ICH E17

General Principles for Planning and Design of Multi-Regional Clinical Trials

Future MRCTs Based on E17 Guideline

- Definition of Region & Consideration of Ethnic Differences -

Hideharu Yamamoto, PhD
E17 JPMA EWG
Chugai Pharmaceutical Col, Ltd

生物統計学シンポジウム Mar.14, 2018

Outline

- Background and Key Principles in E17
- Some case studies of Gastric Cancer in MRCT conducted by Roche
- Impact of ICH-E17 Guideline on Global Industry and Biostatisticians

Outline

- Background and Key Principles in E17
- Some case studies of Gastric Cancer in MRCT conducted by Roche
- Impact of ICH-E17 Guideline on Global Industry and Biostatisticians

Regulatory Guidelines and ICH E17

1998 ICH E5 "*bridging*"
Ethnic Factors in the Acceptability of Foreign Clinical Data

2006 ICH E5 Q&A No.11

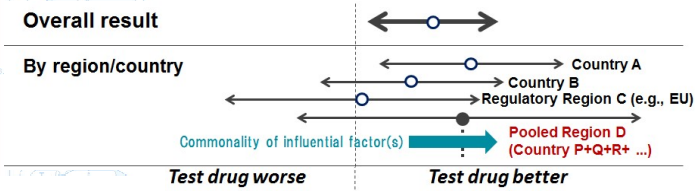
2007 Japan PMDA/MHLW guidance:
Basic Principles on Global Clinical Trials

2009 EU
Reflection paper on the extrapolation of results from clinical studies conducted outside of the EU to the EU population

2015 CFDA IMCT guidance
Guidance for International Multicenter Clinical Trials (IMCT)

Coming ICH E17: *To provide common points to consider in planning/designing MRCTs and minimizing conflicting opinions from regulatory bodies*

How to look at the results from MRCT



5

Possible causes of difference among regions

Non-compliance with GCP and/or protocol

Apparent Differences (Play of chance)

Real differences

6

What makes differences?

Non-compliance with GCP and/or protocol

We don't want to put those causes on the table we are going to discuss

So, E17 guideline emphasizes the importance of
[Planning] Risk assessment, Common training etc.
[Conducting] Monitoring, Quality Management System

But we always need to keep in mind this possibility

7

Our Question is...

Apparent Differences (Play of chance)

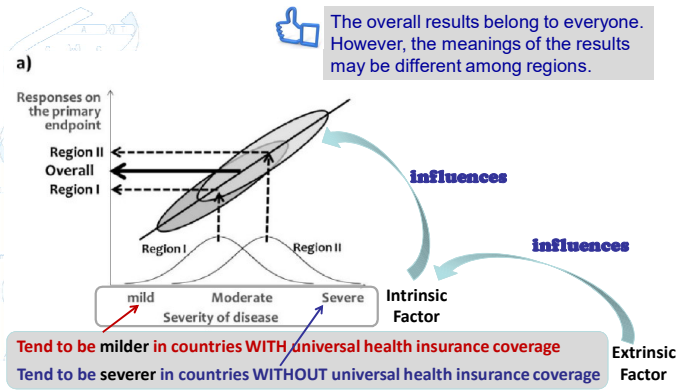
The smaller the local sample sizes, the more likely false signals are observed

Real differences

Real differences are *foreordained* by influential ethnic factor(s) or those distribution

