国立がん研究センターにおける
生物統計家の活動と海外との連携

Biostatisticians' activities and collaboration with foreign investigators at National Cancer Center

Taro SHIBATA
Biostatistics Division,
Center for Research Administration and Support,
National Cancer Center

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

National Cancer Center

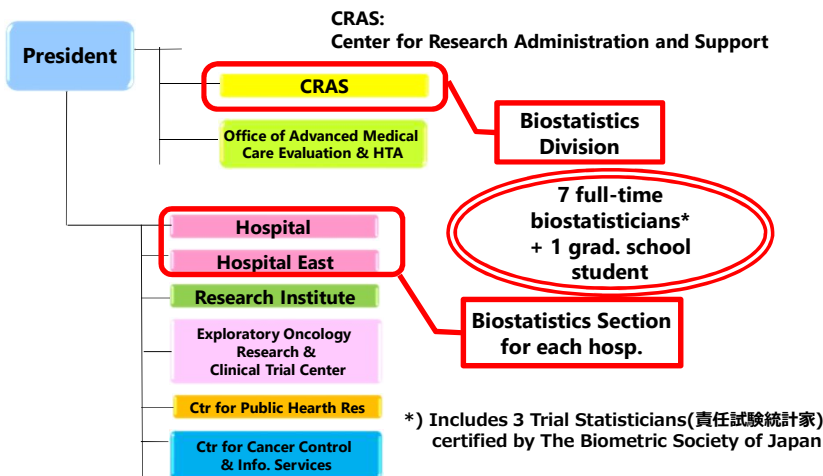Est. 1962, one of six national centers in Japan

Missions

1. **Discovering the fundamental causes of cancer and realizing its earliest diagnosis and prevention**
2. **Developing innovation in medical prevention, diagnosis and treatment**
3. **Establishing and making available the most advanced standard of care to all patients**
4. **Exploring and providing the best "cancer survivorship" for patients**
5. **Gathering and disseminating comprehensive cancer related information to the community**
6. **Talent development of all NCC staff members**
7. **Recommending new initiatives and policy to the government**
8. **Contributing to global society in collaboration with international organizations**

2

Organization of NCC

CRAS:
Center for Research Administration and Support

- President
  - CRAS
    - Biostatistics Division
    - 7 full-time biostatisticians* + 1 grad. school student
    - Biostatistics Section for each hosp.
  - Office of Advanced Medical Care Evaluation & HTA
  - Hospital
  - Hospital East
  - Research Institute
  - Exploratory Oncology Research & Clinical Trial Center
  - Ctr for Public Hearth Res
  - Ctr for Cancer Control & Info. Services

*) Includes 3 Trial Statisticians(責任試験統計家) certified by The Biometric Society of Japan

3

Mission & Activity of Biostatistics Div.

Mission

- **To contribute to the providing best evidence and the improvement of clinical practice and public health through the development and application of statistical methods.**

Activity

- **Collaboration**
- **Consultation**
- **Training and education**
- **Methodological Research**

https://www.ncc.go.jp/en/cras/biostatistics/   4

Slide 5
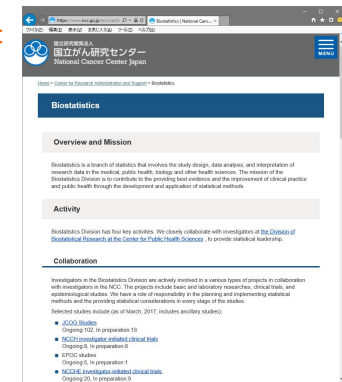
Examples of our activity

- **Collaboration, as a trial statistician**
  - **JCOG Studies**: Ongoing 101, in preparation 18
  - **NCCH investigator-initiated clinical trials**: Ongoing 8, in preparation 8
  - **EPOC Studies**: Ongoing 5, in preparation 1
  - **NCCHE investigator-initiated clinical trials**: Ongoing 20, in preparation 9

  (as of March 2017, includes ancillary studies of clinical trial, and IIT includes "Chiken")
- **136 consultations/FY2016 (_not includes_ consultation activity within above collaboration as a trial statistician)**

