towards high-quality clinical trials and
implementation of genomic medicine

ATLAS Training Program

Course : CRC Training Course

Lecture Title : Supporting efficacy evaluation in cancer clinical trials: management and management tools

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ATLAS
ASIAN CLINICAL TRIALS NETWORK FOR CANCERS PROJECT

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Supporting Efficacy Evaluation In Cancer Clinical Trials

[Content of this lecture]

1. What is efficacy in cancer clinical trials?

2. Efficacy evaluation methods in cancer clinical trials

3. CRC support for efficacy evaluation in cancer clinical trials

4. Summary

1. What is efficacy in cancer clinical trials?

What is efficacy in clinical trials?

- Clinical trials are conducted to evaluate new treatments
- Efficacy is an objective evaluation index used to develop better treatments
- Methods for evaluating efficacy differ depending on the purpose of the clinical trial

Japan Society of Medical Oncology, New Clinical Oncology, Revised Sixth Edition, Nankodo (2021)

Characteristics of efficacy in cancer clinical trials

- There are significant individual differences in the degree of efficacy compared to in other fields of pharmacotherapy
- Objective and accurate evaluation of efficacy is necessary.
- There are established methods for evaluation.

Jpn J Clin Pharmacol Ther 2016; 47(2)

2. Efficacy evaluation methods in cancer clinical trials

Efficacy in cancer clinical trials

English	Start date	End of evaluation
Overall survival	Trial enrollment date	At death
Progression-free survival	Trial enrollment date Trial start date	At death, progression
Relapse-free survival	Trial enrollment date Date of surgery	At death, relapse
Disease-free survival	Enrollment date Date of surgery	At death, relapse

Partially modified from Jpn J Clin Pharmacol Ther 2016; 47(2)

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

Methods used to evaluate efficacy in cancer clinical trials

- Overall Survival: OS
- Progression-free survival: PFS
- Objective response rate: ORR

Public Health Research Foundation Cancer Clinical Trial Operations Education & Training Subcommittee: Cancer Clinical Trial Textbook
Igaku-Shoin (2013)

Overall survival (OS) evaluation methods

- Investigate the time from enrollment date to date of death.
- The survey period is the period stipulated in the protocol. (Example: every 3 months, every 12 weeks, etc.)
- The survey method is implemented based on the method stipulated in the protocol, including hospital visits, telephone calls, and patient referral documents.

Partially modified from The Japanese Society of Clinical Pharmacology and Therapeutics, CRC Textbook Fourth Edition, Igaku-Shoin (2021)
Public Health Research Foundation Cancer Clinical Trial Operations Education & Training Subcommittee: Cancer Clinical Trial Textbook Igaku-Shoin (2013)
Guidelines for clinical evaluation of anti-cancer drugs (2021), https: //www.pmda.go.jp/rs-std-jp/standards-development/guidance-guideline/0001.html