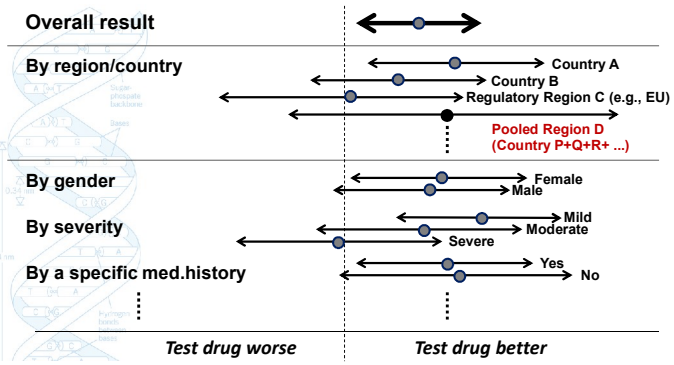
8

Real differences illustrated in Fig.2



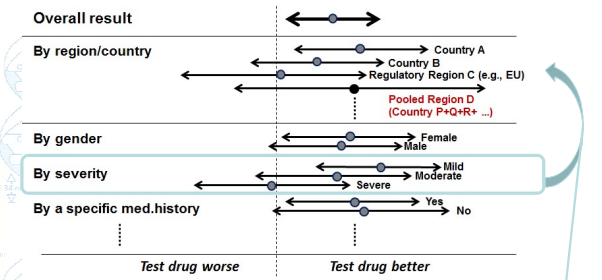
9

Forest Plot: Summary of subgroup analyses



10

If you found influential factor(s)...

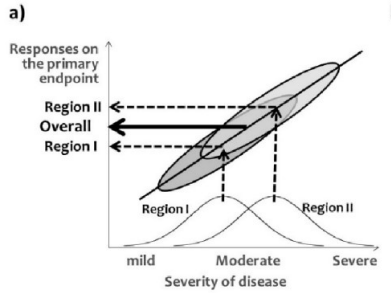


Try to explain by different distribution of influential intrinsic ethnic factor(s) among regions

11

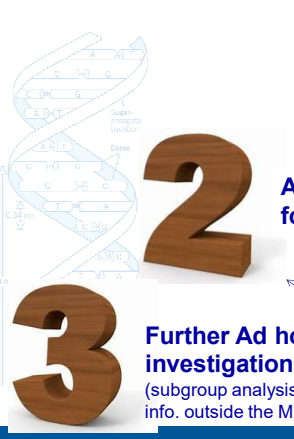
If you found influential factor(s)...

Can we explain like this?



12

Structured exploration of regional differences



1 **Preplanned analysis for Known factors**

2 **Ad hoc analysis for possible factors**

3 **Further Ad hoc investigation** (subgroup analysis, info. outside the MRCT)

- **Prognostic factors** of the disease
- **Predictive factors** of the treatment outcome

13

Outline

- Background and Key Principles in E17
- Some case studies of Gastric Cancer in MRCT conducted by Roche
- Impact of ICH-E17 Guideline on Global Industry and Biostatisticians

14

Example：ToGA Trial (2005-2008)

3807 patients screened
810 HER2-positive (22.1%)
→ HER2-positive advanced GC n=584
→ R
→ 5-FU or capecitabine + cisplatin (n=290)
→ 5-FU or capecitabine + cisplatin + trastuzumab (n=294)

- ToGA was an open-label, international, phase 3, randomized controlled trial undertaken in 24 countries in Asia, Europe and Central and South America.
- Patients with gastric or gastro-oesophageal junction cancer were eligible for inclusion if their tumors overexpressed the HER2 receptor
- Primary endpoint was OS (overall survival)

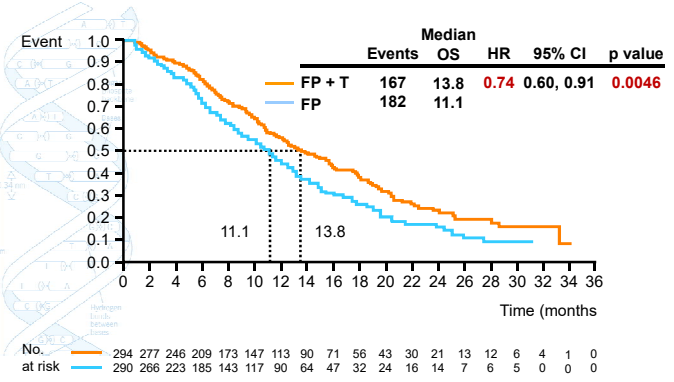
ToGA Sample Size in Japan

- ToGA Overall Sample Size
  - MST: 10 months vs 13 months (HR=0.77)
  - 460 events (α=5% 1-β=80%, log-rank test), 584 pts
- Japanese Sample Size
  - Pre-specification of Japanese sample size
  - "Signal" of efficacy in Japan is at least needed when the overall population demonstrates a significant difference
    - P_1=Pr(HR_{Japan} < **0.88** | true HR_{Japan}=$HR_{Overseas}$=0.77)
    - P_0=Pr(HR_{Japan} < **0.88** | true HR_{Japan}=1.0)

