May 22, 2024
SCT Annual Meeting

Overview of Patient Engagement Activities in Japan

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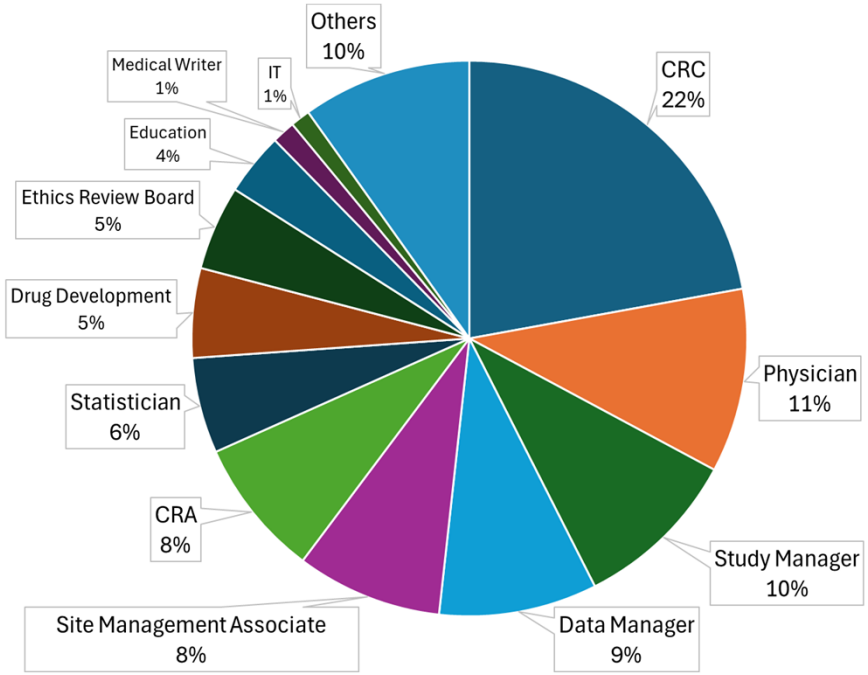
Japan Society of Clinical Trials & Research (JSCTR)

- A counterpart of SCT in Japan est. in 2009
  - Mission
    - Enhance the knowledge and skills of all professionals involved in clinical trials & research
    - Promote interdisciplinary information exchange and research activities
    - Contribute to the improvement of the quality of clinical trials and research in Japan



1,401 members
as of Dec 2023

Japan Society of Clinical Trials & Research (JSCTR)

- 14th JSCTR Annual Meeting @Osaka (Mar 2024)
  - >= 1,500 participants
  - Joint symposium with SCT
    - Revisit of the SCT Trial of the Year (CHAP trial)
    - Dr. Susan Halabi's lecture about the future of clinical trials

Examples of PE in Japan

- JCOG
  - Largest cancer clinical trial group in Japan
- AMED
  - Japanese public funding agency
- KISEKI trial
  - Patient-proposed registration-intended IIT

What is JCOG?

JCOG
Japan Clinical Oncology Group

- Japan Clinical Oncology Group
  - The largest cooperative group in Japan founded in 1990
  - Funded by National Cancer Center and the Ministry of Health, Labour and Welfare, Japanese government
  - Headquarter; National Cancer Center Hospital, Tokyo
- Mission
  - Develop better cancer treatment (late phase)
  - Key indicator is the number of clinical trials adopted in treatment guidelines
  - Phase III trials with multi-disciplinary treatment
- Activity
  - About 100 ongoing clinical trials
  - Yearly patient accrual; 3,000-4,000

History of PE in Japan/JCOG

JCOG
Japan Clinical Oncology Group

- Past unfortunate incidence
  - There was a clinical trial where a patient advocacy group criticized investigators intensely for a lack of evidence in a randomized treatment
    - RCT comparing CMF vs. UFT for breast cancer patients
    - UFT did not have solid evidence but was widely used in clinical practice
- JCOG Annual Meeting in 2015
  - The meeting theme was ‘Collaboration between JCOG and Patient Groups’
  - Two patient group representatives gave lectures
  - Agreement was reached on promoting PE within JCOG
    - Some JCOG researchers who know about the past conflict seemed somewhat worried
- The relationship has been gradually improved by…
  - Establishing the committee with patient representatives
  - Starting roundtable meetings with patient group in each JCOG disease-group
  - Holding a JCOG Patient Engagement Seminar

Patient engagement in the revised ICH-GCP (1)

- ICH-E6(R3) draft guidance
  - 3.1.3. Sponsors should consider inputs from a wide variety of stakeholders, for example, healthcare professionals and patients, to support the development plan and clinical trial protocols as described in ICH E8(R1) and when developing the informed consent material and any other participant-facing information.

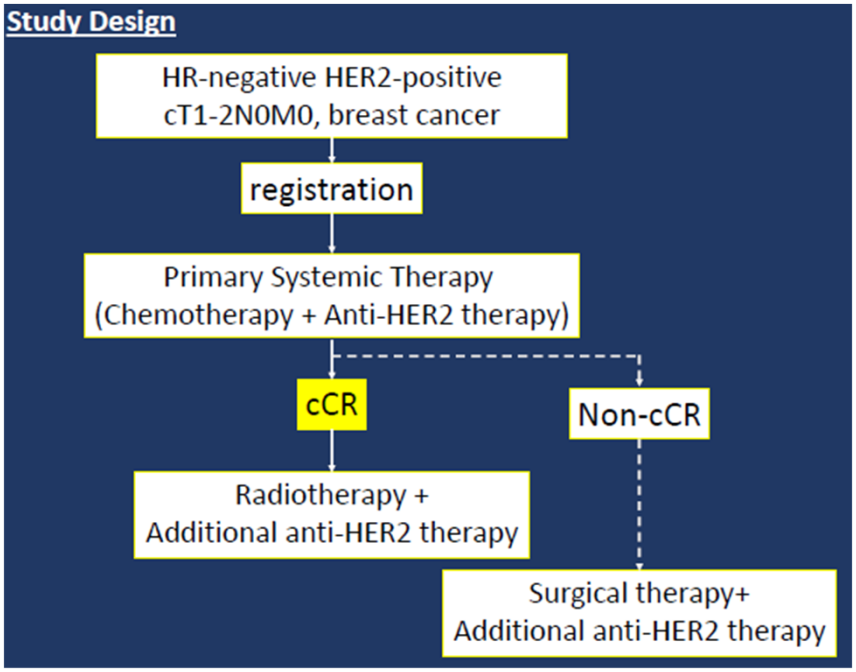
Why we need inputs from patients?

✓ Investigators don't know much about patients

✓ Understanding patient needs will lead to a good clinical question

Example: What is true patient needs?

- Discussion about study design with patient advocates
  - JCOG1806
    - Single-arm confirmatory study to evaluate the efficacy of nonsurgical therapy for HER2-positive early breast cancer with cCR after primary systemic therapy



HR(-) HER2(+) Breast Cancer
Current standard treatment after cCR after primary systemic therapy is breast resection

Hypothesis: Surgery can be omitted if we can confirm that recurrence will rarely occur in the clinical trial

✓ Patient's voice "The hardest thing wasn't the surgery, but the 5-10 years of hormone therapy that follows. Can't we have a trial to shorten this?"

Example: Priority of treatment development

- from the case of JCOG Patient Engagement Seminar

- Planning a Clinical Trial for a New Treatment for Cancer X
  - 5-year survival with the standard treatment is 60%
  - With the standard treatment, 15% of patients experience diarrhea more than 5 times a day, 10% suffer from oral mucositis that prevents eating, and 10% experience numbness and pain in their hands and feet
  - The treatment cost is 2,000 USD per month

- If only one new treatment can be tested in a clinical trial, which treatment should be prioritized?
  - A) A treatment that improves the 5-year survival to 75%
  - B) A treatment that reduces the frequency of side effects by half
  - C) A treatment that reduces the treatment costs by half

✓ Almost all investigators chose (A) efficacy
✓ Almost all patients/citizens chose (B) safety

Johari Window

- Framework designed to help people better understand their relationship with themselves and others

	Known to self	Not known to self
Known to others	**Open** ✓ Enables smooth communication with others	**Blind** ✓ Helps you understand strengths you didn't notice yourself
Not known to others	**Hidden** ✓ Reduces misunderstandings and makes it easier to gain trust and cooperation	**Unknown** ✓ Provides tips for growth and skill development

✓ The key to improving interpersonal relationships is to expand the Window of Openness

Johari Window in PE

- The key is to expand the Window of Openness

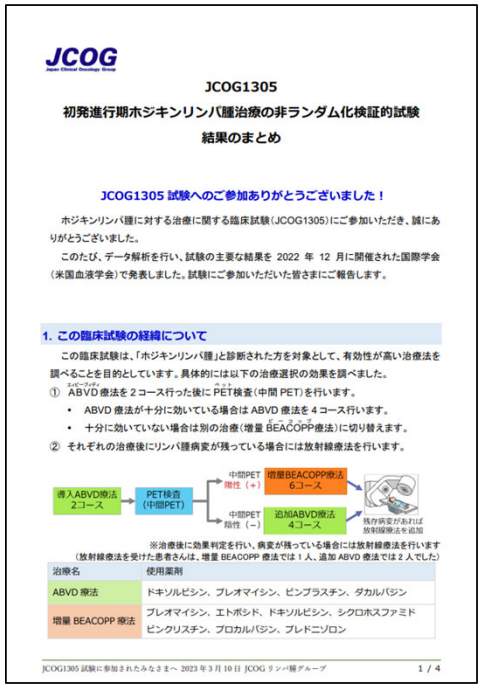
	Known to **Investigators**	Not known to **Investigators**
Known to **Patients**	**Open**	**Blind** ✓ Understand patient needs that investigators might not notice
Not known to **Patients**	**Hidden** ✓ Deepen understandings of clinical research through dialogue and communication	**Unknown** ✓ Uncover hidden true needs through conversations

✓ The goal is to create better research ideas through collaboration between investigators and patients

Patient engagement in the revised ICH-GCP (2)

- ICH-E6(R3) draft guidance
  - 2.9.3. Where relevant, the investigator should inform the participant about the trial results and treatment received when this information is available from the sponsor after unblinding, with due respect to the participant's preference to be informed
  - 3.17.2. Consideration should be given to providing the investigator with information about the final treatment taken by their participants for blinded trials and a brief summary of the overall outcome of the trial. Where this information is provided to participants, the language should be non-technical, understandable to a layperson and non-promotional.

