Designs for clinical trials on cancer

Part 2 of 2

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The 23rd JCOG Clinical Trial Seminar
10/10/2020

*** Japan Clinical Oncology Group** (https://jcog.jp/en/)

JCOG
Japan Clinical Oncology Group

ATLAS
ASIAN CLINICAL TRIALS NETWORK FOR CANCERS PROJECT

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

Outline

- Anticancer drug development flow and endpoints
- Phase I designs
- **Phase II designs**
- Phase III designs

Purpose and Overview of Phase II Trials

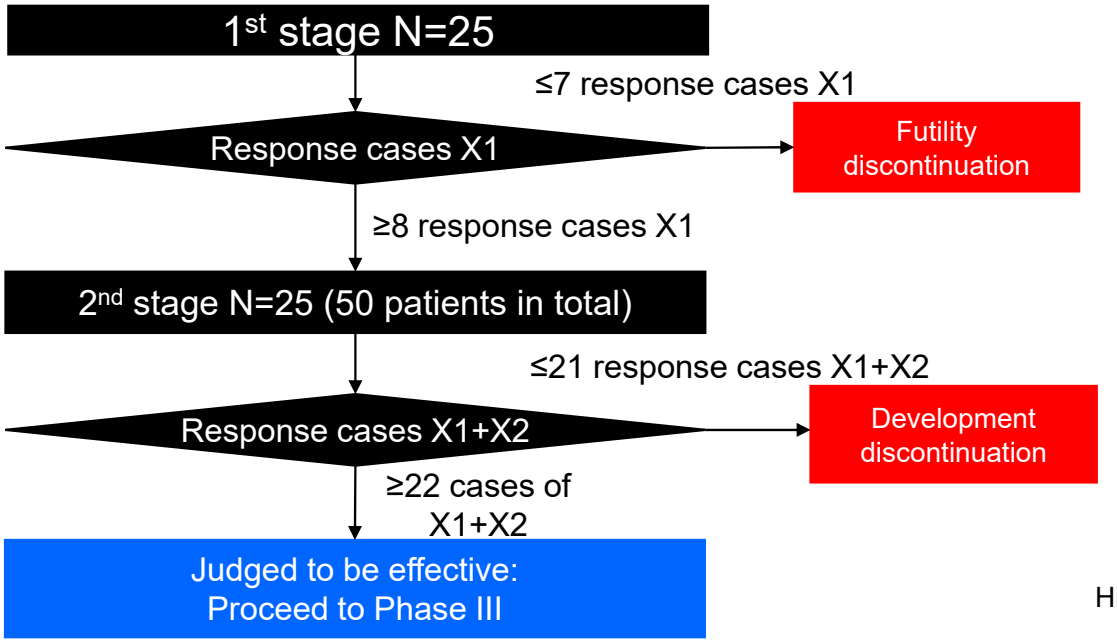
- Purpose: To decide whether to proceed to Phase III
  - Does the study treatment have efficacy that is likely superior to that of the standard treatment?
  - Enhancement of the toxicity profile that was not observed in Phase I
  - Optimization of the dosage, usage, treatment modification criteria, etc.

- Typical design
  - Target: Limited cancer types
  - Number of patients enrolled: 20-60 patients
  - Participating facilities: A larger number of facilities than that in Phase I
  - Short-term endpoints (**response rate**, etc.) by RECIST in a **single-arm trial**
    - To decide whether to proceed to Phase III as soon as possible
    - Screening for **efficacy**
    - Premise: Tumor response is an alternative for the prolongation of prognosis (OS)

Single-Arm Design using Threshold and Expected Value

- Threshold: If the drug/treatment is only effective at this level, its development is not worthwhile to be continued.
- Expected value: If the drug/treatment is effective at this level, its development is worthwhile to be continued.
- The primary endpoint is the response rate.
- Considering the futility stopping of the ongoing trial (two-stage design)

- Example: JCOG0807 (DCF therapy for unresectable recurrent esophageal cancer)
  - Threshold=35% (response rate of CF therapy), expected value=50%, α=10%, statistical power=80%



Actual result: 33/53=62%

↓

Phase III trial
JCOG1314 (CF vs DCF)
In progress
(jRCTs031180143)

Hironaka S, et al. Cancer science. 2014;105(9):1189-95.

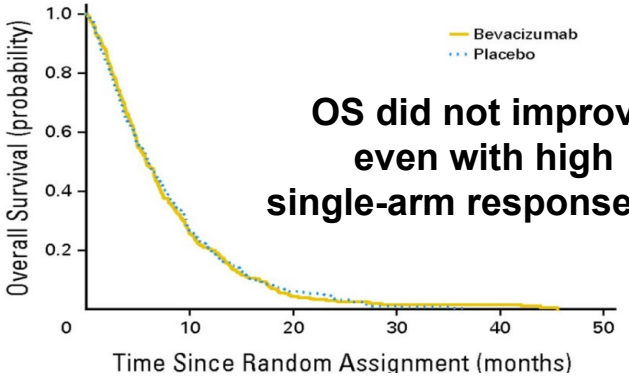
Is single-arm suitable?

Is response rate suitable?