#event	P_1	P_0	Sample size
60	0.697	0.310	76
70	**0.712**	**0.296**	**89**
80	0.725	0.284	102
90	0.737	0.272	114
100	0.748	0.261	127

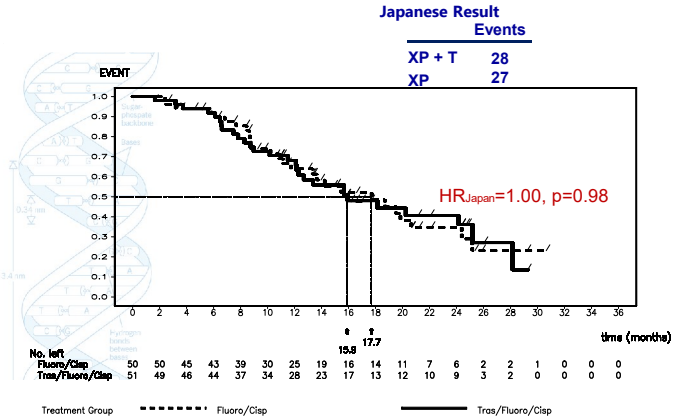
16

Primary Endpoint: OS



17

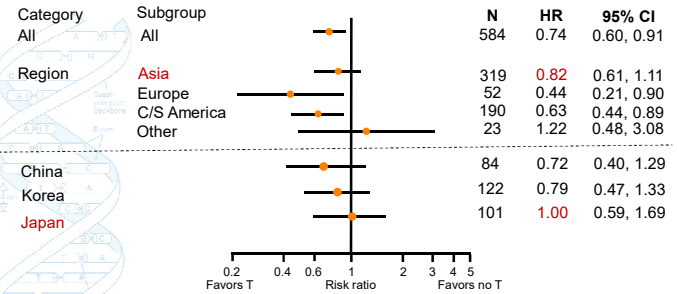
OS for Japanese Population



Roche

18

OS Subgroup Analysis



No benefits of Trastuzumab for Japanese patients?

Roche

19

Pre-planned Analysis in Japanese Population

- Document similar to the protocol that addresses particular matters concerning Japan (additional information for conducting ToGA study in Japan)
  - Possibility that some demographic or baseline factors might be imbalanced because of the small number of Japanese patients
  - Pre-planning to use an adjustment HR in the Japanese subgroup using multivariate Cox regression with 15 factors
  - All factors were pre-specified in the ToGA study protocol

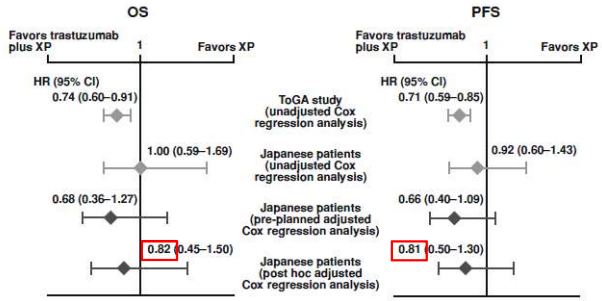
20

Preplanned & Post hoc Analysis for Japanese Population

- As a result of Multivariate analysis, adjusted HR for Japan subgroup changed to 0.68 from 1.00
- Estimates of effects were extremely unstable for covariates that contained a category which include only one patient
- To ensure stability of the model, a post hoc analysis was conducted
  - HER2 status was divided into two categories: high vs low expression
  - Covariates that contained a category with only one patient were excluded from the model
- Adjusted HR=0.82 (95%CI: 0.45-1.50)
- PFS had a similar result to OS
- Adjusted HRs for Korea and China subgroup were not changed so large

21

OS and PFS in Preplanned & Post hoc Analysis for Japanese Population



These results suggest that the same benefit was obtained in the Japanese subgroup as in the overall population

22

Why were Different HRs Observed?