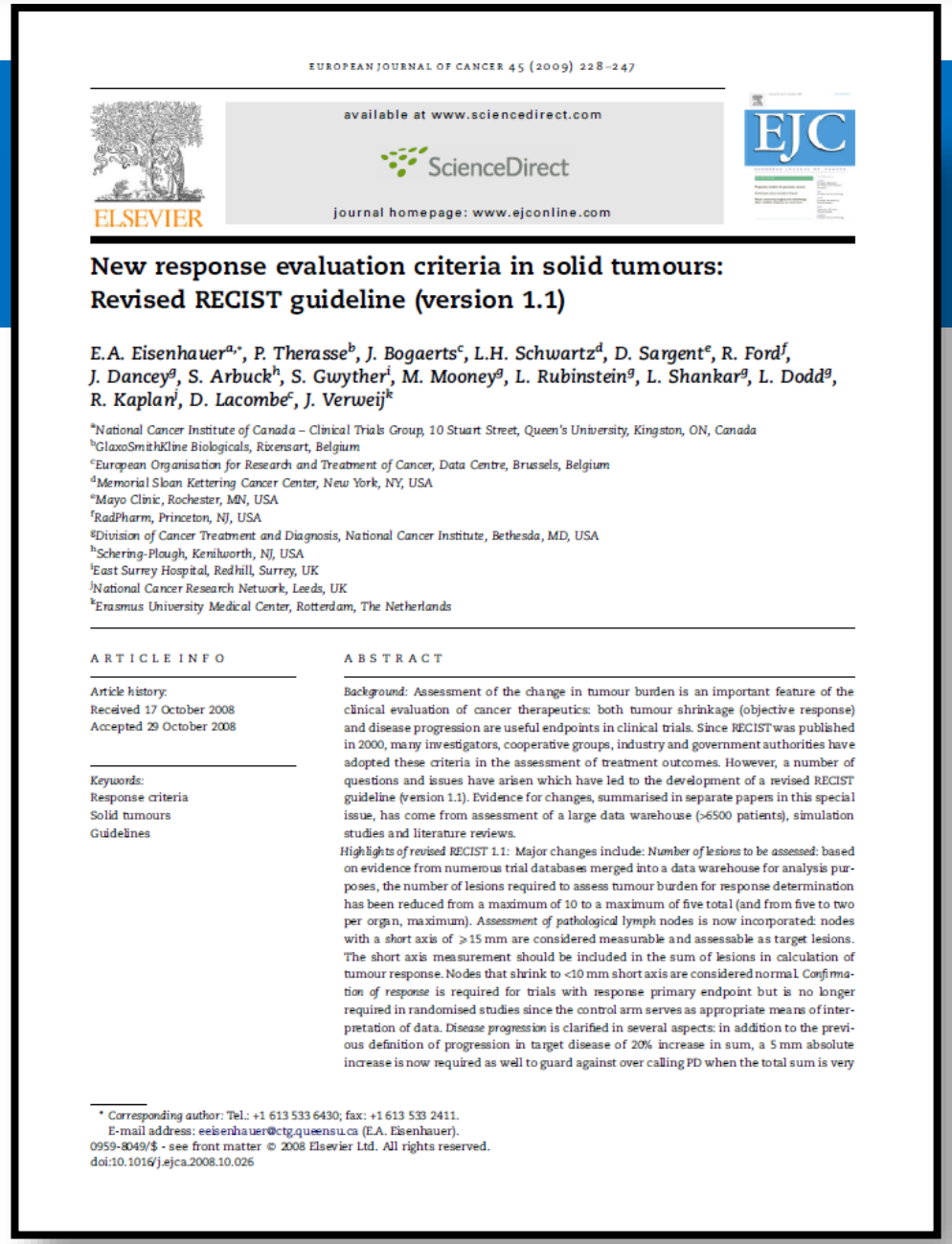
Progression-free survival (PFS) evaluation methods

- Investigate the time from enrollment date until disease progression is determined.
- The survey period is the period stipulated in the protocol. (Example: every 6 weeks, every 12 weeks, etc.)
- The evaluation methods differ for each protocol.
- RECIST is a typical evaluation method.

Partially modified from The Japanese Society of Clinical Pharmacology and Therapeutics, CRC Textbook Fourth Edition, Igaku-Shoin (2021)

Public Health Research Foundation Cancer Clinical Trial Operations Education & Training Subcommittee: Cancer Clinical Trial Textbook Igaku-Shoin (2013)

Guidelines for clinical evaluation of anti-cancer drugs (2021), https: //www.pmda.go.jp/rs-std-jp/standards-development/guidance-guideline/0001.html



EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247

available at www.sciencedirect.com

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New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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ARTICLE INFO

Article history:
Received 17 October 2008
Accepted 29 October 2008

Keywords:
Response criteria
Solid tumours
Guidelines

ABSTRACT

Background: Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics: both tumour shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1). Evidence for changes, summarised in separate papers in this special issue, has come from assessment of a large data warehouse (>6500 patients), simulation studies and literature reviews.