- Unresectable pancreatic cancer
  - Results of single-arm Phase II trial
  - Response rate
    - Bevacizumab group: 21%
    - Gemcitabine monotherapy (standard treatment at the time): <10%

To Phase III

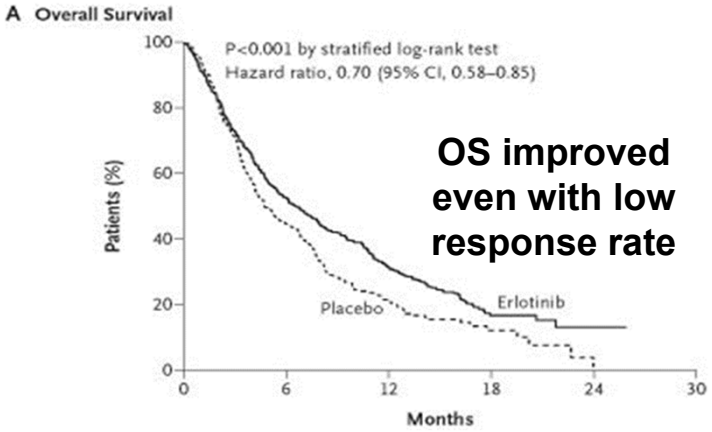
Kindler, Hedy L., et al. *JCO* 2005;23



OS did not improve even with high single-arm response rate

Kindler, H. L., et al. *JCO 2010;* 28: 3617-3622

- Previously treated stage IIIB/IV non-small cell lung cancer
  - Results of a randomized controlled Phase III trial
  - Response rate
    - Placebo group: 0.7%
    - Erlotinib group: 8.2%



OS improved even with low response rate

Shepherd FA et al. N Engl J Med 2005;353:123-132.

Why not use annual survival rates or annual progression-free survival rates in single-arm trials?

- Annual survival rate (e.g., 1-year survival rate)
  - Variation is likely to occur depending on the general conditions of the enrolled patients.
  - Easily influenced by subsequent treatment

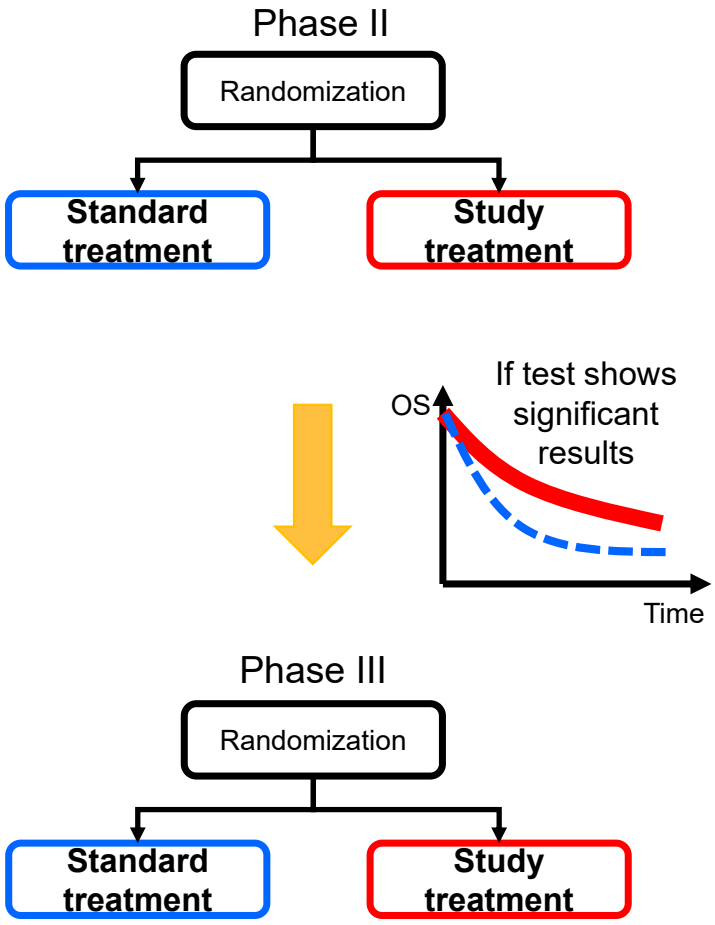
- Annual progression-free survival rate (e.g., 1-year progression-free survival rate)
  - Imaging intervals easily influence the objective tumor response
  - Definition of progression in some diseases varies between trials and groups
    - Definitions of PSA levels and progression of pain in prostate cancer are unclear.

→ **Difficult to compare with historical controls**

Green et al., *Clinical trials in Oncology, Third edition, Chapman&Hall/CRC*

Randomized Screening Design

- Randomized **standard treatment** and **study treatment**
- The number of patients enrolled is greater than that in single-arm trials and fewer than that in Phase III
  - About 100-200 patients
  - Slightly larger significance level, α error (10-20%)
- Endpoints
  - PFS is used in many cases.
  - OS and response rate are used occasionally.
- It is not a small-scale Phase III
  - Preliminary test prior to Phase III
  - Phase III is required even if significant results are obtained.



Rubinstein et al., JCO 2005:23;7199–7206

Example of Treatment Development using a Randomized Screening Design

Phase II

Previously treated stage IV colorectal cancer

Randomization — One-sided α=10%

57 patients: **Placebo**

112 patients: **TAS-102**

Yoshino et al. Lancet Onc. 2012;13 :993-1001.