Lay summaries in JCOG



JCOG

JCOG1305

初発進行期ホジキンリンパ腫治療の非ランダム化検証的試験

結果のまとめ

JCOG1305 試験へのご参加ありがとうございました！

ホジキンリンパ腫に対する治療に関する臨床試験（JCOG1305）にご参加いただき、誠にありがとうございました。

このたび、データ解析を行い、試験の主要な結果を 2022 年 12 月に開催された国際学会（米国血液学会）で発表しました。試験にご参加いただいた皆さまにご報告します。

1. この臨床試験の経緯について

この臨床試験は、「ホジキンリンパ腫」と診断された方を対象として、有効性が高い治療法を調べることを目的としています。具体的には以下の治療選択の効果を調べました。

① ABVD 療法を 2 コース行った後に PET 検査（中間 PET）を行います。

- ABVD 療法が十分に効いている場合は ABVD 療法を 4 コース行います。
- 十分に効いていない場合は別の治療（増量 BEACOPP 療法）に切り替えます。

② それぞれの治療後にリンパ腫病変が残っている場合には放射線療法を行います。

※治療後に効果判定を行い、病変が残っている場合には放射線療法を行います
（放射線療法を受けた患者さんは、増量 BEACOPP 療法では 1 人、追加 ABVD 療法では 2 人でした）

治療名	使用薬剤
ABVD 療法	ドキソルビシン、ブレオマイシン、ビンブラスチン、ダカルバジン
増量 BEACOPP 療法	ブレオマイシン、エトポシド、ドキソルビシン、シクロホスファミド ビンクリスチン、プロカルバジン、プレドニゾロン

2. 結果について

2022 年 6 月のデータ解析では、2015 年 11 月 20 日から 2020 年 2 月 1 日に登録された 93 人の患者さんを対象として解析しました。

解析(1)すべての登録患者さんを対象として集計する 2 年無増悪生存割合※

解析(2)中間 PET が陽性の患者さんを対象として集計する 2 年無増悪生存割合※

※2 年無増悪生存割合（登録から 2 年後に病気が悪化することなく生存している人の割合）

すべての登録患者さんを対象として集計した 2 年無増悪生存割合が 75%を上回ること、中間 PET が陽性の患者さんを対象として集計した 2 年無増悪生存割合が 35%を上回ることを調べる設定で、105 人の患者さんの登録を目標としました。

主な結果（1）無増悪生存割合 すべての患者さん（92人）

2年無増悪生存割合	84.8%
80% 信頼区間	79.2-88.9
95% 信頼区間	75.7-90.7

主な結果（2）無増悪生存割合 中間PET陽性患者さん（19人）

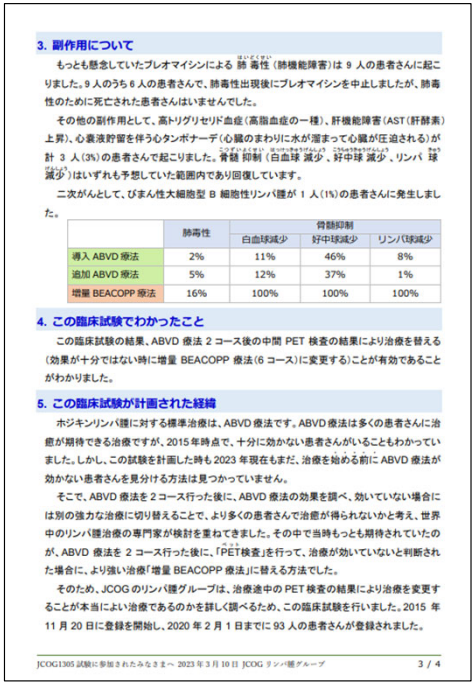
2年無増悪生存割合	84.2%
80% 信頼区間	69.7-92.1
95% 信頼区間	58.7-94.6

主な結果（1）登録患者さん全体の 2 年無増悪生存割合が 75%を上回りました

解析の結果「すべての登録患者さんを対象として集計した 2 年無増悪生存割合が 75%を上回る」が満たされ、**「ABVD 療法 2 コース後の中間 PET 検査の結果、効果が十分でない場合に強い治療に切り替える」という治療が有効である**ことが示されました。

主な結果（2）中間 PET 検査陽性患者さんの 2 年無増悪生存割合が 35%を上回りました

解析の結果、「中間 PET 検査が陽性であった患者さんを対象として集計した 2 年無増悪生存割合が 35%を上回る」が満たされ、**「中間 PET 検査の結果、効果が十分でない時に行う増量 BEACOPP 療法」も有効である**ことが示されました。



3. 副作用について

もっとも懸念していたブレオマイシンによる肺毒性（肺機能障害）は 9 人の患者さんに起こりました。9 人のうち 6 人の患者さんで、肺毒性出現後にブレオマイシンを中止しましたが、肺毒性のために死亡された患者さんはいませんでした。

その他の副作用として、高トリグリセリド血症（高脂血症の一種）、肝機能障害（AST（肝酵素）上昇）、心嚢液貯留を伴う心タンポナーデ（心臓のまわりに水が溜まって心臓が圧迫される）が計 3 人（3%）の患者さんで起こりました。骨髄抑制（白血球減少、好中球減少、リンパ球減少）はいずれも予想していた範囲内であり回復しています。

二次がんとして、びまん性大細胞型 B 細胞性リンパ腫が 1 人（1%）の患者さんに発生しました。

	肺毒性	骨髄抑制		
		白血球減少	好中球減少	リンパ球減少
導入 ABVD 療法	2%	11%	46%	8%
追加 ABVD 療法	5%	12%	37%	1%
増量 BEACOPP 療法	16%	100%	100%	100%

4. この臨床試験でわかったこと

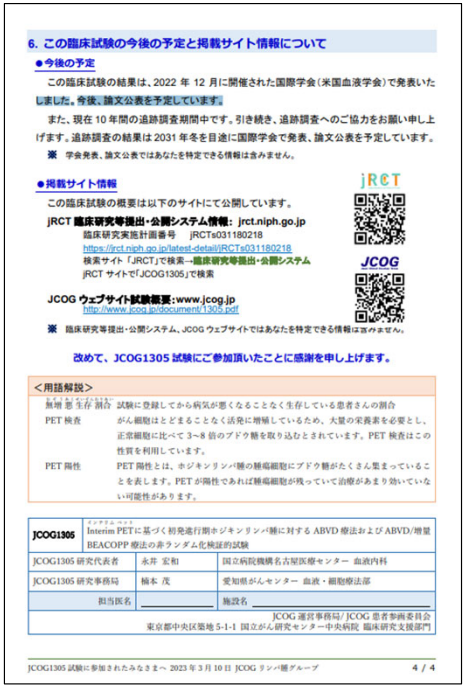
この臨床試験の結果、ABVD 療法 2 コース後の中間 PET 検査の結果により治療を替える（効果が十分ではない時に増量 BEACOPP 療法（6 コース）に変更する）ことが有効であることがわかりました。

5. この臨床試験が計画された経緯

ホジキンリンパ腫に対する標準治療は、ABVD 療法です。ABVD 療法は多くの患者さんに治癒が期待できる治療ですが、2015 年時点で、十分に効かない患者さんがいることもわかっていました。しかし、この試験を計画した時も 2023 年現在もまだ、治療を始める前に ABVD 療法が効かない患者さんを見分ける方法は見つかっていません。

そこで、ABVD 療法を 2 コース行った後に、ABVD 療法の効果を調べ、効いていない場合には別の強力な治療に切り替えることで、より多くの患者さんで治癒が得られないかと考え、世界中のリンパ腫治療の専門家が検討を重ねてきました。その中で当時もっとも期待されていたのが、ABVD 療法を 2 コース行った後に、「PET 検査」を行って、治療が効いていないと判断された場合に、より強い治療「増量 BEACOPP 療法」に替える方法でした。

そのため、JCOG のリンパ腫グループは、治療途中の PET 検査の結果により治療を変更することが本当によい治療であるのかを詳しく調べるため、この臨床試験を行いました。2015 年 11 月 20 日に登録を開始し、2020 年 2 月 1 日までに 93 人の患者さんが登録されました。



6. この臨床試験の今後の予定と掲載サイト情報について

● 今後の予定

この臨床試験の結果は、2022 年 12 月に開催された国際学会（米国血液学会）で発表いたしました。今後、論文公表を予定しています。

また、現在 10 年間の追跡調査期間中です。引き続き、追跡調査へのご協力をお願い申し上げます。追跡調査の結果は 2031 年冬を目途に国際学会で発表、論文公表を予定しています。

※ 学会発表、論文公表ではあなたを特定できる情報は含みません。

● 掲載サイト情報

この臨床試験の概要は以下のサイトにて公開しています。

jRCT 臨床研究等提出・公開システム情報：jrct.niph.go.jp
臨床研究実施計画番号 jRCTs031180218
https://jrct.niph.go.jp/latest-detail/jRCTs031180218
検索サイト「jRCT」で検索→臨床研究等提出・公開システム
jRCT サイトで「JCOG1305」で検索

JCOG ウェブサイト試験概要：www.jcog.jp
http://www.jcog.jp/document/1305.pdf

※ 臨床研究等提出・公開システム、JCOG ウェブサイトではあなたを特定できる情報は含みません。

改めて、JCOG1305 試験にご参加頂いたことに感謝を申し上げます。

＜用語解説＞

無増悪生存割合 試験に登録してから病気が悪くなることなく生存している患者さんの割合

PET 検査 がん細胞はとどまることなく活発に増殖しているため、大量の栄養素を必要とし、正常細胞に比べて 3~8 倍のブドウ糖を取り込むとされています。PET 検査はこの性質を利用しています。

PET 陽性 PET 陽性とは、ホジキンリンパ腫の腫瘍細胞にブドウ糖がたくさん集まっていることを表します。PET が陽性であれば腫瘍細胞が残っていて治療があまり効いていない可能性があります。

JCOG1305	Interim PET に基づく初発進行期ホジキンリンパ腫に対する ABVD 療法および ABVD/増量 BEACOPP 療法の非ランダム化検証的試験	
JCOG1305 研究代表者	永井 宏和	国立病院機構名古屋医療センター 血液内科
JCOG1305 研究事務局	楠本 茂	愛知県がんセンター 血液・細胞療法部
担当医名		施設名

JCOG 運営事務局/ JCOG 患者参画委員会
東京都中央区築地 5-1-1 国立がん研究センター中央病院 臨床研究支援部門

- ✓ JCOG has published easy-to-understand summaries of trial results for patients in 10 trials
- ✓ Patient members helped us in making these summaries
- ✓ JCOG plans to systematically create lay summaries for all trials that have results

https://jcog.jp/topic/general/jcog1305.html

Various collaboration with Patient Group

- Joint request for rare cancers/fractions for the Japanese government led to de-regulation
  - Previously it was mandate to apply for Companion Diagnostic (CDx) when we make a regulatory application of targeted drugs
  - Through the de-regulation, it has become acceptable to use cancer genome profiling tests as a temporally diagnostic of targeted drugs

- Joint events
  - Rare Cancer Community Day
  - Patients, healthcare professionals, families, industries, and government officials all had the same yellow T-shirt for the event

Difficulties of PE in Japan

- Difficulties of PE
  - Paternalism has existed historically
  - Sometimes it is difficult to take enough time for dialogue during outpatient visits
  - Patient groups are smaller with shorter history

- Understanding patient needs is not easy
  - Active dialogue in JCOG has only started in the past five years, and the relationship has been gradually improving
  - The KISEKI trial is a remarkable success as a patient-proposed trial, that not only listened to patients' voices but also turned them into an actual clinical trial

Examples of PE in Japan

- JCOG
  - Largest cancer clinical trial group in Japan
- AMED
  - Japanese public funding agency
- KISEKI trial
  - Patient-proposed registration-intended IIT

45th SCT Annual Meeting

Session "Empowering Patient-Investigator-Industry Collaborations: The KISEKI Trial Story and Patient engagement in Japan and beyond."