Highlights of revised RECIST 1.1: Major changes include: *Number of lesions to be assessed:* based on evidence from numerous trial databases merged into a data warehouse for analysis purposes, the number of lesions required to assess tumour burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum). *Assessment of pathological lymph* nodes is now incorporated: nodes with a short axis of ⩾15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumour response. Nodes that shrink to <10 mm short axis are considered normal. *Confirmation of response* is required for trials with response primary endpoint but is no longer required in randomised studies since the control arm serves as appropriate means of interpretation of data. *Disease progression* is clarified in several aspects: in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.10.026

New Guideline for Response evaluation criteria in solid tumors (RECIST Guideline Version 1.1)

- One of the guidelines on response evaluation criteria in solid tumors
- Standardized method for measuring solid tumors in adults and children
- Defines objective evaluation of changes in tumor size

EUROPEAN JOURNAL OF CANCER 45: 228, 2009
New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) (cancer.gov)

What is RECIST?

- RECIST: Response Evaluation Criteria In Solid Tumors
- An objective method used to measure changes in tumor burden in solid tumors
- Evaluation methods can be standardized (international common guidelines for determining response)
- RECIST is often used for the precise measurement of changes in tumor burden in trials using ORR and PFS as efficacy indices.

Japan Society of Medical Oncology, New Clinical Oncology, Revised Sixth Edition, Nankodo (2021)
RECIST ver. 1.1 Japanese JCOG (2010), http: //www.jcog.jp/doctor/tool/recistv11.html

RECIST: Capturing images

- Computed tomography (CT) and magnetic resonance imaging (MRI) are recommended

- Perform imaging methods specified in the protocol

RECIST ver. 1.1 Japanese JCOG (2010), http: //www.jcog.jp/doctor/tool/recistv11.html

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

RECIST: Classification of lesions

- **All lesions are classified as measurable or non-measurable**

  Definition of a measurable lesion
  - Non-nodal lesions: Lesions with maximum diameter of ≥10 mm
  - Nodal lesions: Lesions with short axis of ≥15 mm
  - Maximum diameter of ≥20 mm on simple chest X-ray

- **Selection of target lesions and non-target lesions**
  - Target lesions: Use measured values for evaluation (maximum of two lesions per organ, with a maximum of five lesions in total)
  - Non-target lesions: Do not use measured values for evaluation

RECIST ver. 1.1 Japanese JCOG (2010), http: //www.jcog.jp/doctor/tool/recistv11.html

RECIST: Tumor response criteria

- Determining response for target lesions

Determination	Determination criteria
CR (Complete response)	Disappearance of all target lesions. Any pathological lymph nodes must have a reduction in the short axis to <10 mm
PR (Partial response)	At least a 30% decrease, using the baseline sum diameters as a reference
SD (Stable disease)	Neither sufficient shrinkage/nor sufficient increase to qualify for PR/PD
PD (Progressive disease)	At least a 20% increase and absolute increase of at least 5 mm, using the smallest lesion diameter as a reference

RECIST ver. 1.1 Japanese JCOG (2010), http: //www.jcog.jp/doctor/tool/recistv11.html

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

RECIST: Tumor response criteria

- Determining response for non-target lesions and new lesions

Determination	Determination criteria
CR (Complete response)	Disappearance of all non-target lesions and normalization of tumour marker level All lymph nodes must be <10 mm on the short axis
Non-CR/non-PD	Persistence of one or more non-target lesions and/or maintenance of tumour marker level above normal limits
PD (Progressive disease)	Unequivocal progression of existing non-target lesions Appearance of one or more new lesions

RECIST ver. 1.1 Japanese JCOG (2010), http: //www.jcog.jp/doctor/tool/recistv11.html

RECIST: Tumor response criteria

- Best overall response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	No evaluation	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE: Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

RECIST ver. 1.1 Japanese JCOG (2010), http: //www.jcog.jp/doctor/tool/recistv11.html

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

Understanding the CRC support guidelines

- Helps to understand the protocol.