Phase III

Previously treated stage IV colorectal cancer

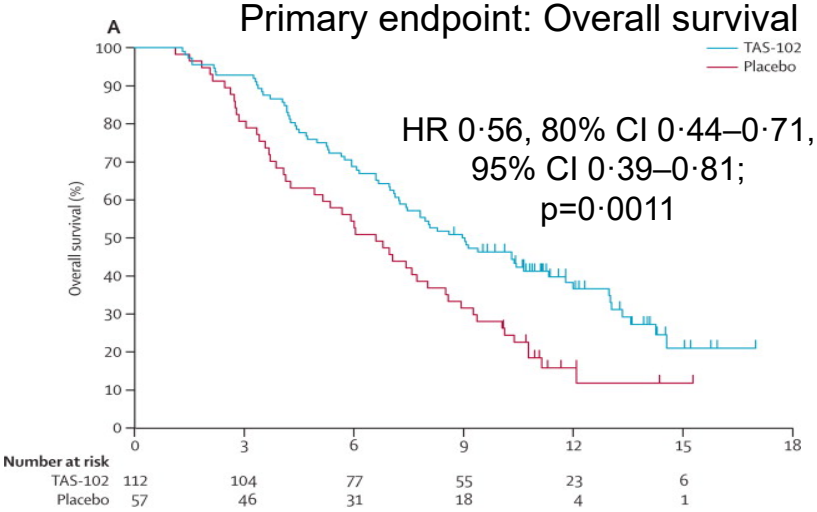
Randomization — One-sided α=2.5%

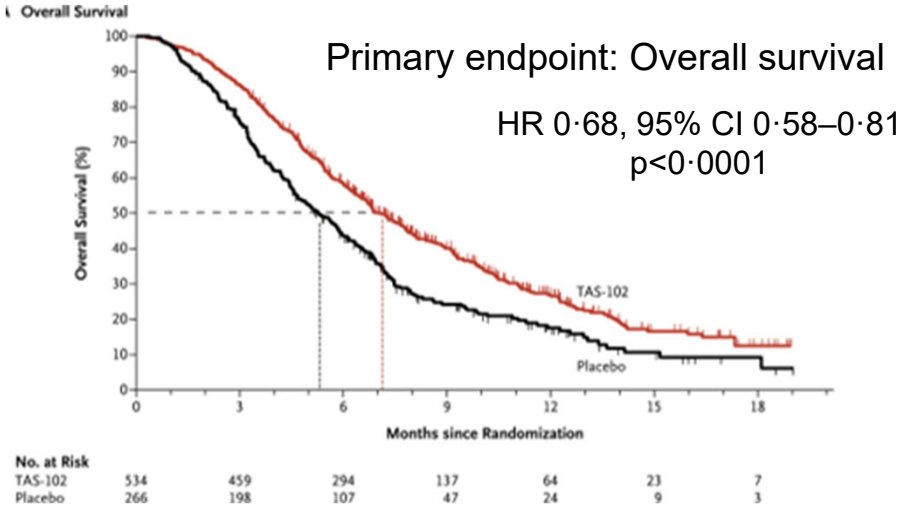
266 patients: **Placebo**

534 patients: **TAS-102**

Mayer RJ, et al. NEJM. 2015;372(20):1909-19.