Japan Agency for Medial Research and Development support the Sustainable Development Goals

Importance and Challenges of Patient Engagement in Japan

From Funding Agency's Perspective

Japan Agency for Medical Research and Development (AMED)

Keiko KATSUI PhD

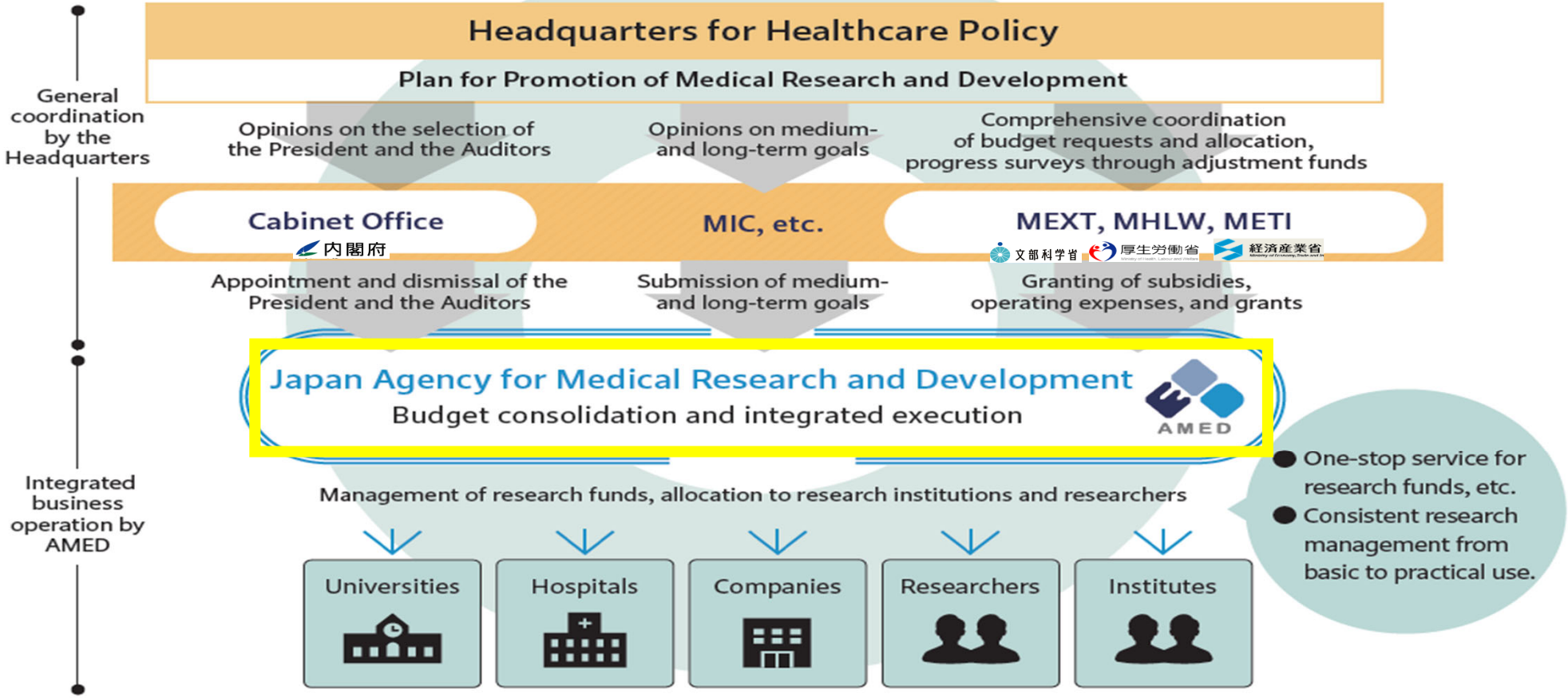
keiko-katsui@amed.go.jp

There are no entities or relationships, etc. presenting a potential conflict of interest requiring disclosure in relation to this presentation.

established in 2015

Implementation of the Healthcare Policy and the role of AMED

Japan Agency for Medical Research and Development (AMED) is a funding agency tasked with promoting medical R&D and improving the environment for research in Japan under the government's Healthcare Policy.

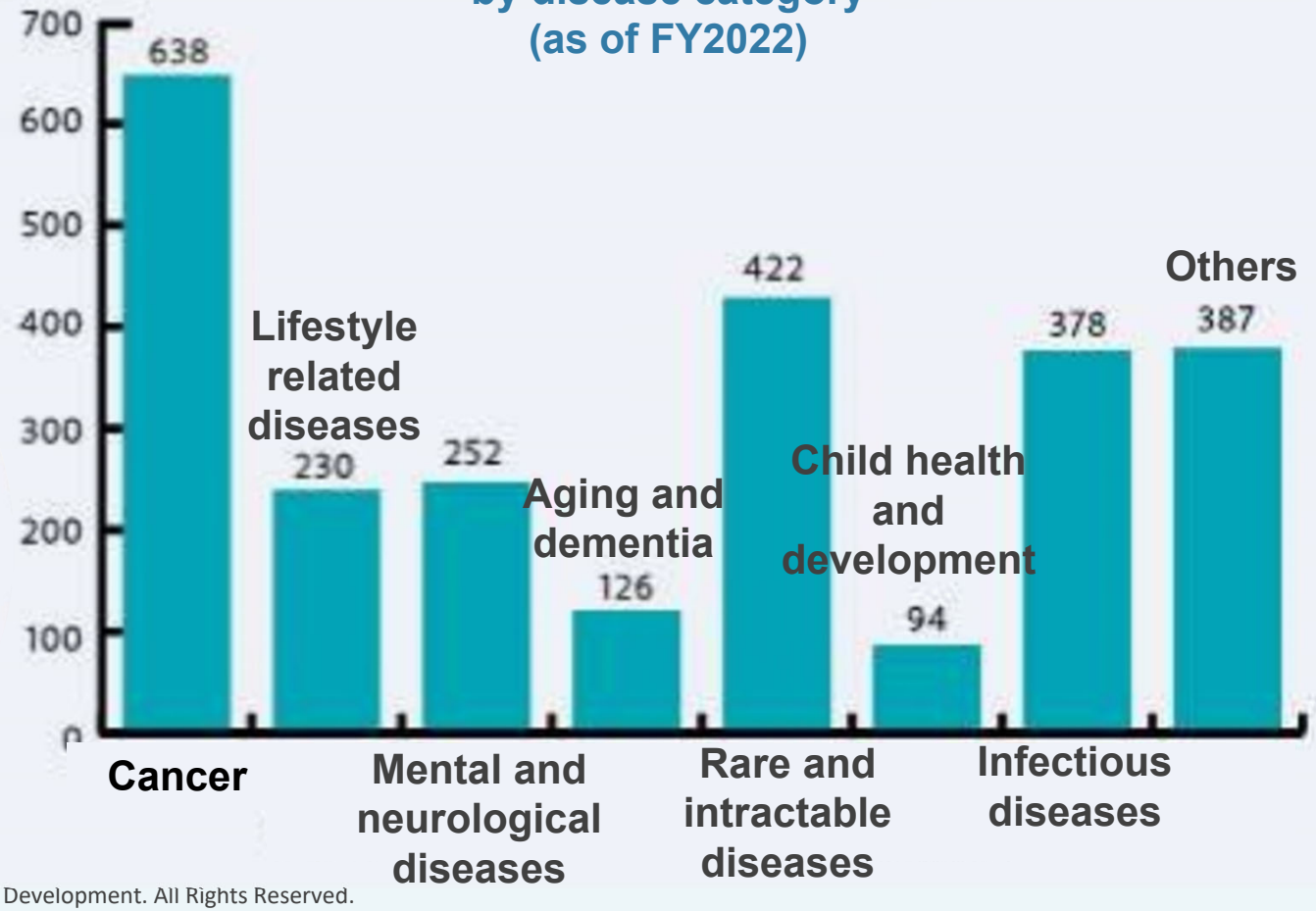


Status of AMED funding : disease/institutional category of projects

FY2022
AMED supported
2,527
R&D projects
from basic research
to practical
applications.

R&D projects

by disease category
(as of FY2022)



Before AMED-PPI was established……

- AMED Research group of Ethical, Legal and Social Issues on Regenerative medicine
- Dialogues between stem cell researchers and potential participants to input their ideas to research designs

Achievements

- 2013.10 Japanese Retinitis Pigmentosa Society meets Dr. Masayo Takahashi
- 2014.5 Steven's Johnson Syndrome Society meets Dr. Koji Nishida
- 2016.11 Urea Cycle Disorders Society meets Dr. Shin Enosawa
- 2018.11 Japanese Retinitis Pigmentosa Society will meet Dr. Masayo Takahashi (2nd round)

History of AMED-PPI

The Plan for Promotion of Medical Research and Development

(approved by the Headquarters for Healthcare Policy on July 22, 2014; partially amended on February 17, 2017)

- In conducting clinical research and trials, from the phase of planning, **it is necessary to promote the involvement of test subjects and patients**, as well as actively promoting activities to raise awareness among patients and the public as a whole regarding the significance of clinical research and trials, as well as the benefits they bring to citizens

➡ AMED conducted a survey on Patient and Public Involvement (PPI) in medical research and clinical trials.

The 3rd Basic Plan to Promote Cancer Control Programs (October 2017)

- "In FY2018, **AMED takes on new initiatives to accelerate cancer patients and survivors involvement, in order to let them join in the process of research designs and evaluations**."
- "The government launches new programs to train patients and survivors who join PPI activities."