5

Slide 6
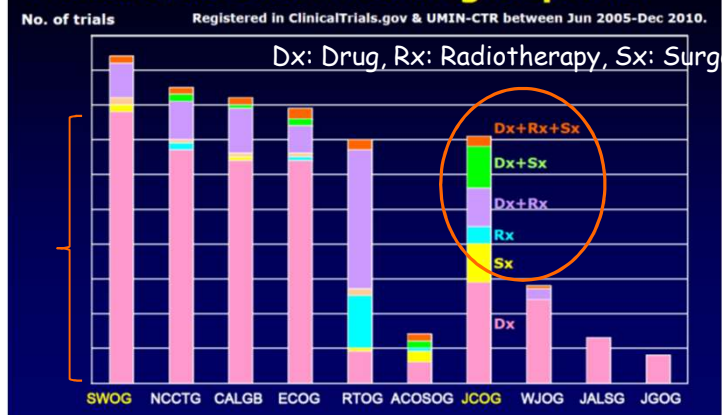
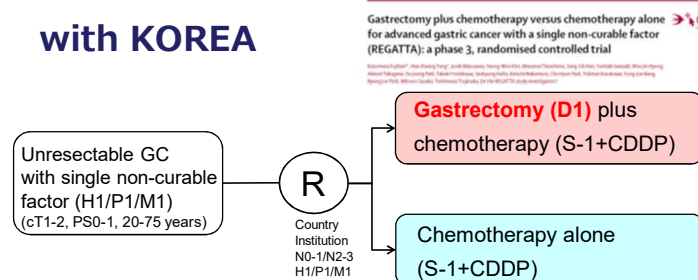Kunieda F., Nakamura K. et al., J Clin Oncol 29: 2011 (suppl; abstr e16554) .

6

Slide 7

JCOG0705/KGCA01 (REGATTA trial) with KOREA

Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial

- Primary endpoint: OS
- Planned accrual: n=330 (at least 110 pts from each country)
- Two data centers, One primary analysis (publication)

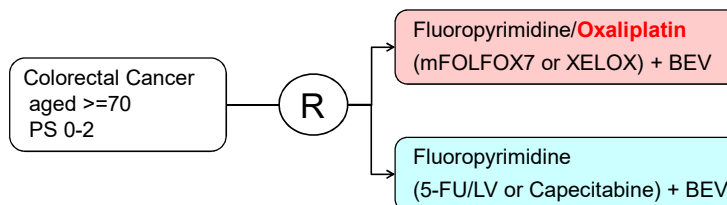JCOG
Japan Clinical Oncology Group

7

Slide 8

JCOG1018 with NCCTG

NCCTG JCOG
Japan Clinical Oncology Group

- Primary endpoint in each country: PFS (n=380)
- Primary endpoint for combined analysis: OS (n=760)
- Two data centers
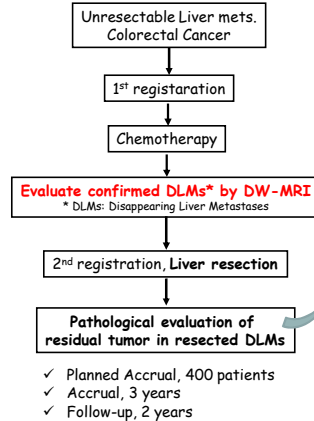- Two primary analyses (publications) followed by pre-planned combined analysis

8

DREAM study with EORTC

UMIN000024890

(EORTC-1527-GITCG-IG/JCOG 1609INT)

Unresectable Liver mets. Colorectal Cancer
↓
1st registration
↓
Chemotherapy
↓
Evaluate confirmed DLMs* by DW-MRI
* DLMs: Disappearing Liver Metastases
↓
2nd registration, **Liver resection**
↓
Pathological evaluation of residual tumor in resected DLMs

✓ Planned Accrual, 400 patients
✓ Accrual, 3 years
✓ Follow-up, 2 years

Study Chair
✓ Serge Evrard (Institut Bergonie, France)
✓ Manabu Shiozawa (Kanagawa Cancer Center)

Participating sites
✓ Japan, 12 sites
✓ EU/US, 16 sites

Role of NCCH
✓ Liaison between Japan and EORTC HQ (Agreement, Site management, Study progress, Query assistance etc.)
✓ Project management on Japanese side
✓ Participation in the Steering Committee

Funding
✓ AMED (2016-) research fund on Japanese side

● One data center
● One primary analysis (publication)

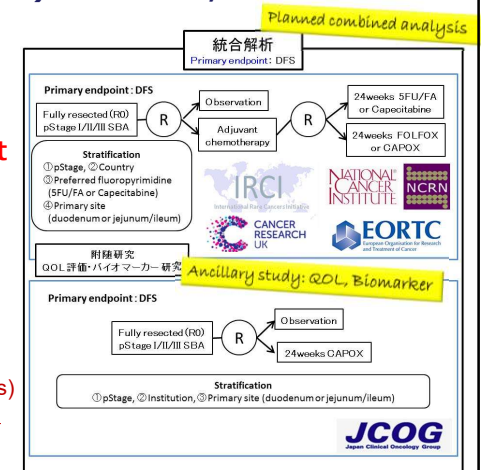Slide by Dr.Ken-ichi NAKAMURA @ NCCH (partially modified)

9

JCOG1502C(J-BALLAD) with IRCI, NCI etc.