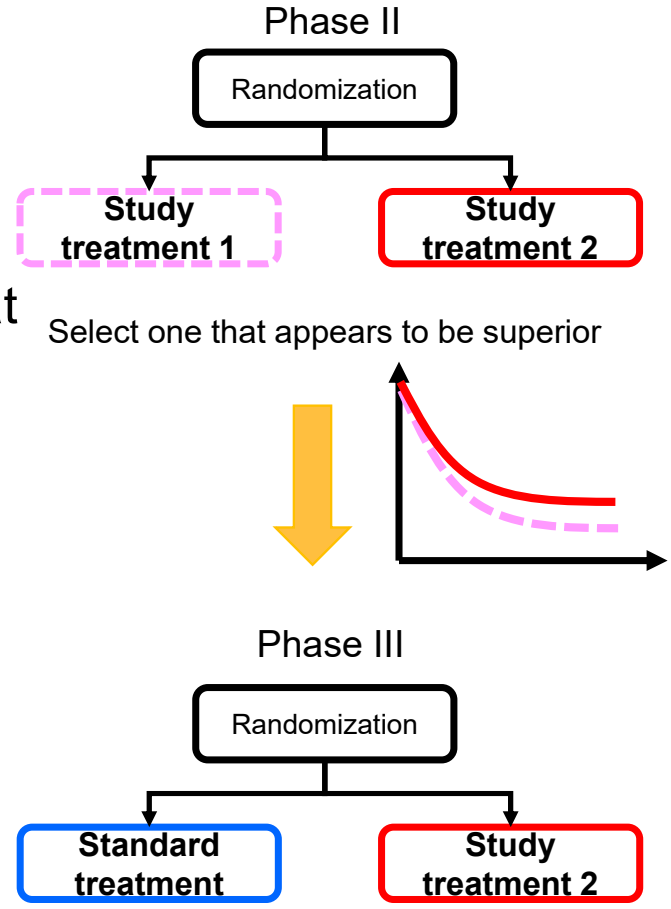
Primary endpoint: Overall survival





Randomized Selection Design

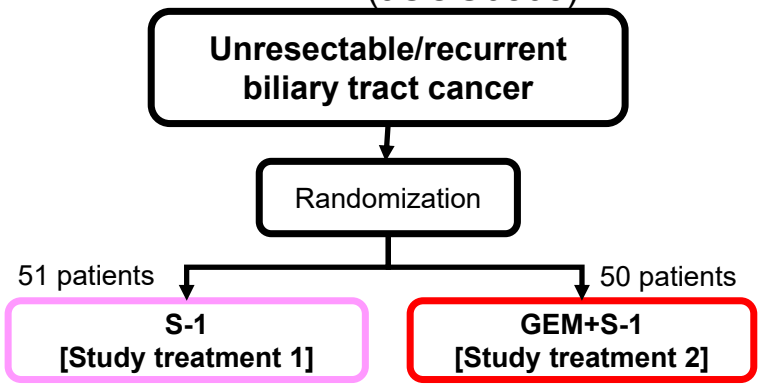
- Used to select one of the multiple study treatment candidates for Phase III
- Randomization between multiple **study treatments**
- Number of patients enrolled: equivalent to that in about two single-arm Phase II trials
  - About 100 patients as a guide
- Endpoints
  - Response rate, 6-month progression-free survival rate, 1-year survival rate, etc.
- Treatment that is even slightly more effective is selected.
  - Confident that it is not worse than other study treatments



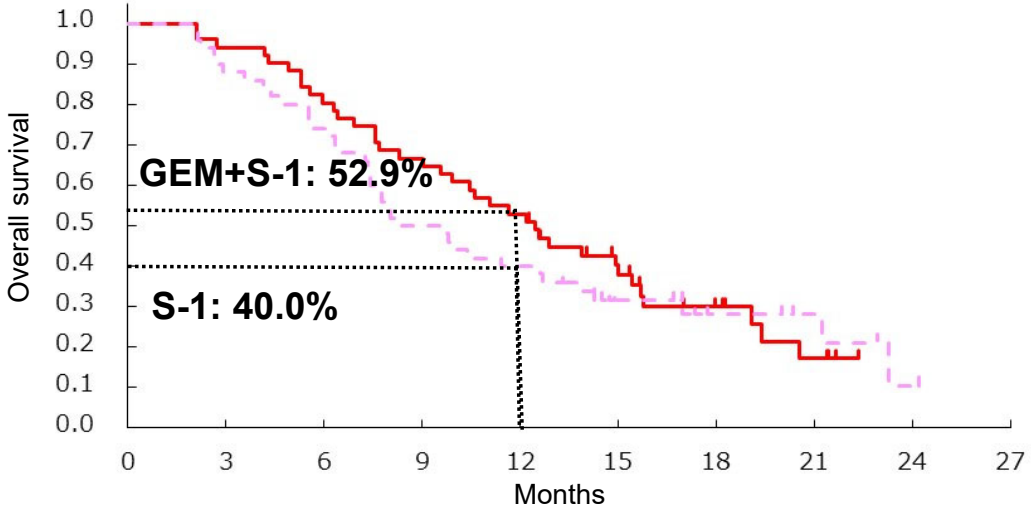
Simon R, Wittes RE, Ellenberg SS. Cancer Treat Rep. 1985;69(12):1375-81.

Example of Treatment Development using the Selection Design

Phase II (JCOG0805)

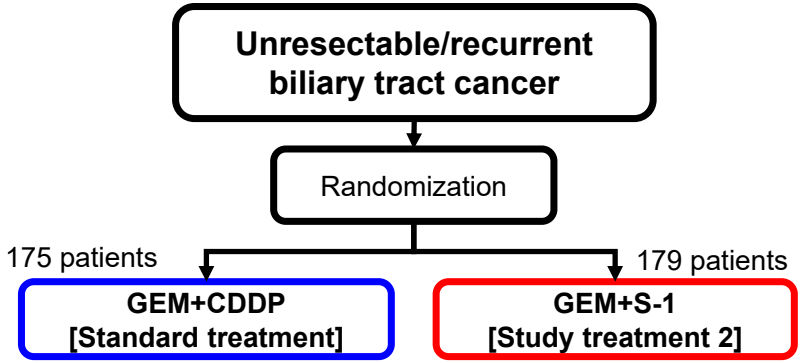


Primary endpoint: 1-year survival rate



Morizane C et al. Cancer science. 2013;104(9):1211-6.

Phase III (JCOG1113)



Primary endpoint: Overall survival

GEM+S-1 therapy with a superior 1-year survival rate by point estimate (not with a statistically significant difference) was selected as the study treatment for the Phase III trial, which was conducted with GEM+CDDP therapy as the standard treatment.

Morizane C et al. Annals of oncology.2019;30(12):1950-8.

Summary of Phase II Trial Designs

- Phase II trials primarily involve screening of candidate drugs by **efficacy**
- If there is adequate historical controls:
  - **Single-arm trial** with **response rate** as the primary endpoint
  - Two-stage design considering futility stopping
- Randomization if there is no adequate historical control
  - **Screening design** with randomized standard and study treatments
  - Phase III is required even if a large effect is observed and is significant
- Randomization if there are multiple study treatment candidates
  - **Selection design** with randomized study treatments
  - Next, Phase III for comparison against the standard treatment is required.