- Some factors with imbalanced in the ratio of enrollment to each arm in the Japanese population (GC type, prior gastrectomy, PS 0 vs. 1, No. of metastatic sites)
- Chemo arm was imbalanced towards a better prognosis for these factors compared with Herceptin arm
- To confirm that the HR is robust, it is necessary to analyze different combinations of factors
  - We found that the HRs were approximately 0.7 for all combinations of factors, supporting the robustness of our results (Sawaki, et.al 2011)

23

Conclusion: ToGA Trial

- Pre-planned and post-hoc analyses suggest that the benefits of Herceptin are of the same magnitude in Japanese patients
- Herceptin can be considered a new standard therapy for Japanese patients with HER2 + mGC

Herceptin for mGC was approved in Japan in March 2011

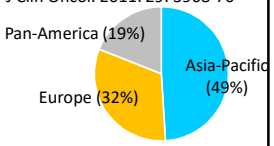
24

Examples: AVAGAST Trial (2007-2008)

Phase III trial assessing the clinical efficacy and safety of bevacizumab added to chemotherapy for first-line treatment of advanced gastric cancer

J Clin Oncol. 2011: 29: 3968-76

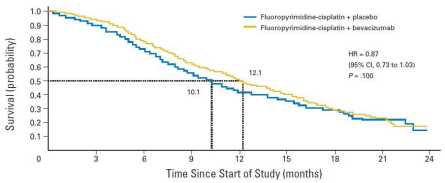
AVAGAST was a prospective, random-assignment, double-blind, placebo-controlled global phase III clinical trial.



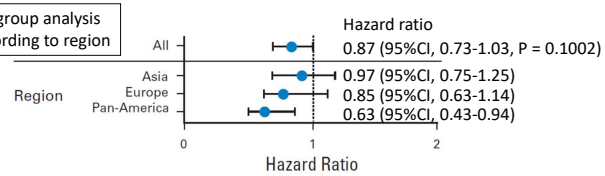
774 Pts with previously untreated advanced gastric cancer → R 1:1
- Bevacizumab + Standard Chemotherapy
- Placebo + Standard Chemotherapy

- Primary endpoint: Overall survival
- Stratification factors: Geographical region (Asia, Europe, Pan-America)

Examples: AVAGAST Trial



Subgroup analysis according to region



Bevacizumab seems to be effective in Pan-American patients, but not in Asian patients.

Examples: AVAGAST Trial

Author's explanation about the inconsistent result on overall survival among populations

(J Clin Oncol. 2011: 29: 3968-76)

- Although gastric cancer is a global disease, it is not uniform. There are differences in the presentation and management of gastric cancer patients in different countries and regions.
- Asian patients
  - more commonly receive second and further lines of therapy
  - more frequently have a prior history of gastrectomy
  - less frequently have liver metastases of proximal or gastroesophageal junction tumors.

⇒ These difference in extrinsic ethnic factors might have caused the inconsistent result.

Examples: AVAGAST Trial

Region	OS			PFS		
	PL (months)	BV (months)	HR (95%CI)	PL (months)	BV (months)	HR (95%CI)
Asia / Pacific	12.1	13.9	0.97 (0.75-1.25)	5.6	6.7	0.92 (0.74-1.14)
Japan	14.2	15.4	0.96 (0.67-1.39)	5.7	6.8	0.99 (0.73-1.35)
Korea	10.9	13.8	0.89 (0.60-1.33)	5.4	6.6	0.79 (0.56-1.11)
Non- Asia / Pacific	8.0	11.1	0.76 (0.60-0.97)	4.4	6.8	0.69 (0.56-0.85)
Europe	8.6	11.1	0.85 (0.63-1.14)	4.4	6.9	0.71 (0.54-0.93)
Americas	6.8	11.5	0.63 (0.43-0.94)	4.4	5.9	0.65 (0.46-0.93)

Especially no benefits of Bevacizumab for Japanese patients?

