.6, 1.4)
  - Target posterior probability of the exceeding the threshold ORR: >95%
- **Sample size**: 5-15 patients
  - ≥2 responders are needed in 5 to 11 patients
  - ≥3 responders are needed in 12 to 15 patients

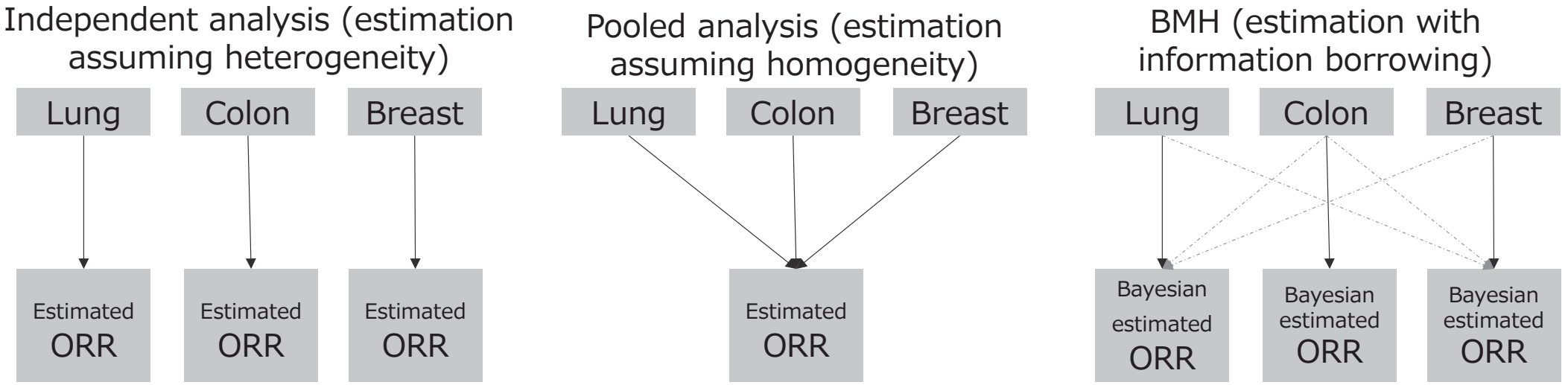
Results: ORRs at central review was 60% (6/10)



Clin Cancer Res (2023) 29 (24): 5079–5086.

More complex design for Basket trial

- **Bayesian hierarchical model (BMH)**
  - BMH estimates the ORR of different cohorts by borrowing information across cohorts using a pooled ORR and the observed variance between the different cohorts
  - Cancer types with small sample sizes may be benefit from information borrowed from others.



- https://www.cda-amc.ca/sites/default/files/hta-he/MH0020-Bayesian-Hierarchical-Models.pdf
- Hirakawa A, Master protocol trials:A novel strategy for streamlining drug development, DIA Japan 2021

HERALD/EPOC1806 trial

Original Reports | Translational Oncology

Trastuzumab Deruxtecan in Advanced Solid Tumors With Human Epidermal Growth Factor Receptor 2 Amplification Identified by Plasma Cell-Free DNA Testing: A Multicenter, Single-Arm, Phase II Basket Trial

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DOI https://doi.org/10.1200/JCO.23.02626

ABSTRACT

PURPOSE HERALD/EPOC1806 was conducted as a multicenter phase II trial assessing trastuzumab deruxtecan (T-DXd) therapy for patients with human epidermal growth factor receptor 2 (*HER2*)–amplified progressive stage solid tumors detected by cell-free DNA (cfDNA) testing.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Data Supplement

Table 2-4 Simulation scenarios (the figures in the table are ORR, and the figures in bold are when the expected values were met)

	Esophagus	Pancreas	Urothelium	Uterine cervix	Uterine body	Ovaries	Salivary glands	Head and neck	Other
Scenario 1	0.05	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**
Scenario 2	**0.25**	**0.25**	**0.25**	0.05	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**
Scenario 3	**0.25**	0.05	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**
Scenario 4	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	0.05	**0.25**	**0.25**
Scenario 5	**0.25**	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Scenario 6	0.05	0.05	0.05	**0.25**	0.05	0.05	0.05	0.05	0.05
Scenario 7	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**	**0.25**
Scenario 8	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