Outline

- Anticancer drug development flow and endpoints
- Phase I designs
- Phase II designs
- Phase III designs

Purpose and Overview of Phase III Trials

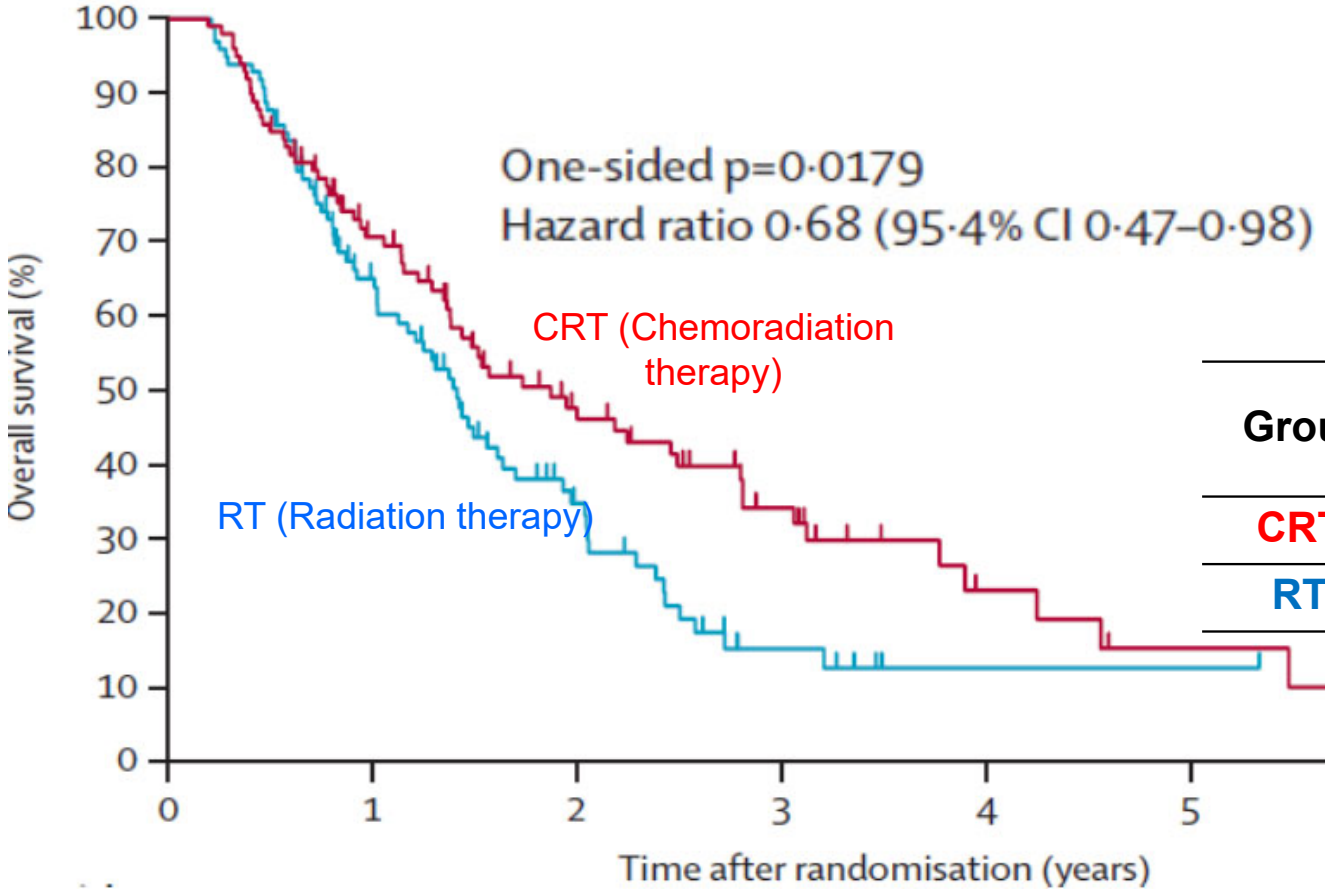
- Purpose
  - To determine whether the study treatment is going to become the standard treatment (or receive approval)

- Typical design
  - Target: Patients meeting broader eligibility criteria than Phase I or Phase II criteria
    - Considering the extent to which the conclusions drawn are applicable (**generalizability [external validity]**)
  - Number of patients enrolled: Several hundred to several thousand patients
  - Participating facilities: Including general hospitals
  - Endpoints: OS, relapse-free survival, etc.
    - True endpoints that directly reflect a patient benefit
  - Ensuring **comparability** by **randomization**

Positive Primary Outcome in Phase III Trials

National Cancer Center Japan

Because the study treatment (CRT) is superior to the standard treatment (RT) in terms of overall survival, CRT becomes the new standard treatment.