Basic Concept of “AMED-PPI”

https://www.amed.go.jp/content/000097557.pdf

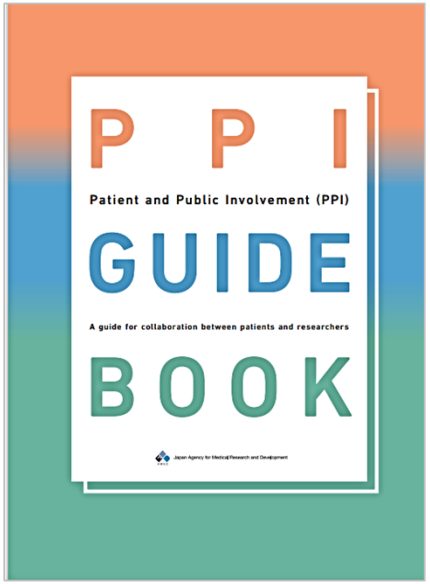
Definition

AMED envisions a form of PPI in which researchers refer to the knowledge of patients and the public in the medical research and clinical trial processes

- ***Patient and the Public are defined as patients, their families, former patients (survivors) and future patients.***

Principles：“AMED-PPI” will realize……

- **Produce research outcomes that are more useful for patients and the public**
- **Promote smooth implementation of medical research and clinical trials**
- **Contribute human subject protection (reduce risk)**



AMED PPI guidebook
(published in 2019)

available in English

Significance for Researchers

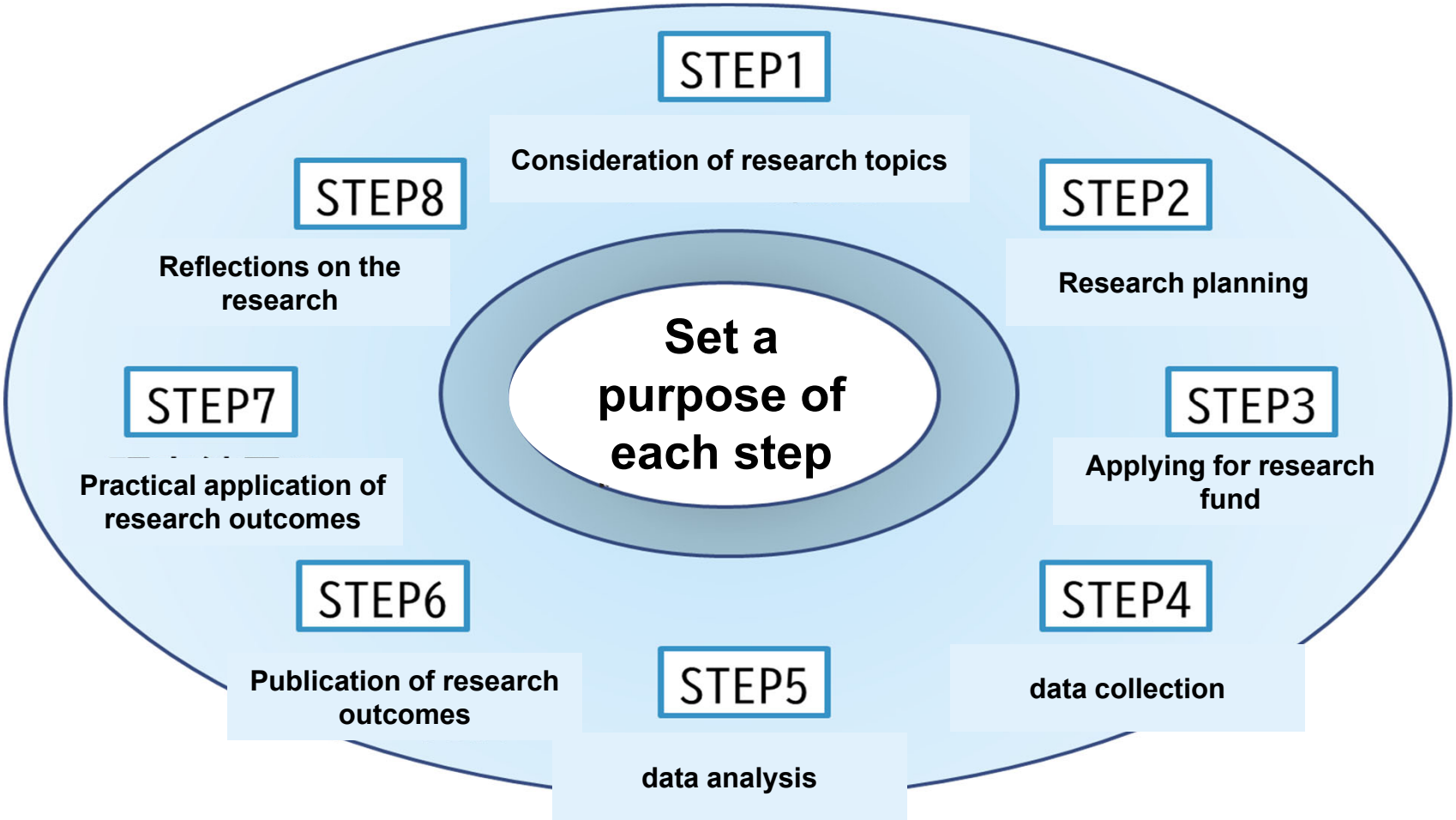
- **Give new perspectives and value for further advancement of R&D**
- **Address patient anxiety and concerns, and facilitate understanding of medical research and clinical trials**

Significance for Patients and the Public

- **Improve the convenience and understanding of medical research and clinical trial for research participants**
- **Make medical research and clinical trials more accessible to patients and the public and increase their interest in healthcare**

8 steps in the research for PPI

At each steps, researchers can have opportunities to try PPI activities：



PPI description on research proposal form

75% of AMED projects require researcher to describe their PPI activity plans on grant call

As it is an important perspective in medical research and development, it is required to be mentioned in the research and development proposals of AMED projects. Unless conditions are attached as special notes in the call for applications, they have no effect on the acceptance or rejection of the application. The information provided will be used to analyze research trends that will contribute to the future management of AMED projects, and the results of the analysis may be made public in a form that does not identify the research and development tasks.

(1) 【optional】 explain your plans to refer to experience and/or knowledge of patient and the public as part of your medical research / clinical trial process

PPI description by researcher : good examples

- Our research group will **consider the opinions of patients and their families** on cancer through dialogue with patient groups **when we develop our protocols for cancer prediction studies**.
- In 20XX, our research group conducted group work entitled 'Cooperation between medicine and society to conquer disease X' with the public, and discussed social and ethical aspects of pre-onset diagnosis and treatment about disease X.
- Our research group will **ask patients who meet the study criteria to monitor to create audio material as explanatory aids**
- Our research group have been conducting **needs assessments for our medical device in collaboration with patient groups** for 10 years

Examples of incorrect description:

- ✗ **Recruit of research participants**
- ✗ **Report research outcomes to the Public**
- ✗ **Conversations during medical consultation**

For promotion of researcher's PPI activities

Challenges: AMED needs to ・・・・・・

✓ provide PPI educational opportunities and training for researchers

- Raising awareness of the importance of PPI activity to improve medical R&D process
- Supporting PPI activities by reseachers who are not in the medical profession
- Collecting good PPI practices in each disease area (e.g. mental diseases)

✓ consider of the PPI facilitator as a medical R&D profession

(voice from patient)

- *"we need to meet facilitator who flatly supports patients to deepen their discussions"*
- *"Professionals are needed to match researchers with patients, to understand the issues on both sides and to support communication"*

✓ communicate the progress and outcomes of medical R&D to society through interactive communication

(voice from patient)

- *"I would like to see more dialogue-oriented roundtable discussions rather than one-way presentation."*
- *"I would like to see opportunities for researchers and patients to talk more easily."*

The idea of “Social Co-creation”（社会共創）in AMED

AMED’s mission is to ensure that the outcomes of medical research and development are applied and delivered to patients and their families as soon as possible.

also, through dialogue and collaboration with society, we need to……

- \+ **Fulfil the real needs of society to produce research outcomes that are more useful for patients**
- \+ **Ensure the safety and security of medical R&D to the public**
- \+ **Gain public understanding and trust in medical R&D**

AMED
“Social Co-creation”

Medical R&D with Society

Medical R&D for Future (Society)

AMED Social Co-creation Exhibition（AMED社会共創EXPO）

- AMED Social Co-creation Exhibition has started in FY2022 as a forum where **patients / public, researchers, pharmaceutical companies, AMED can meet and engage in 'dialogue' on a variety of topics**.
  - How to conceive of 'manufacturing' in the future of healthcare?
  - Will AI change our healthcare and life?
- To set this exhibition, **AMED sets up an executive committee, which is consisted of leaders of patient groups (cancer / rare disease) and various experts on medical R&D**

FY2022

FY2023

President of AMED

[redacted]
11分 ・

(From Leader of Patient Group)

Today I attended the AMED Co-creation EXPO. It was a stimulating day of interactive communication. ……

I'm always asked about my fears and difficulties about being ill at PPI activities. But, in this EXPO, researchers, patients and the public share their strengths and joys through open-dialogue, and try to collaborate each other for future medicine. It's a day for me to know the new possibility of PPI.

ホーム　友達　プロフィール　お知らせ　メニュー

Thank you for your attention!

May 22, 2024
SCT Annual Meeting

Introduction of the KISEKI trial

A phase II study to assess the efficacy of osimertinib in patients with EGFR mutation-positive NSCLC who developed systemic disease progression (T790M negative) after treatment with first- or second-generation EGFR-TKI and platinum-based chemotherapy

Kenichi NAKAMURA, MD PhD MBA
National Cancer Center Hospital

The slides were made based on those provided
by Prof. Masayuki Takeda from the Nara Medical University

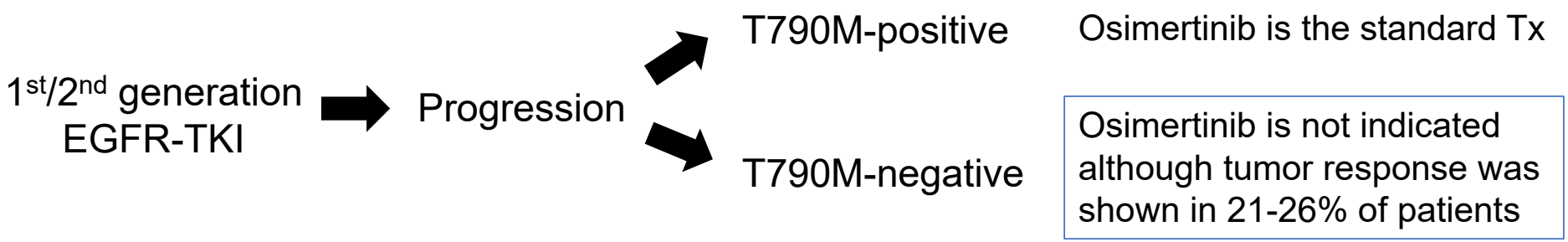
JLCA 日本肺がん患者連絡会 Japan Lung Cancer Alliance

認定特定非営利活動法人 WJOG 西日本がん研究機構 West Japan Oncology Group

Background

- Osimertinib is currently the preferred first-line therapy in patients with NSCLC that contains activating mutations of *EGFR.*

- Osimertinib is also an alternative treatment after progression of first- or second-generation EGFR-TKI



Purpose

- The KISEKI trials was a multicenter, prospective phase II clinical trial (WJOG12819L) to assess the efficacy of osimertinib in treating *EGFR* mutation-positive NSCLC.
  - ✓ Cohort 1: Patients with isolated CNS progression (T790M-negative or T790M status unknown) after treatment with first- or second-generation EGFR-TKIs
  - ✓ Cohort 2: Patients with systemic disease progression (T790M-negative) after treatment with first- or second-generation EGFR TKIs and platinum-based chemotherapy

Efficacy Assessment (cohort 2)

The primary end point: Objective response rate assessed by an independent review committee.

The secondary end point: Progression-free survival, disease control rate, safety, and overall survival

Cohort 1 is currently being recruited, but we now report the results for cohort 2.