- Rules not stated in the protocol may be described and supplemented in the guidelines.

Non-RECIST evaluation methods

- Glioma: Response Assessment in Neuro-Oncology (RANO)
- Gastrointestinal stromal tumor (GIST): Choi Criteria
- Lymphoma: International workshop criteria

…etc.

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

3. Supporting efficacy evaluation in cancer clinical trials

From before the start to completion of the clinical trial

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

Supporting efficacy evaluation in cancer clinical trials

1. Before starting the clinical trial

2. During the clinical trial

3. After the end of the clinical trial

Before starting the clinical trial: Confirm the protocol

- **Confirm the schedule and test methods for evaluating efficacy.**

- Confirm the test methods used for evaluating efficacy.
- Confirm the schedule for the entire clinical trial.
- Sometimes additional tests may suddenly be required, in addition to the regular tests.

Before starting the clinical trial: Confirm evaluation procedures

- **Check whether procedures can be implemented in hospitals in accordance with imaging method regulations.**

- An imaging manual may also be provided.
- The clinical trial may use imaging methods not used in general medical care.
- Check the CT/MRI ordering methods (request comments, etc.) for each department.

Before starting the clinical trial: Confirm procedures after evaluation

- **Confirm procedures for handling information after efficacy evaluation.**

- Confirm submission of test data such as CT/MRI and deadlines for submission.
- Confirm submission methods.
- Confirm whether other material must be submitted.
- Confirm masking of personal information.

During the clinical trial: Confirm participant background information

- **Confirm the target participant profiles.**

- Test methods and efficacy evaluation methods differ depending on the cancer type.

- Confirm history of contrast use, concomitant medication, and confirm whether the tests required for efficacy evaluation are possible.

- Confirm the lesion site and present the information or consult with the doctor regarding matters such as test methods and imaging range.

During the clinical trial: Confirmation of baseline evaluation

- **Request the doctor to confirm in a timely manner that implemented tests such as CT and MRI were conducted in accordance with the protocol.**

- Additional tests may be required depending on the results of the baseline tests.
- Confirm whether images taken before consent was obtained can be used.
- If submission of images is required, consult about the test schedule to ensure that the images are submitted as soon as possible after capture.
- Input (information) into the case report form (CRF) in a timely manner.

During the clinical trial: Managing participants

- **Arrange the schedule for each participant.**
- **Confirm medication and allergies before each test.**

- Confirm the next evaluation date and arrange the schedule.

- Confirm the necessity of contrast, and whether the participant is taking drugs that are contraindicated for the test.

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

During the clinical trial: Confirmation of efficacy evaluation results

- **Confirm the results of efficacy evaluation, confirm whether there are additional tests, and confirm whether the clinical trial discontinuation criteria are met.**

- Additional tests may be necessary depending on the results of efficacy evaluation.

- Confirm the schedule if the discontinuation criteria are met.

A protocol example, and points to note

[Phase II clinical trial investigating the safety and tumor response of study drug A in patients with metastatic breast cancer]

- Participants undergo evaluation every 8 weeks (±3 days) within 12 months of enrollment and every 12 weeks thereafter (±3 days) until disease progression is confirmed (determined by a doctor at the clinical trial site). Administration may be continued even after disease progression is first confirmed based on RECIST Version 1.1, providing that the criteria are met. Submit images within 5 days of capture.
- Points to note when setting the schedule
  - ① Evaluation base date and intervals: Every 8 weeks within 12 months of the enrollment date, and every 12 weeks thereafter
  - ② Allowable window: specified date ±3 days
  - ③ Evaluation method: RECIST ver1.1
  - ④ Evaluator: Clinical trial site doctor
  - ⑤ Submission of images: Yes within 5 days
  - ⑥ Handling after PD: Administration may be continued

2022 January Subject No.XXXXX

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
27	28	29	30	31	1	2
3	4 Cycle 3 administration CT: Week 6±7 days Contrast CT: Yes Allergies: No Imaging range: Neck to pelvis Bone scintigraphy: No (every 12 weeks)	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25 Cycle 4 administration	26	27	28	29	30
31	1	2	3	4	5	6

During the clinical trial: Consideration for the participant

- **Consider the impact that the results of efficacy evaluation may have on the participant.**

- The evaluation results are communicated by the doctor and not by the CRC.
- The results of efficacy evaluation may be good or bad news for the participant.
- Be sensitive to the participant's feelings and provide mental/psychological support.