UMIN000027280

Japanese trial -A Global Study To Evaluate The Potential Benefit of **Adjuvant Chemotherapy** for Small Bowel Adenocarcinoma [小腸腺癌]

● Primary endpoint: RFS (n=150)
● Two data centers
● Two primary analyses (publications) followed by pre-planned combined analysis

10

NCCH1607 with Korea, Taiwan & Singapore

UMIN000030816/NCT03423199

A Randomized, Double Blind, Placebo Controlled, Phase 3 Trial for Hormone Receptor Positive, HER2 Negative Locoregionally Recurrent or Metastatic Breast Cancer（NCCH1607, PATHWAY)

Placebo +Tamoxifen +/- Goserelin
vs
Palbociclib +Tamoxifen +/- Goserelin

● Investigator initiated "Chiken"
● Pfizer as a collaborator/sponsor
● One data center
● One primary analysis (publication)

11

Collaborative research with SWOG
－SWOG0124 and JCOG9511－

• Combined analyses of safety data from two similar RCTs of
  – CDDP+VP16 vs CDDP+CPT-11 for ED-SCLC
• To explorer the difference of AE/ADR between two trials

	CDDP+VP16		CDDP+CPT-11	
	JCOG9511	SWOG0124	JCOG9511	SWOG0124
	n=77	n=276	n=75	n=278
Neutropenia	92%	66%	65%	32%
Leukopenia	53% >	33%	27% >	17%
Anemia	32%	13%	28%	6%
Platelets	18%	15%	5%	4%
Infection	4%	16%	5%	11%
Vomiting	6%	9%	13%	10%
Diarrhea	0%	3%	16%	18%

from Lara *et al.* ASCO2007 abstract#7524.
Lara *et al*. Cancer 116:5710-5715, 2010.

12

Methodological Projects with Foreign Investigators

- Statistical methods in studying etiologic heterogeneity among disease subtypes
  - Motivated by large prospective cohort studies with retrieving tumor tissues from incidence cancer patients
  - A cancer can be classified into subtypes by molecular and pathological features
  - Epidemiological research questions may be
    whether disease subtypes have similar or distinct etiology?
    which are the etiologically distinct subtypes?
    - e.g., smoking moderately increases the risk of overall CRC.
      Some evidence shows that smoking may increase the risk of BRAF-mutated CRC, but not be associated with BRAF wild-type CRC.
- Statistical issues include:
  - Developing statistical models to address those questions
  - Study design consideration
  - Missing data problems on molecular data   etc…

13

Collaborative Research Activities

- Specific activities:
  - Writing research papers together
  - Proposed and organized Invited Session in ENAR spring meeting
  - Skype meeting as appropriate
    - a short catch-up, usually once a month

- Preparation for submitting NIH grant application
  - Have formal subcontract agreement between PI's institute (US) and NCC
    - Including budget plan for the activities

14

Collaboration between JCOG & EORTC

A new global partnership to improve surgical care: EORTC 1527 DREAM opens

http://www.eortc.org/c/news/

(Evrard S et al. Ann Surg 2016)

(Kataoka K et al. JJCO2016)

- SURCARE program (Surgical QC/QA program)
- Exchange program for young investigators
- JCOG-EORTC international symposium (Dec 2017)
- New study concept discussed in gastric cancer & pathology

Slide by Dr.Ken-ichi NAKAMURA @ NCCH

15

http://www.eortc.org/blog/2018/02/01/european-and-japanese-clinical-research-organisations-meet-to-collaborate-on-future-studies-in-cancer/

16

MASTER KEY PROJECT(NCCH1612) — UMIN000027552

Slide by Dr.Ken-ichi NAKAMURA @ NCCH (partially modified) 17

Summary

- **Strength**
  - **Supportive environment, e.g. mind of clinicians, for biostatisticians**
  - **Many clinical trials are ongoing or in-preparation**
  - **Experience of multi-modality, non-pharmaceutical clinical trials**
  - **Network of international collaboration**

- **Perspective**
  - **New framework for clinical trial, i.e. collaboration with basic scientists, informaticians, outreach specialists etc.**

18