Eligibility Criteria (cohort 2)

- 20 years of age or older
- Histologically or cytologically confirmed nonsquamous NSCLC
- Local advanced or recurrent NSCLC, not amenable to curative surgical or radical radiation therapy
- Having EGFR-TKI-sensitizing mutation of *EGFR* (including G719X, L858R, L861Q, and an exon 19 deletion) before initial EGFR TKI therapy
- No previous treatment with a third-generation EGFR-TKI (such as osimertinib, ASP8273, and CO-1686)
- ECOG performance status 0-2
- Radiologically confirmed progression of systemic disease after first- or second-generation EGFR-TKI therapy and platinum-based chemotherapy
- Tumor tissue collected after disease progression during first- or second-generation EGFR TKI therapy revealed positivity for an EGFR-TKI-sensitizing mutation of *EGFR* (G719X, L858R, L861Q, or an exon 19 deletion) and negativity for *EGFR* T790M.

Statistical considerations

- In the phase I AURA study, the response rate to osimertinib was 21-26% among patients with *EGFR* mutation-positive, T790M-negative NSCLC after resistance to first- or second-generation EGFR TKI.
- In an earlier phase III comparing docetaxel and pemetrexed for previously treated NSCLC, the response rate for docetaxel was 8.8%.

- We assumed the threshold and expected response rate as 9% and 25%. According to an exact test based on binomial distribution with a two-sided significance level of 5% and a statistical power of 80%, the study population would have to be at least 49 to verify the efficacy. Considering some patients ineligible or withdrawal, we set a target sample size as 53.

- If the lower limit of the 95% CI exceeded the threshold response rate of 9%, study treatment would be considered promising.

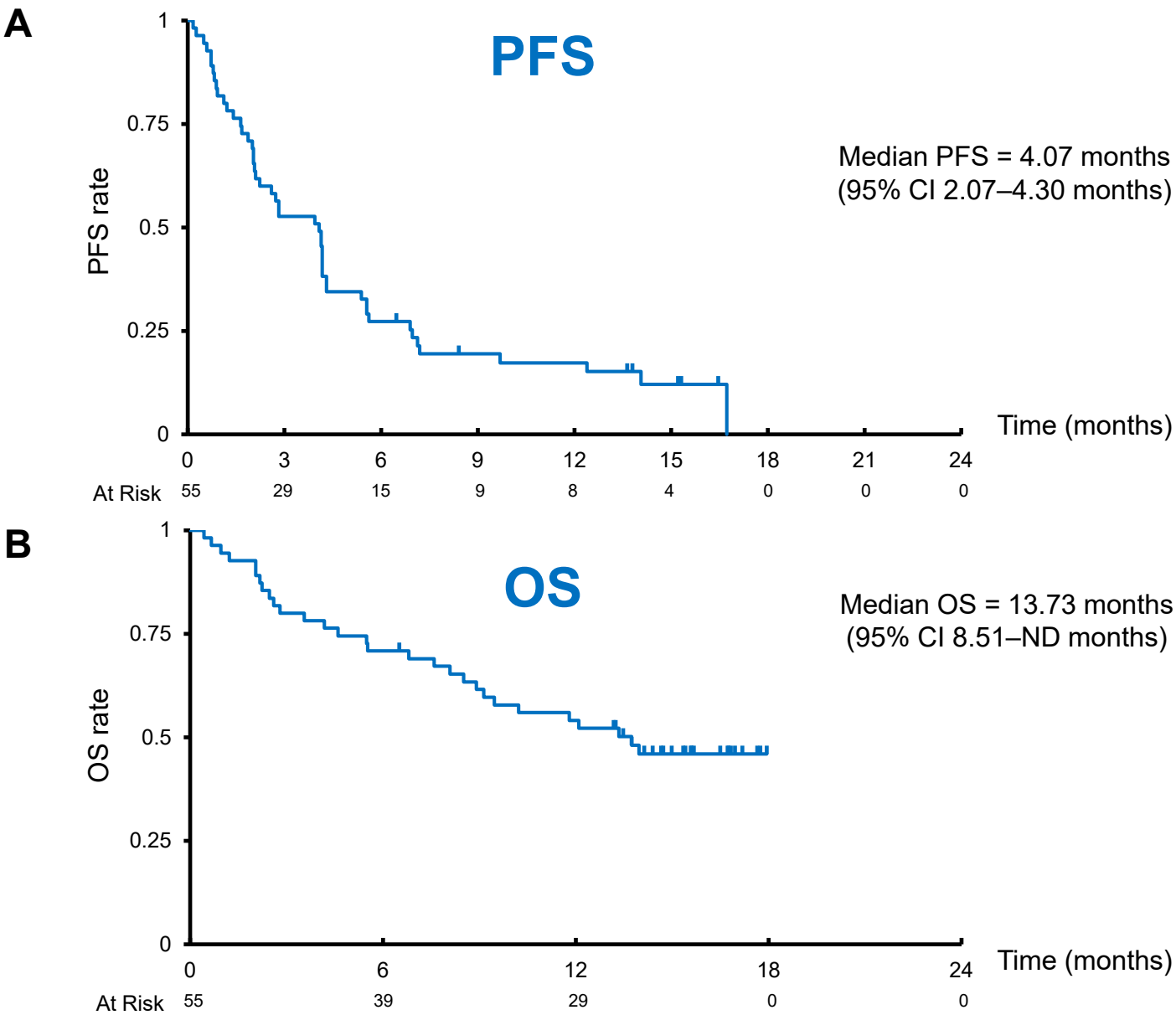
Patient Characteristics (n=55)

Characteristics	No. (%)
Median age, years (range)	67 (35–82)
Sex	
Male	21 (38.2%)
Female	34 (61.8%)
ECOG performance status	
0	20 (36.4%)
1	29 (52.7%)
2	6 (10.9%)
Histological findings	
Adenocarcinoma	53 (96.4%)
NOS	2 (3.6%)
Other	0 (0.0%)
Smoking status	
Never smoker	30 (54.5%)
Current or past smoker	25 (45.5%)
EGFR mutation status before treatment with first- and second-generation EGFR TKI*	
Exon 19 deletion	28 (50.9%)
L858R	22 (40.0%)
G719X	4 (7.3%)
L861Q	2 (3.6%)
Tissue T790M status after treatment with first- and second-generation EGFR TKI	
Positive	0 (0.0%)
Negative	55 (100.0%)
Prior cytotoxic chemotherapy	
Platinum-based chemotherapy	55 (100.0%)

Response to treatment by central independent review (n=55)

Response	No. (%)
CR	0 (0.0%)
PR	16 (29.1%)
SD	16 (29.1%)
PD	18 (32.7%)
Not evaluable	5 (9.1%)
ORR (95% CI)	29.1% (17.6–42.9)
DCR (95% CI)	58.2% (44.1–71.3)

The overall response rate was 29.1% (95% CI, 17.6–42.9), which exceeded the threshold response rate (9%) for theprimary analysis.


A
PFS
PFS rate
1
0.75
0.5
0.25
0
0
3
6
9
12
15
18
21
24
At Risk
55
29
15
9
8
4
0
0
0
Time (months)
Median PFS = 4.07 months
(95% CI 2.07–4.30 months)
B
OS
OS rate
1
0.75
0.5
0.25
0
0
6
12
18
24
At Risk
55
39
29
0
0
Time (months)
Median OS = 13.73 months
(95% CI 8.51–ND months)

Adverse Events of Any Grade in at least 10%

Adverse event	No. (%)	
	All grades	Grade ≥3
All adverse events	51 (92.7%)	18 (32.7%)
Hematologic		
Leukopenia	12 (21.8%)	2 (3.6%)
Neutropenia	8 (14.5%)	2 (3.6%)
Thrombocytopenia	16 (29.1%)	2 (3.6%)
Nonhematologic		
Body weight loss	6 (10.9%)	1 (1.8%)
Decreased appetite	8 (14.5%)	2 (3.6%)
Nausea	7 (12.7%)	1 (1.8%)
Mucosal inflammation	6 (10.9%)	0 (0.0%)
Diarrhea	18 (32.7%)	1 (1.8%)
Acneiform eruptions	9 (16.4%)	0 (0.0%)
Rash	11 (20.0%)	0 (0.0%)
Dry skin	7 (12.7%)	0 (0.0%)
Pyrexia	10 (18.2%)	0 (0.0%)
Paronychia	15 (27.3%)	0 (0.0%)
Increased CPK level	7 (12.7%)	1 (1.8%)

Discussion

- The KISEKI trial demonstrated that osimertinib had modest antitumor activity (ORR of 29.1%) and that PFS lasted a median of 4.07 months in patients with *EGFR* T790M-negative NSCLC.

- It was unclear whether osimertinib has a certain effect on T790M-negative tumors; however, we hypothesized some potential mechanisms.
  - ✓ First, some tumors without T790M mutations may still depend on EGFR signaling, and osimertinib, which has stronger EGFR kinase inhibitory activity than do the first-generation EGFR TKIs, may have been effective.
  - ✓ Second, lung cancer is a highly heterogeneous disease, and small tissue samples might not be representative of all genetic clones. Therefore, in certain cases, tissues might be falsely negative for T790M.

- Further randomized trials are not planned to confirm the efficacy of osimertinib in comparison with docetaxel for T790M-negative tumors in patients treated with EGFR TKIs and platinum-based regimens.
  - ✓ Based on the results of the KISEKI trial, expanding drug indication is planned in Japan

Conclusion

Osimertinib demonstrated modest antitumor activity against progressive *EGFR* T790M-negative disease.