Original settings

- **Primary endpoint**: Objective Response rates
- **Sample size**: 60 patients
  - Considering feasibility
  - Target sample size was defined in each cancer types (3～12 patients)
- **Design**: Bayesian design
  - Threshold ORR:5%
  - Expected ORR :25%
  - Simulation studies were done across various scenarios assuming the ORR in each cancer types

Table 2-5 Results of a total of 1,000 simulations [Type 1 error rates and power of detection (binomial test/Bayesian adaptive design)]

	Esophagus	Pancreas	Urothelium	Uterine cervix	Uterine body	Ovaries	Salivary glands	Head and neck	Other
Scenario 1									
Binomial	4.3%	44.3%	46.6%	30.4%	45.6%	45.0%	59.0%	45.7%	42.5%
Bayesian	10.0%	54.9%	56.7%	34.2%	57.0%	56.3%	67.2%	55.7%	57.4%
Scenario 5									
Binomial	66.4%	2.9%	4.3%	4.5%	3.6%	3.5%	4.9%	4.8%	3.0%
Bayesian	65.5%	4.3%	3.3%	2.8%	3.1%	4.2%	4.4%	4.9%	3.5%

Yagisawa M,et al., J Clin Oncol. 2024 Nov 10;42(32):3817-3825.

HERALD/EPOC1806 trial

- The primary analysis was changed to a single-stage binomial design (frequentist approach) because of slow accrual
  - One-sided alpha of 2.5%
  - Power of >90%
  - Threshold ORR of 5%
  - Expected ORR of 20%-25%

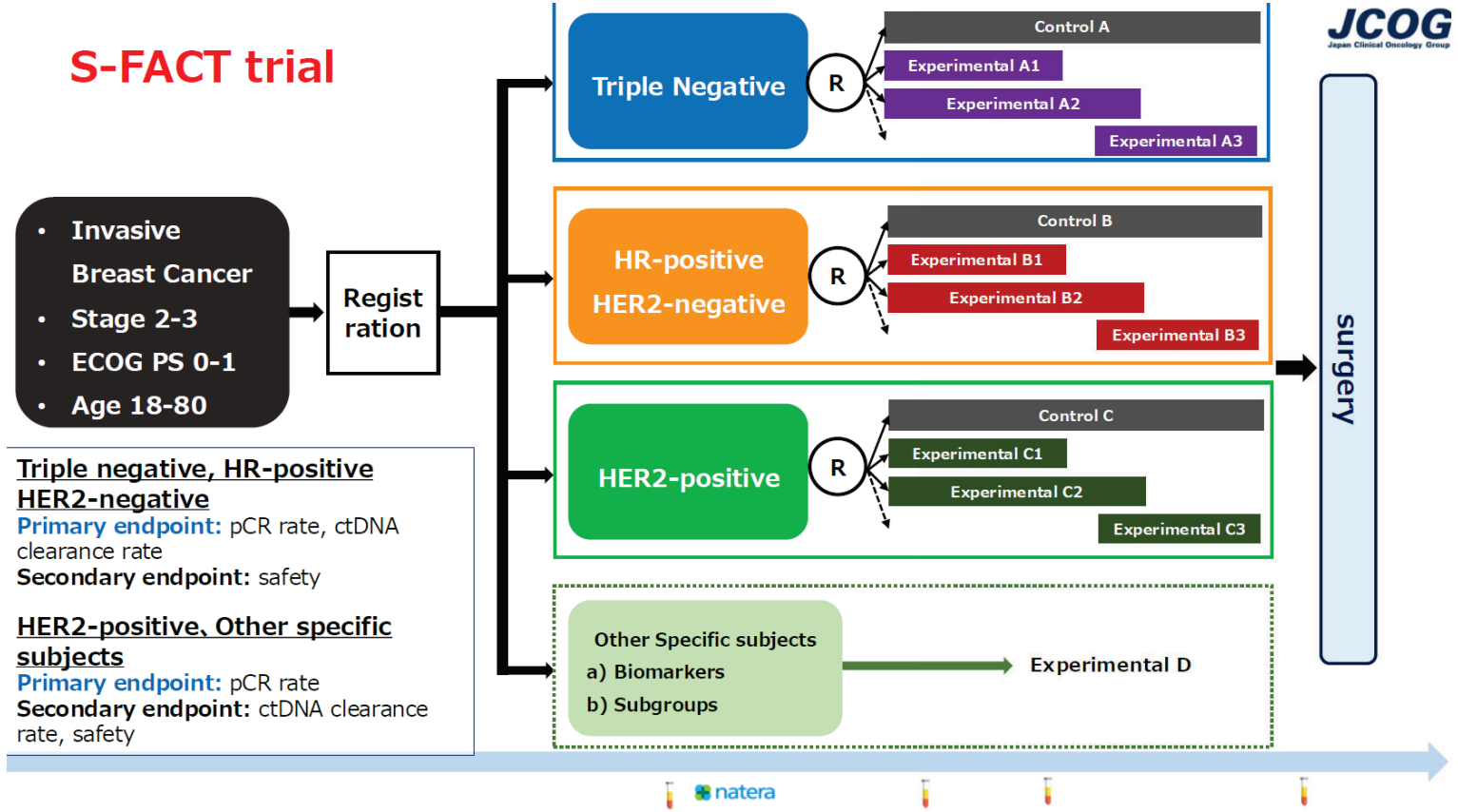
- Because the distribution of the number of enrollments for each cancer type differed significantly from expectations, the Bayesian analysis was abandoned.