At the end of the clinical trial: Confirmation of discontinuation/completion criteria

- **Confirm the clinical trial discontinuation criteria.**

- Pre-calculate the values that indicate PD in tumor evaluation.
- Confirm whether evaluation of efficacy is needed after PD.
- In some clinical trials, participants may continue treatment after PD.
- Some clinical trials require imaging evaluation even after discontinuation.

After the end of the clinical trial: Survival follow-up

- **Confirm the follow-up schedule and establish follow-up methods, including methods of contacting the participant.**

- Confirm the follow-up base date.
- Confirm the participant’s future hospital visit schedule.
- Confirm the follow-up content.
- Confirm telephone contact details and the transfer hospital and establish a means of maintaining contact.

PFS, OS evaluation case example ①

- 2010.01.XX Diagnosed as progressive lung cancer
- 2010.02.XX Enrolled in clinical trial, started study drug A
- 2011.02.XX CT: Decided to discontinue clinical trial because of tumor growth (PD)

In the protocol…

- Implement next treatment and survival follow-up at 90 ± 14 days from the date of discontinuation decision
- Determine response every 6 weeks from the date of the first administration of the study drug for patients who discontinued because of adverse events

- Prepare to make contact at 90 ± 14 days from 2011.02.XX.
- This patient discontinued the trail because of PD, so follow-up imaging is not required.

PFS, OS evaluation case example ②

- 2010.01.XX　Diagnosed as progressive lung cancer
- 2010.02.XX　Enrolled in clinical trial, started study drug A
- 2011.02.XX　CT: Decided to discontinue clinical trial because of adverse events

In the protocol…

- Implement next treatment and survival follow-up at 90 ± 14 days from the date of discontinuation decision
- Determine response every 6 weeks from the date of the first administration of the study drug for patients who discontinued because of AE