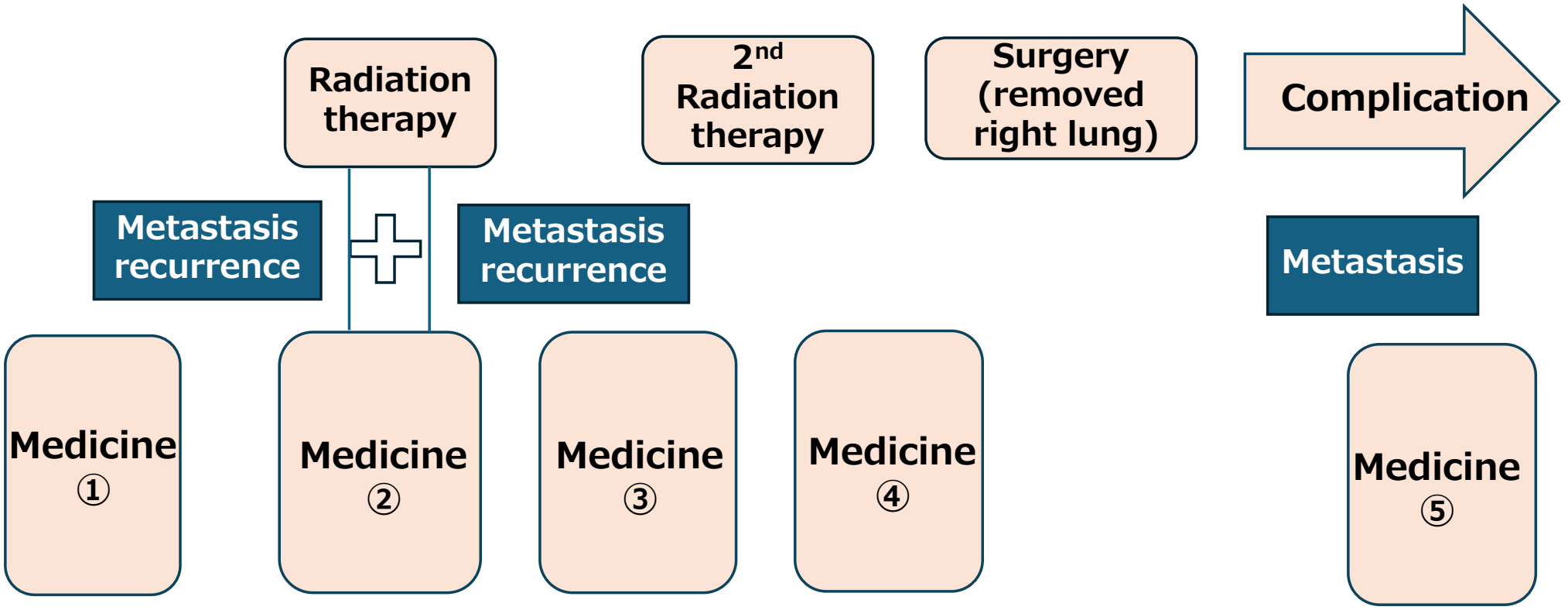
The uniqueness of the KISEKI trial is that the study proposal was made by the patient advocacy group and the trial was conducted in collaboration with patients, investigators, and the industry

KISEKI STORY
PATIENT PERSPECTIVE

About me

- **Kazuo Hasegawa**
- **53 years old**
- **Wife and two kids**
- **Live in Kanagawa pref**
- **Stage 4 lung cancer patient for the past 15 years**

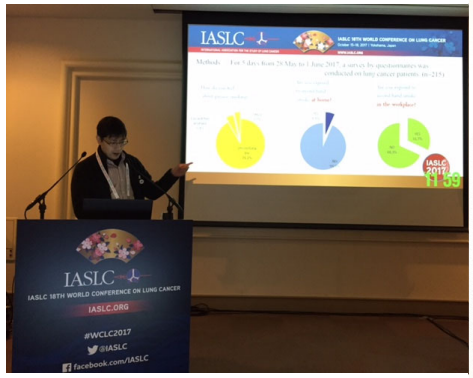
Treatment history



NPO法人 肺がん患者の会
ワンステップ

About One Step

- **Established in April 2015**
- **Operate in Japan**
- **10,000+ members**
- **Cherished word: “courage”**
- **What we do**
  - **①create community for patients**
  - **②provide education**
  - **③advocate**



Four factors that contributed the start of KISEKI trial

①will of the patient groups in the world
②will of the patients and family members
③will of the researchers
④will of the pharmaceutical companies

①patient groups in the world

World Conference on Lung Cancer 2018 Toronto Canada

International patient groups for each rare genetic disease

GROUP	FOCUS	STARTED	MBRS	CNTRY
ROS1ders	ROS1+cancer	May 2015	323	22+
ALK Positive	ALK+NSCLC	Apr 2015	1210	41+
Exon 20 Group	EGFR & HER2 Exon 20 insertions	Jun 2017	243	22
EGFR Resisters	EGFR+NSCLC plus cancers resistant to EGFR TKIs	Aug 2017	650	24
RET Renegades	RET+NSCLC	May 2018	43	2

How did it happen?

Patient groups contribute to speedup the process of trials

EGFR Exon 20 Insertion Trials Have Accrued Rapidly

Luminespib Phase 2 Trial:

August 2013 – October 2016: 29 patients

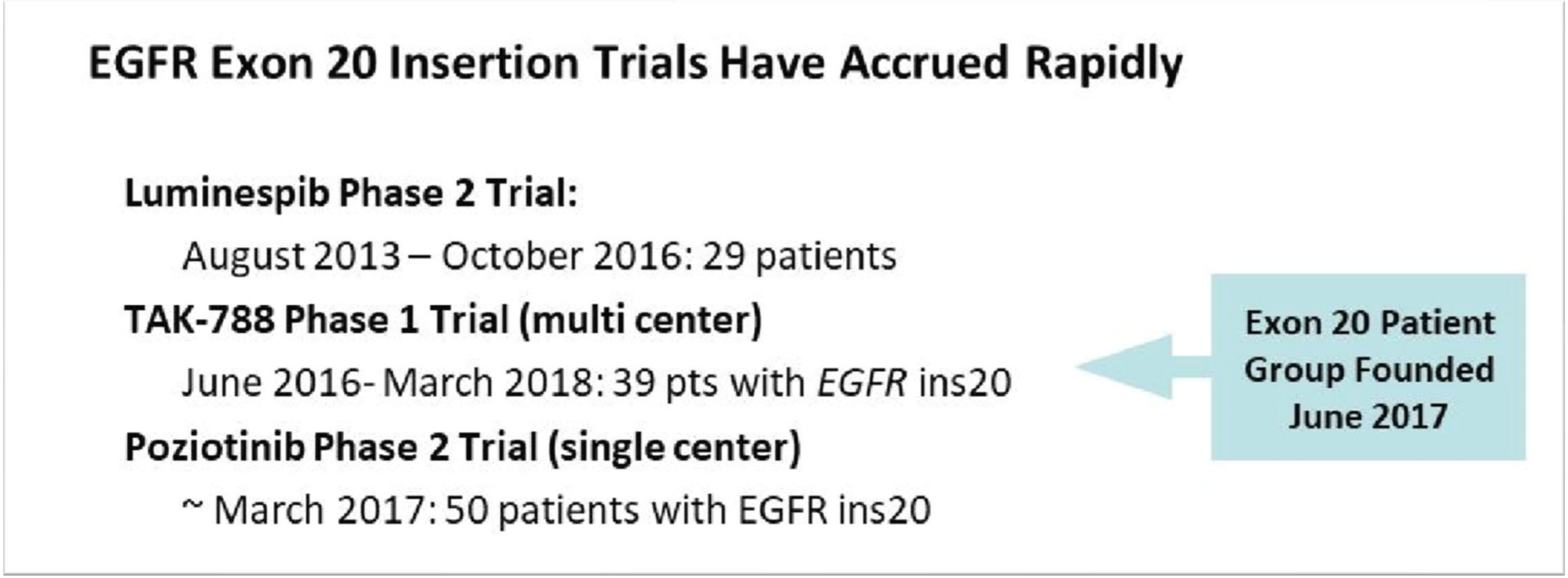
TAK-788 Phase 1 Trial (multi center)

June 2016- March 2018: 39 pts with *EGFR* ins20

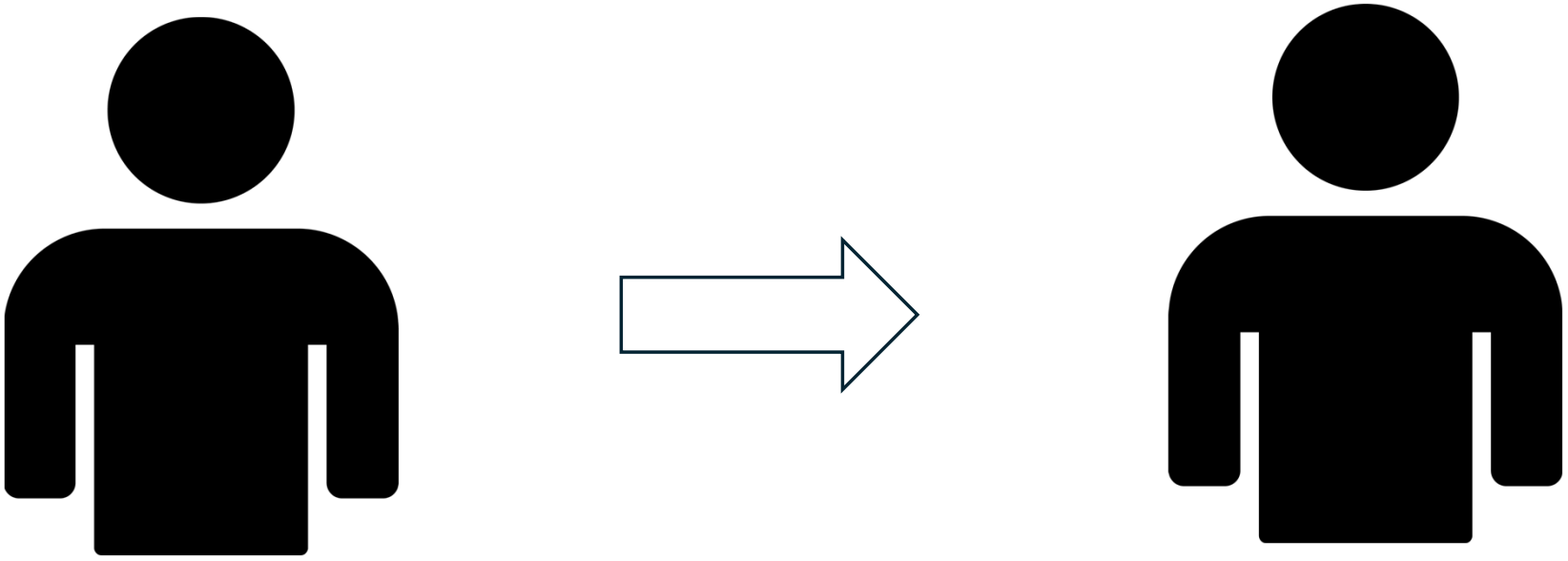
Poziotinib Phase 2 Trial (single center)

~ March 2017: 50 patients with EGFR ins20

Patient groups contribute to speedup the process of trials



Exon 20 type is more difficult to treat.
What is the standard care.
Which clinical trials are available.
This information was shared across the countries.



If one country is too small, involve more countries and get more patients.
The network grew world-wide and information was shared with many patients.
As a result, it helped speed up the process.

small county

World

“We build our own future”

small county

World

Four factors that contributed the start of KISEKI trial

①will of the patient groups in the world
②will of the patients and family members
③will of the researchers
④will of the pharmaceutical companies

Osimertinib in 2018 became the first-line therapy in patients with EGFR mutations

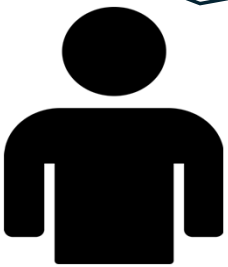
However, it's not applicable to all the patients

Without T790M mutations

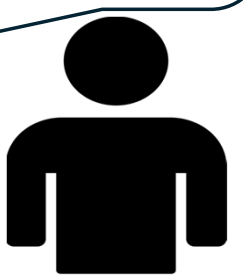
Not applicable ORR21%
PFS 2.8months

Pasi A. Jänne et ak, NEJM, 2015;372:1689-99

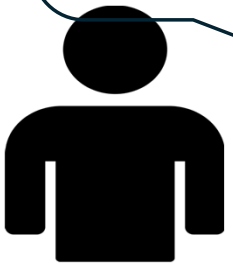
My husband was gone. I wanted him so bad I was going crazy because I had no meds available for anything.