JCOG0301

Unresectable stage III non-small cell lung cancer in patients aged 71 years or older

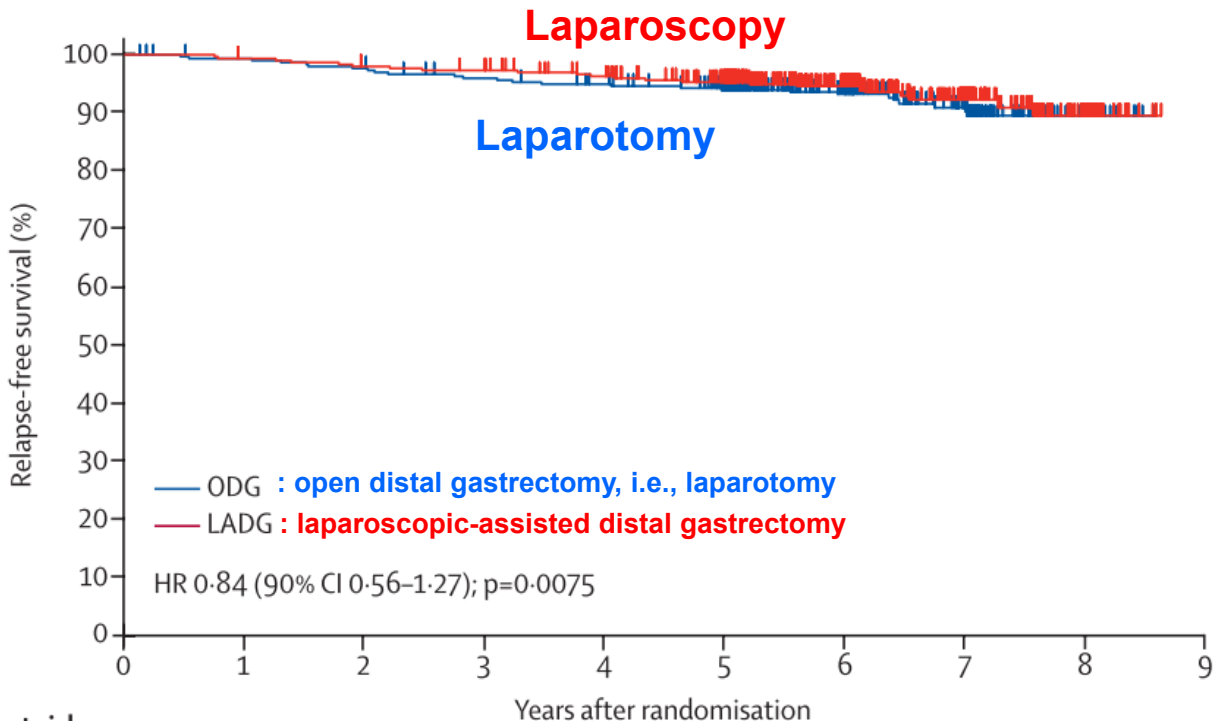
100 patients — Randomization — 100 patients

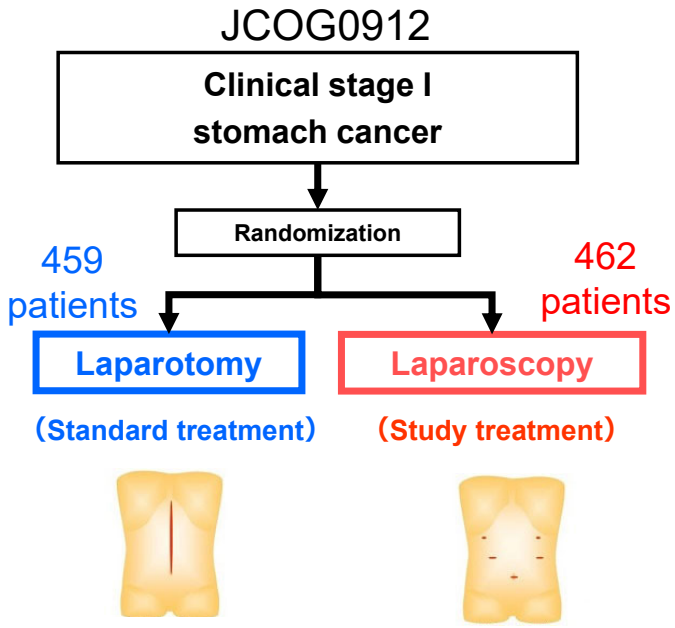
- **Radiation therapy alone (RT)** (Standard treatment)
- **Radiation therapy + chemotherapy(CRT)** (Study treatment)

Group	Median survival	2-year survival rate
CRT	22.4 months	46.3%
RT	16.9 months	35.1%

Atagi S, et al. The Lancet Oncology. 2012;13(7):671-8.

Does the study treatment need to be superior ?



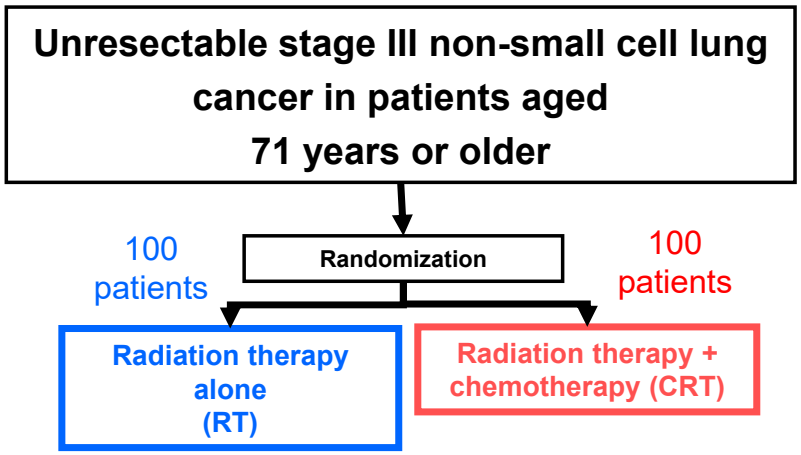


Since the study treatment (laparoscopy) is not superior to the standard treatment (laparotomy) in terms of relapse-free survival, does laparotomy continue to be the standard treatment?