TABLE A2. Tumor Response by Cancer Type

Cancer Type	ORR, No. (%)
Total	35/62 (56.5)
Esophageal (mostly SCC)	6/12 (50.0)
Colorectal	5/10 (50.0)
Salivary gland	7/7 (100.0)
Endometrial	5/6 (83.3)
Cervical	2/5 (40.0)
Biliary tract	1/4 (25.0)
Pancreatic	0/4 (0.0)
Ovarian	2/2 (100.0)
Small intestine	2/2 (100.0)
Urothelial	1/2 (50.0)
Gastric (tissue *HER2*-neg)	1/2 (50.0)
NSCLC	0/2 (0.0)
Melanoma	1/1 (100.0)
Paget's disease	1/1 (100.0)
Prostate	1/1 (100.0)
Unknown primary	0/1 (0.0)

Yagisawa M,et al., J Clin Oncol. 2024 Nov 10;42(32):3817-3825.

JCOG2205/S-FACT (MAMS/platform trial)



- Although not focused rare cancer, JCOG2205 is a MAMS type platform phase II trial to evaluate several experimental treatment compared with control arm
- Bayesian approach is used to judge whether the experimental treatment is effective or not.

Clinical trials identification number: jRCT2031240160

Registry data as a real-world reference

- **Single-arm clinical trial utilizing RWD as an external control**
  - External controls may be needed to provide context to efficacy and/or safety in a trial that is single-arm or becomes single-arm
  - It supports evidence to ensure the experimental drug is effective

- **Registry data is one of data sources for external comparison groups.**
  - Strengths
    - Pre-specified data collection, includes diverse patients and treatment settings
    - Good clinical detail regarding selected health outcomes
  - Limitations
    - Outcome measures may differ from trial, some covariates may not be available
    - Potential for selection bias, low level of reliability

- Although not perfect data, prospective registry data conducted at the same time as the relevant clinical trial may be used as an external control to ensure a certain level of quality.

Seeger JD, et al., Methods for external control groups for single arm trials or long-term uncontrolled extensions to randomized clinical trials. Pharmacoepidemiol Drug Saf. 2020 Nov;29(11):1382-1392