Why can't we use the options available?



Might work...



Patient Voice

Then we looked at the brighter side.
The third therapy of lung cancer has the Overall Response Rate of only 10%. 21% is more than double

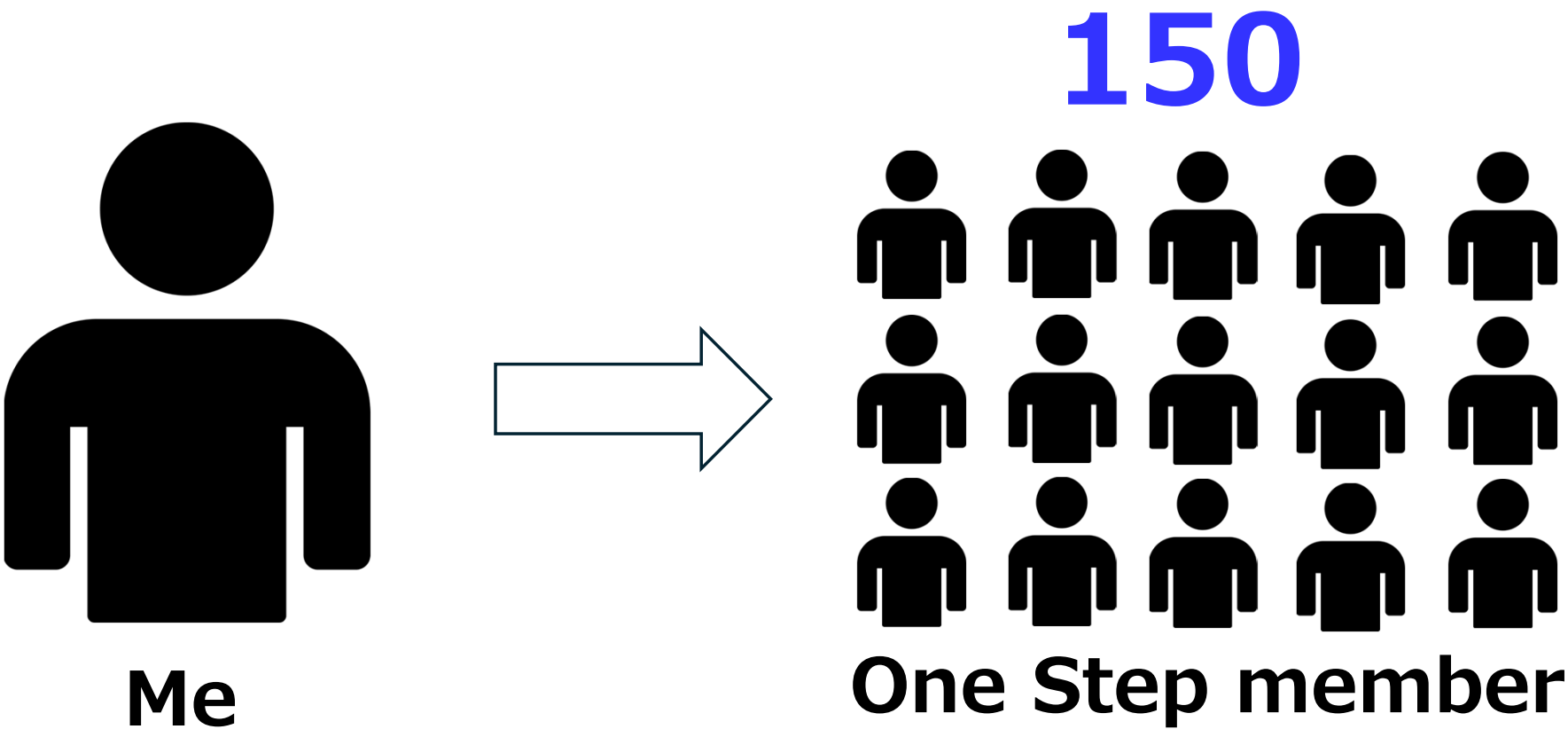
clinical trial

Not applicable ORR21%
PFS 2.8months

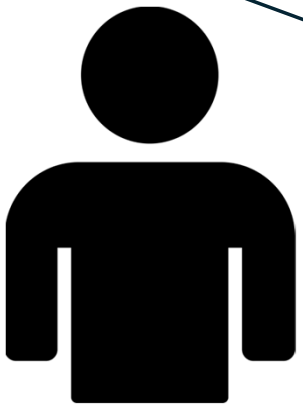
Without T790M mutations

Pasi A. Jänne et ak, NEJM, 2015;372:1689-99

I shared my idea to the member of OneStep.
I could not join the trial.
I wanted to know if the patients in scope wanted the medicine.
.



My wife is a patient, and she needs a different treatment. This clinical trial can bring her hope, so we are all in. If she doesn’t get selected, that’s a pity. But I agree with the trial because it brings hope to patients. Please proceed.



One Step member

WE BUILD OUR OWN FUTURE

Four factors that contributed the start of KISEKI trial

①will of the patient groups in the world
②will of the patients and family members
③will of the researchers
④will of the pharmaceutical companies

認定
特定非営利
活動法人
西日本がん研究機構
West Japan Oncology Group

Dr. KAZUHIKO NAKAGAWA

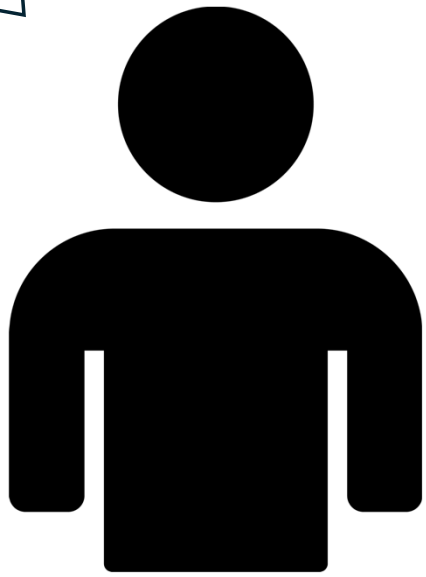
He was the first doctor to have allowed patients to join annual meeting of the Japan Lung Cancer Society. He values patients' experiences and viewpoints.

②Researcher

Yes

Let’s do it together!

If patients can raise money, can you do the clinical trial?

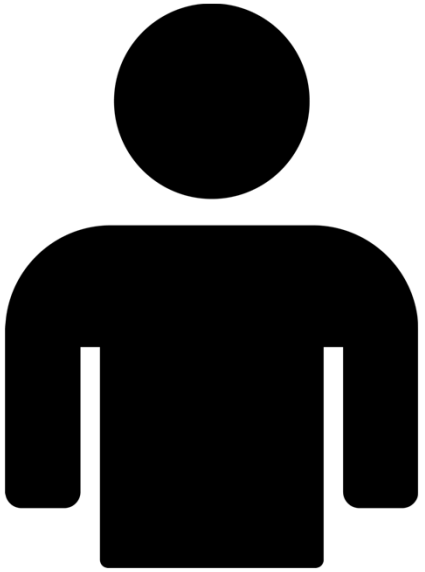


We now have the spirit and capacity, but that's not enough.

We need money.

②Researcher

It’s going to cost $2million and plus $10million for drugs.



②Researcher

It’s going to cost $2million and plus $10million for drugs.

②Researcher

Let’s involve pharmaceutical companies!

Four factors that contributed the start of KISEKI trial

①will of the patient groups in the world
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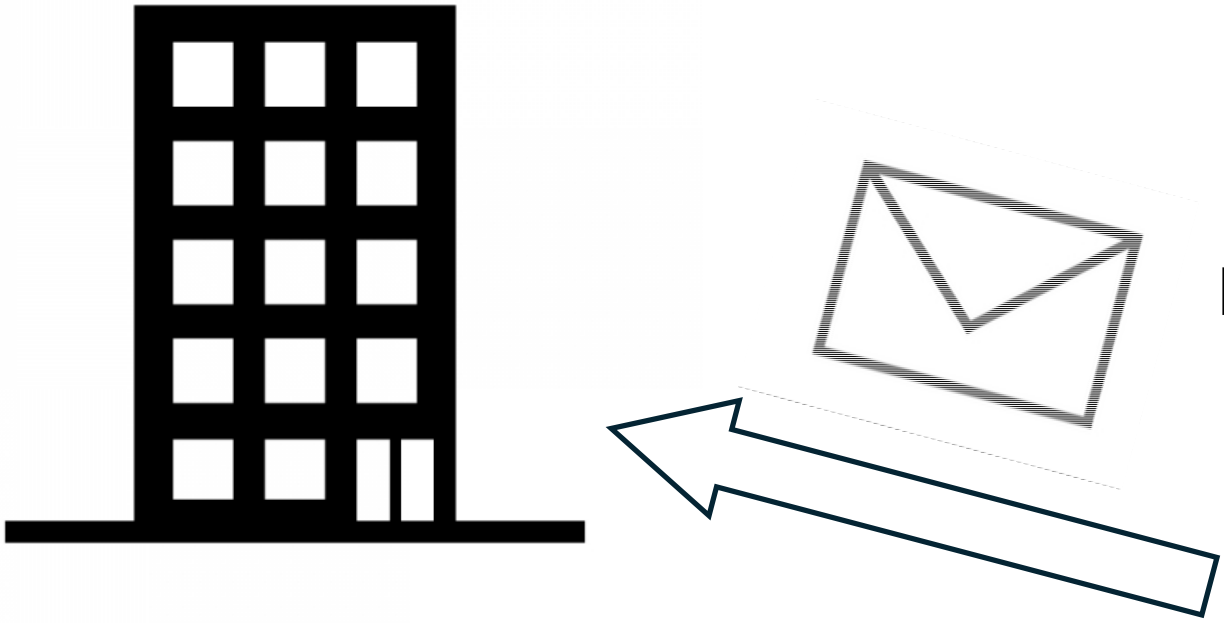
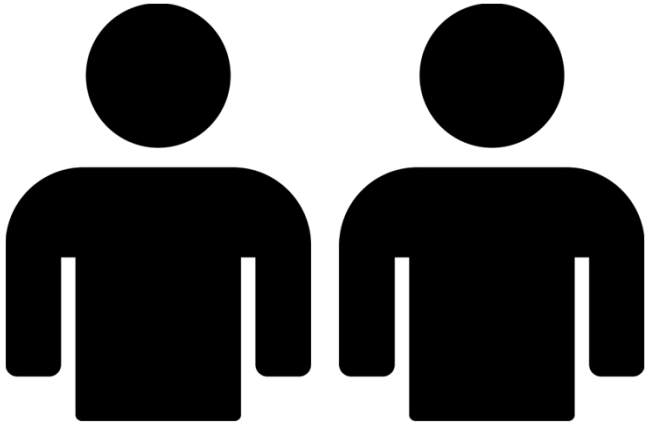
④will of the pharmaceutical companies

③ pharmaceutical company



request

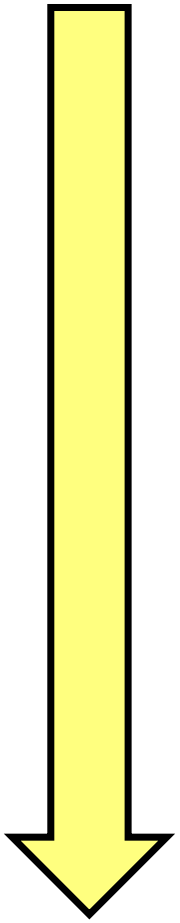


If they judged based on the cost and the company's future, the answer would have been NO.
However, it would bring hope for patients. And that was very important.
Scientifically the trial was not wrong.
That's probably how they gave the green light.