Example: JACOB study (2013-2017)

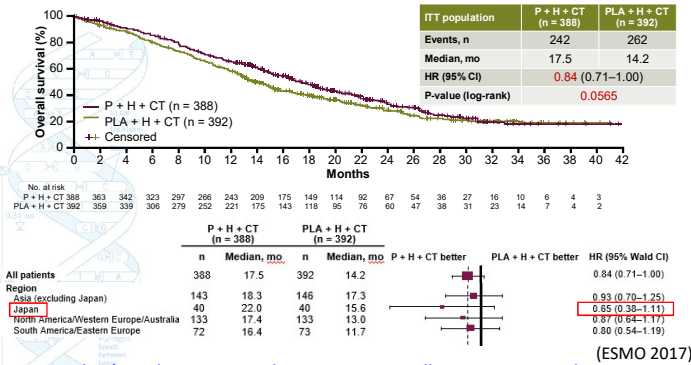
- JACOB was a prospective, random-assignment, double-blind, placebo-controlled global phase III clinical trial.

780 Pts with previously untreated advanced gastric cancer → R 1:1

- Pertuzumab + Trastuzumab + Standard Chemotherapy
- Placebo + Trastuzumab + Standard Chemotherapy

- Primary endpoint: Overall survival
- Key eligibility criteria: HER2-positive mGC/GEJC
- Stratification factors: Geographical region, Prior gastrectomy
  - Asia [excluding Japan]
  - Japan
  - North America/Western Europe/Australia
  - South America/Eastern Europe

Example: JACOB study



ITT population	P + H + CT (n = 388)	PLA + H + CT (n = 392)
Events, n	242	262
Median, mo	17.5	14.2
HR (95% CI)	0.84 (0.71–1.00)	
P-value (log-rank)	0.0565	

	P + H + CT (n = 388) n	P + H + CT (n = 388) Median, mo	PLA + H + CT (n = 392) n	PLA + H + CT (n = 392) Median, mo	HR (95% Wald CI)
All patients	388	17.5	392	14.2	0.84 (0.71–1.00)
Region					
Asia (excluding Japan)	143	18.3	146	17.3	0.93 (0.70–1.25)
Japan	40	22.0	40	15.6	0.65 (0.38–1.11)
North America/Western Europe/Australia	133	17.4	133	13.0	0.87 (0.64–1.17)
South America/Eastern Europe	72	16.4	73	11.7	0.80 (0.54–1.19)

P + H + CT better | PLA + H + CT better

(ESMO 2017)

⇒ Author's explanation was that OS was generally consistent in subgroups. It is difficult to conclude the Japanese patient has no benefit for gastric cancer.

Outline

- Background and Key Principles in E17
- Some case studies of Gastric Cancer in MRCT conducted by Roche
- Impact of ICH-E17 Guideline on Global Industry and Biostatisticians

ICH E17 – Think Globally

- Promote MRCT
  - Reduce the need to conduct standalone regional or national studies, including bridging studies
  - Build up scientific capabilities and infrastructure globally
- Promote international harmonization
  - A globally harmonized approach to drug development should be considered first
- Provide better evidences for drug approval in each region
  - Encourage better planning and design of MRCTs based on the latest scientific knowledge and experiences

From a Global Industry Perspective

- **Big differences** between **"Multi-National Clinical Trials"** and **MRCT** under E17
- Some points to consider for the global industry
- Global industry
  - will take care of regional differences and ethnic factors more than before
  - will consider acceptability from every participating region/country more than before
  - should define the region (pooled region) and determine the sample size allocation to each region ***at the planning stage***
  - should obtain HA's agreement with the proposed analysis strategy about regional consistency

33

Significant Factors to Consider for a Successful MRCT

- Timing of participation to the MRCT
  - late timing of participation to the MRCT can not keep the pre-specified sample size
- How to manage the speed of subject enrollment among regions
  - different speed of enrollment among regions could result in difficulties in evaluating the consistency
- How to manage to obtain the homogeneous baseline characteristics among regions as much as possible
  - different baseline characteristics could influence the consistency of results

34

Significant Factors to Consider for a Successful MRCT

- How to interpret a regional difference in the efficacy among regions
  - important to be able to explain the regional difference
- Pre-specify in the Protocol/SAP not only subgroup analysis but also model analysis adjusted by prognostic factors
  - ad-hoc analysis or exploratory analysis are very helpful to interpret the regional difference

35

Thank you for your attention!