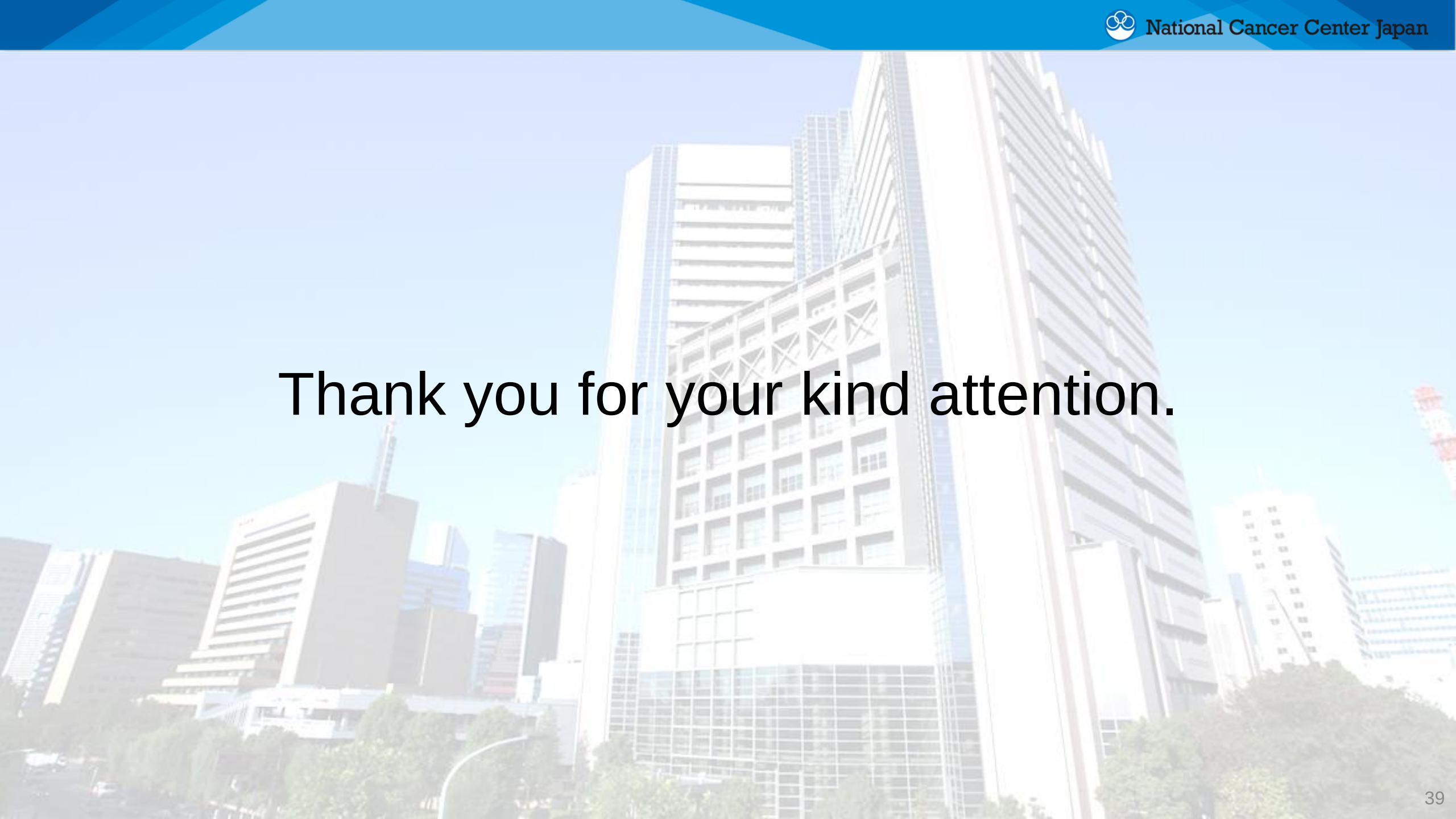
- Prepare to make contact at 90 ± 14 days from 2011.02.XX.
- This patient discontinued the trail because of adverse events, so follow-up imaging is also required.
- The schedule every 6 weeks from 2021.02.XX must be confirmed.

CRC support: Summary

- Confirm the efficacy evaluation methods for each clinical trial.
- Confirm whether the efficacy evaluation is possible at the clinical trial site/for the participant.
- Create a system for evaluating efficacy.
- Manage the efficacy evaluation schedule. Create tools as needed.

References

- Public Health Research Foundation Cancer Clinical Trial Operations Education & Training Subcommittee: Cancer Clinical Trial Textbook Igaku-Shoin (2013)
- The Japanese Society of Clinical Pharmacology and Therapeutics, CRC Textbook Fourth Edition Igaku-Shoin (2021)
- Japan Society of Medical Oncology, New Clinical Oncology, Revised Sixth Edition, Nankodo (2021)
- Ando Y, et al. Jpn J Clin Pharmacol Ther 2016; 47(2)
- Guidelines for clinical evaluation of anti-cancer drugs (2021), https: //www.pmda.go.jp/rs-std-jp/standards-development/guidance-guideline/0001.html
- New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), EUROPEAN JOURNAL OF CANCER 45: 228, 2009, New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) (cancer.gov)
- RECIST ver. 1.0 Japanese JCOG (2000), http: //www.jcog.jp/doctor/tool/index3.html
- RECIST ver. 1.1 Japanese JCOG (2010), http: //www.jcog.jp/doctor/tool/recistv11.html



Thank you for your kind attention.