Katai et al., Lancet Gastroenterol Hepatol. 2020;5(2):142-51.
https://www.ncc.go.jp/jp/ncch/clinic/gastric_surgery/020/index.html

Comparison Types: Superiority and Non-Inferiority Trials

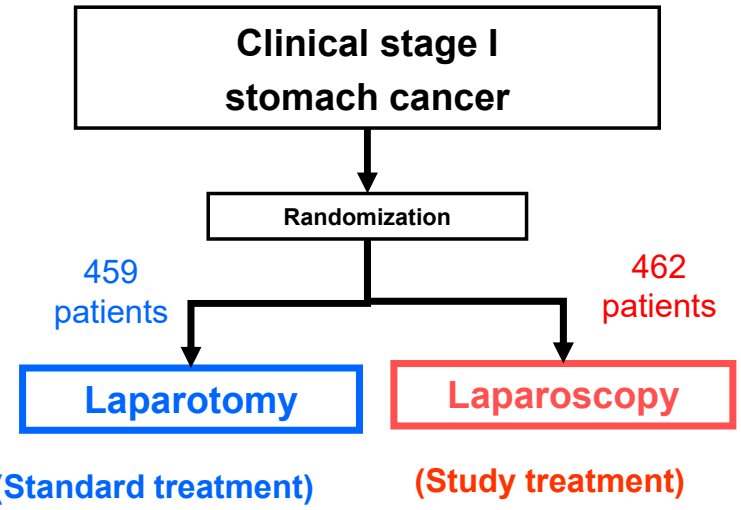
JCOG0301



Superiority trial

- Study treatment must be superior in efficacy.
- Study treatment has a higher toxicity than standard treatment (**Toxic new**).

JCOG0912



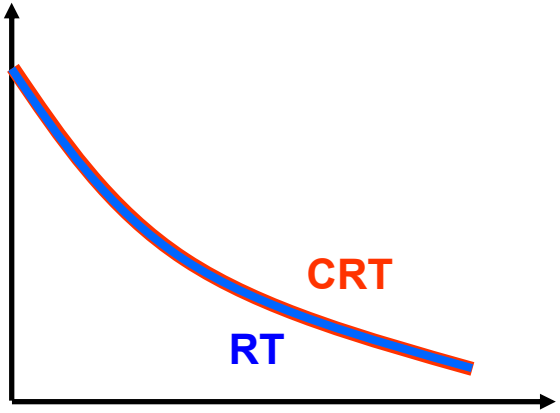
Non-inferiority trial

- Study treatment is preferred if its efficacy is not inferior by a certain degree.
- Study treatment has lower toxicity than standard treatment (**Less toxic new**).

How to decide superiority/non-inferiority when planning a trial

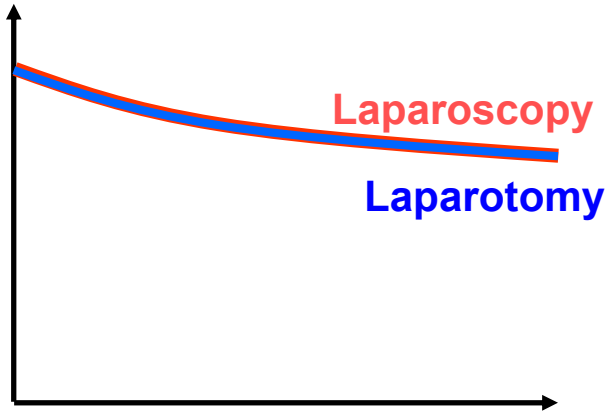
- Decision-making in the context of overlapping **efficacy endpoints** (survival curves)
  - Selecting **standard treatment** → **Superiority trial**
  - Selecting **study treatment** → **Non-inferiority trial**

JCOG0301



If **CRT** **(toxic new)** has high toxicity and requires a lot of time and effort for treatment and if **RT** has the same **overall survival**, then **RT** is the standard treatment .
→ **Superiority trial**