TRIUMPH(EPOC1602) trial with the SCRUM-Japan Registry

nature medicine

BRIEF COMMUNICATION

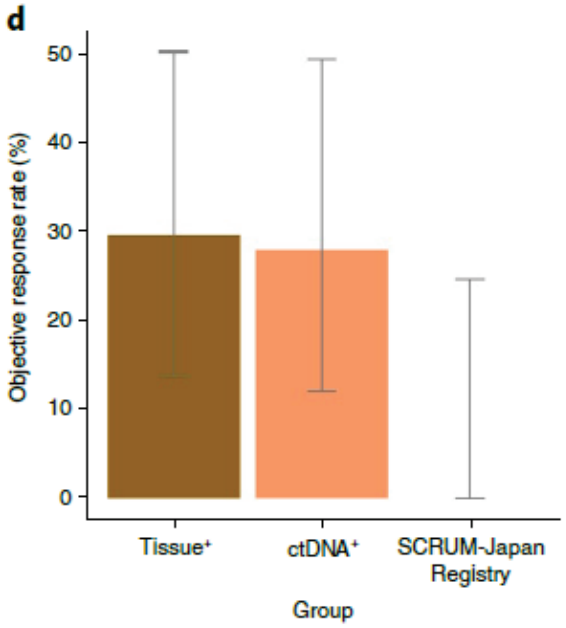
https://doi.org/10.1038/s41591-021-01553-w

Check for updates

OPEN

Circulating tumor DNA-guided treatment with pertuzumab plus trastuzumab for *HER2*-amplified metastatic colorectal cancer: a phase 2 trial

Yoshiaki Nakamura[1,2,19], Wataru Okamoto[1,2,3,19], Takeshi Kato[4], Taito Esaki[5], Ken Kato[6], Yoshito Komatsu[7], Satoshi Yuki[8], Toshiki Masuishi[9], Tomohiro Nishina[10], Hiromichi Ebi[11], Kentaro Sawada[1,12], Hiroya Taniguchi[1,2,9], Nozomu Fuse[13], Shogo Nomura[13], Makoto Fukui[13], Seiko Matsuda[13], Yasutoshi Sakamoto[2], Hiroshi Uchigata[2], Kana Kitajima[2], Naomi Kuramoto[2], Takashi Asakawa[14], Steve Olsen[15], Justin I. Odegaard[16], Akihiro Sato[13], Satoshi Fujii[17,18], Atsushi Ohtsu[1] and Takayuki Yoshino[1]✉



- HER2 amplification was confirmed in tissue and/or ctDNA in 30 patients with mCRC
- Primary endpoint: ORR
- Design: Frequent single-arm design (N=25)
  - Thereshold ORR : 5%
  - Expected ORR : 30%
  - One-sided Alpha of 5%, power of 90%
- RWD reference: the SCRUM-Japan Registry
  - a longitudinal observational study that generates regulatory-grade real-world data of patients with advanced solid tumors harboring rare alterations identified in the SCRUM-Japan project, including those with mCRC with HER2 amplification by HER2-Screening or GOZILA
- ORR of 0% in a matched real-world reference population of 13 patients treated with standard-of-care salvage therapy.

Nakamura Y, et al. Circulating tumor DNA-guided treatment with pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer: a phase 2 trial. Nat Med. 2021 Nov;27(11):1899-1903

Summary

- Innovative trial design including basket, umbrella, and platform trials enhance clinical trials for rare cancer

- Bayesian approach may be useful in a situation with limited sample size, but, careful considerations are required before initiation of the trial

- The use of platforms for clinical research, such as the academia-led Master Key project, SCRUM-Japan and multicenter cooperative study groups such as JCOG, is expected to promote research into rare cancers more efficiently.

Cancer
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ORIGINAL ARTICLE

Efficacy and safety of nivolumab monotherapy in patients with unresectable clear cell sarcoma and alveolar soft part sarcoma (OSCAR Trial/NCCH1510)

Tadaaki Nishikawa MD, PhD, Shigeki Kakunaga MD, PhD, Kenji Tamura MD, PhD, Masashi Ando MD, Toshifumi Ozaki MD, PhD, Akira Kawai MD, PhD, Takafumi Ueda MD, PhD ... See all authors

Planning and implementing Master Protocol Trials in Japan

Hirakawa A, Asakawa T, Tokushige K, Ozaki R, Yoshida M, Okuma HS, Saito S, Shimizu Y, Kitabayashi R, Hanazawa R, Sato H, Uemura Y. Planning and Implementing Master Protocol Trials in Japan: Key Considerations of the Japanese Guideline. Clin Pharmacol Ther. 2025 Mar;117(3):627-632