Patient centricity has always been the core value for pharmaceutical companies in general.
This time they put that into action.

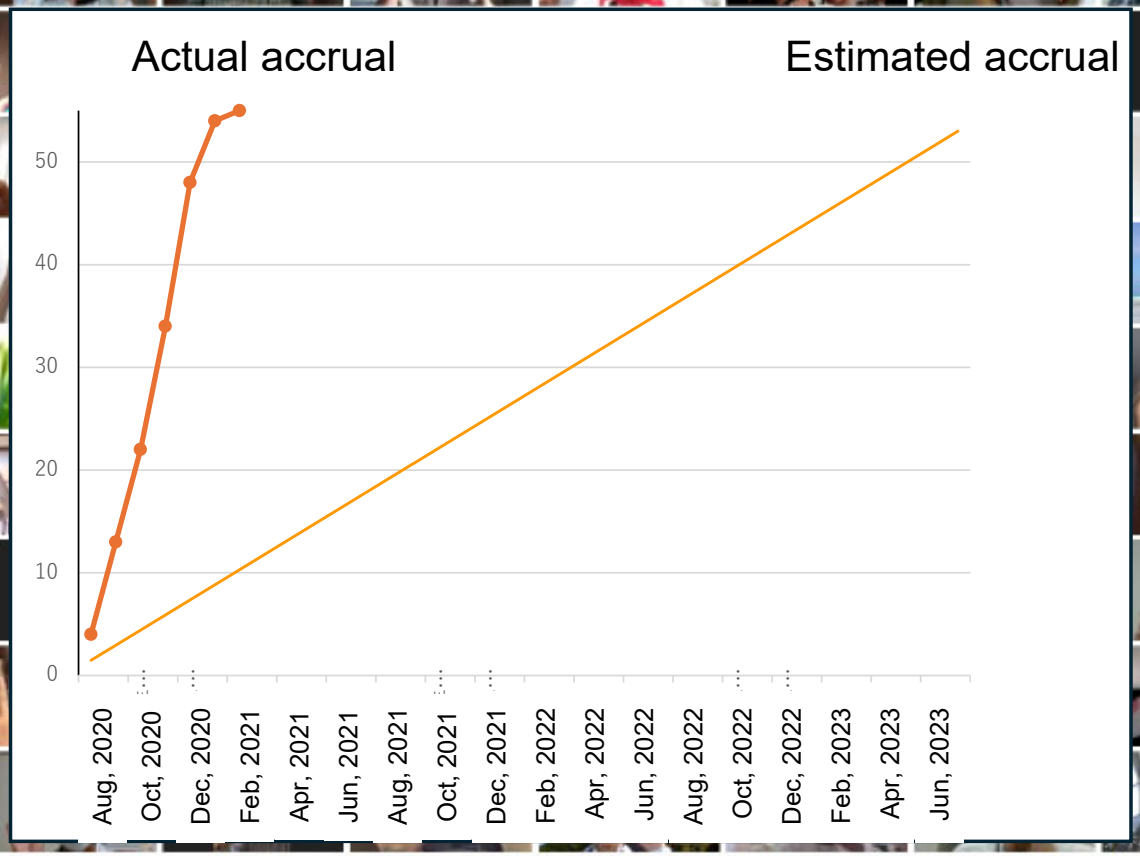
Process of request submission to the start of the trial

Timeline	
Submission of patient request letter	March 8, 2019
WJOG Concept review	
Pharmaceutical ESR submit	
Pharmaceutical concept review (domestic)	
Pharmaceutical concept review (overseas)	
WJOG Permanent Council concept review	
PMDA preliminary interview	
Protocol pharmaceuticals domestic review	
Protocol pharmaceuticals overseas review	
PMDA in-person counseling	
WJOG board approval	
IRB　(Kindai University)	
Contract	
Submission of clinical trial notification	May 29, 2020

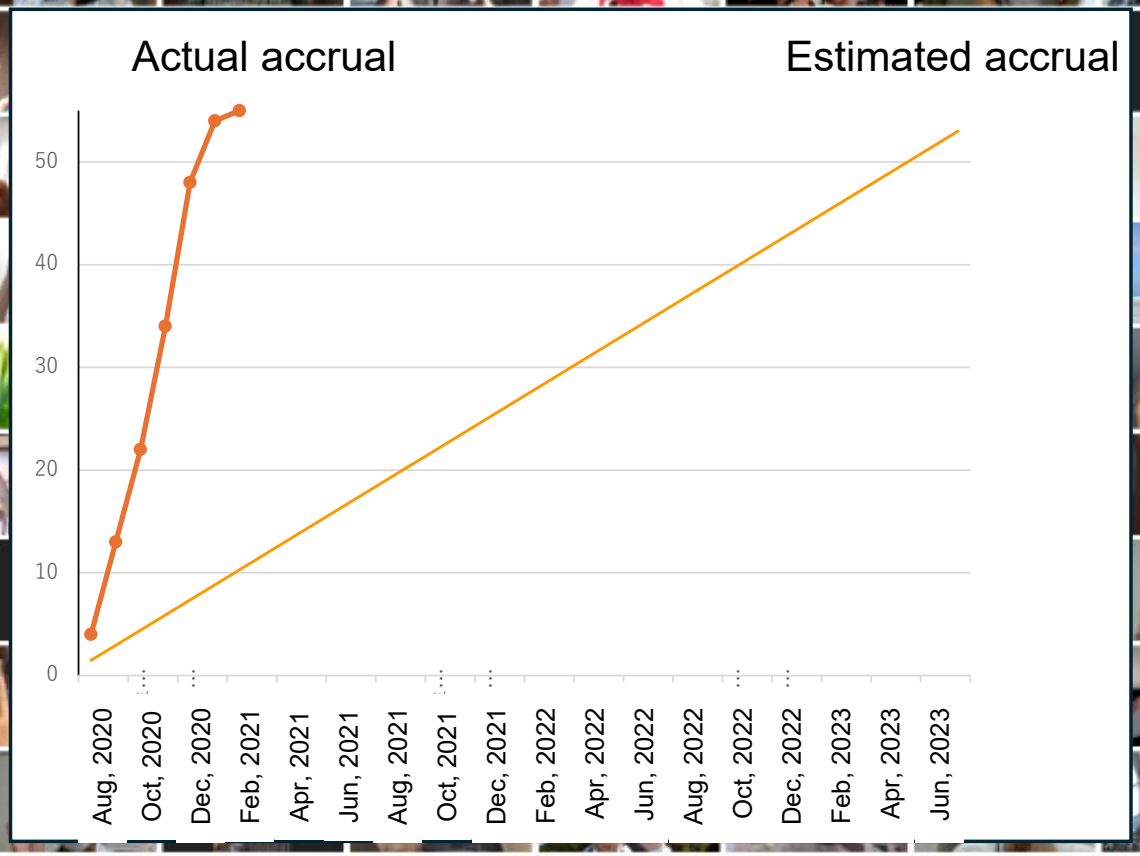


1 year
2 months

We declared that we will change our future.



Response	No. (%)
CR	0 (0.0%)
PR	16 (29.1%)
SD	16 (29.1%)
PD	18 (32.7%)
Not evaluable	5 (9.1%)
ORR (95% CI)	29.1% (17.6–42.9)
DCR (95% CI)	58.2% (44.1–71.3)



Response	No. (%)
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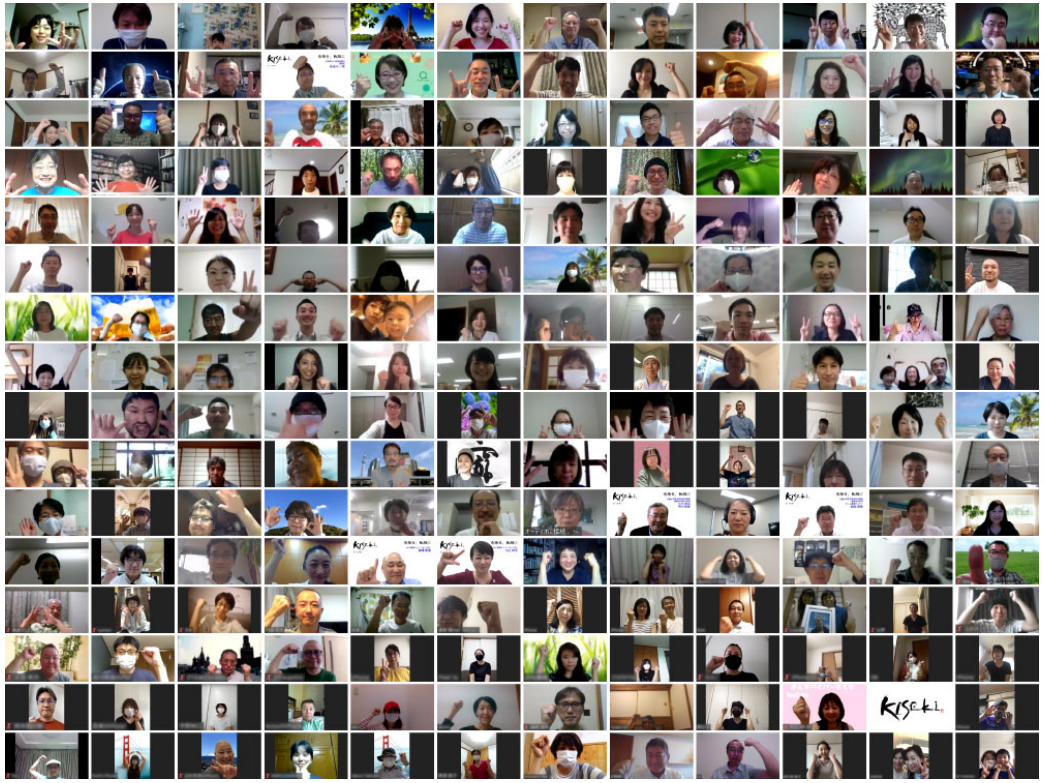
Not evaluable	5 (9.1%)
ORR (95% CI)	29.1% (17.6–42.9)
DCR (95% CI)	58.2% (44.1–71.3)

The will to create our future still lives and the journey continues. Currently we are applying for approval.



MIRACLE/TRAIL