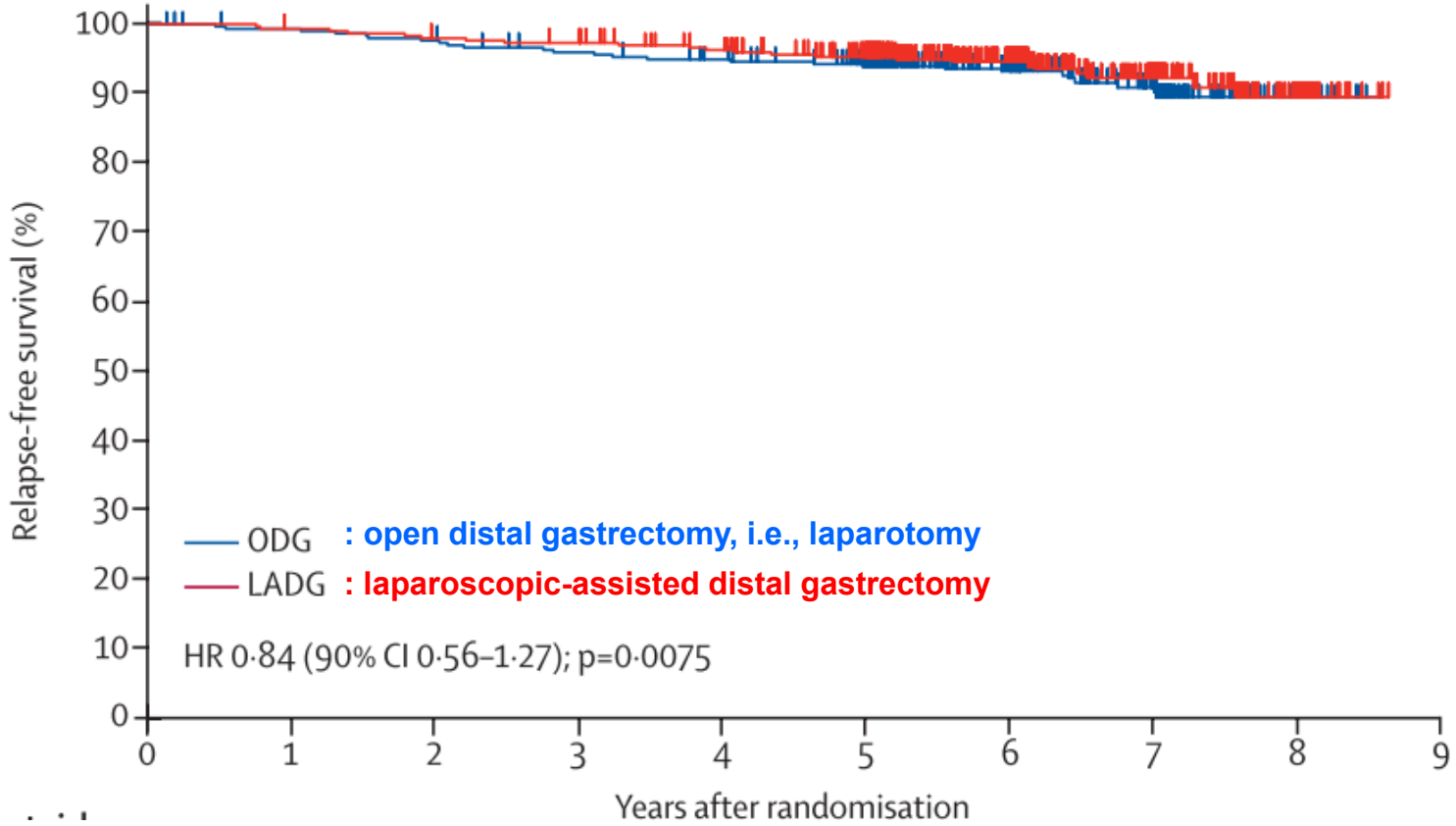
JCOG0912



If **laparoscopy** **(less toxic new)** results in smaller scars and has the same **relapse-free survival** as **laparotomy**, then **laparoscopy** is the standard treatment.
→ **Non-inferiority trial**

Example of Non-Inferiority Trial: JCOG0912

Because the study treatment (laparoscopy) is not inferior to the standard treatment (laparotomy), laparoscopy becomes the new standard treatment.



Katai et al., Lancet Gastroenterol Hepatol. 2020;5(2):142-51

Review Questions: Please choose YES or NO

1. CRM is a Phase II trial design.

2. Screening design is one of the Phase II trial designs comparing the standard treatment and study treatment.

3. A non-inferiority trial involves a type of comparison used when the study treatment is “less toxic new.”

4. In selection design, when tests show significant results, the trial is proceeded to Phase III.

Review Questions: Please choose YES or NO

1. CRM is a Phase II trial design. NO

2. Screening design is one of the Phase II trial designs comparing the standard treatment and study treatment. YES

3. A non-inferiority trial involves a type of comparison used when the study treatment is “less toxic new.” YES

4. In selection design, when tests show significant results, the trial is proceeded to Phase III. NO

Take-Home Messages

- Phase I: Any cancer types, high patient risk, single to a few specialized facilities
  - **Screening by safety**: Toxicity (DLT) as an endpoint
  - Determination of the recommended dose
- Phase II: Cancer type-specific, medium patient risk, a limited number of facilities, mainly specialized hospitals
  - **Screening by efficacy**: Response rate, etc., as an endpoint
  - Is there a reliable historical control?
    - Yes: Single-arm
    - No: Randomized screening design with standard treatment
  - Prioritization of study treatments: Selection design
- Phase III: Cancer type-specific, low patient risk, many facilities, including general hospitals
  - **Final match against** conventional **standard treatment**: Evaluation using true endpoints
  - Superiority trial: Standard treatment vs. "toxic new" study treatment
  - Non-inferiority trial: Standard treatment vs. "less toxic new" study treatment