PMDA Workshop

Future Perspectives in the Development of Novel Medications for IBD

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# Present Situation and Problems of Clinical Trials for inflammatory bowel disease in Japan

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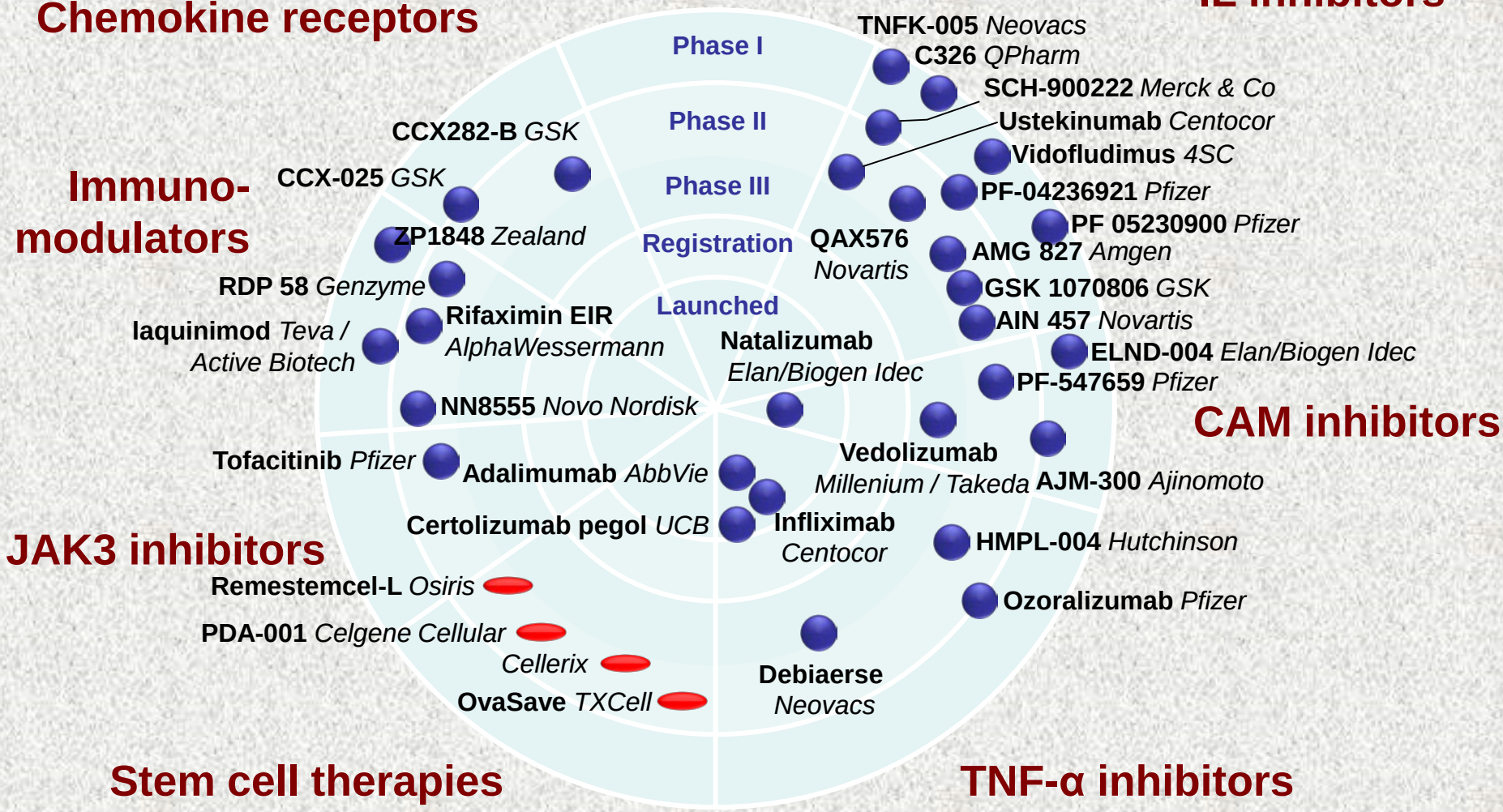
# Available or Provisionally Applicable Biologics for the Treatment of Crohn's Disease




*Danese S: Gut 2012*

# Present Situation and Problems of Efficacy Assessment in Biologics for Crohn's Disease

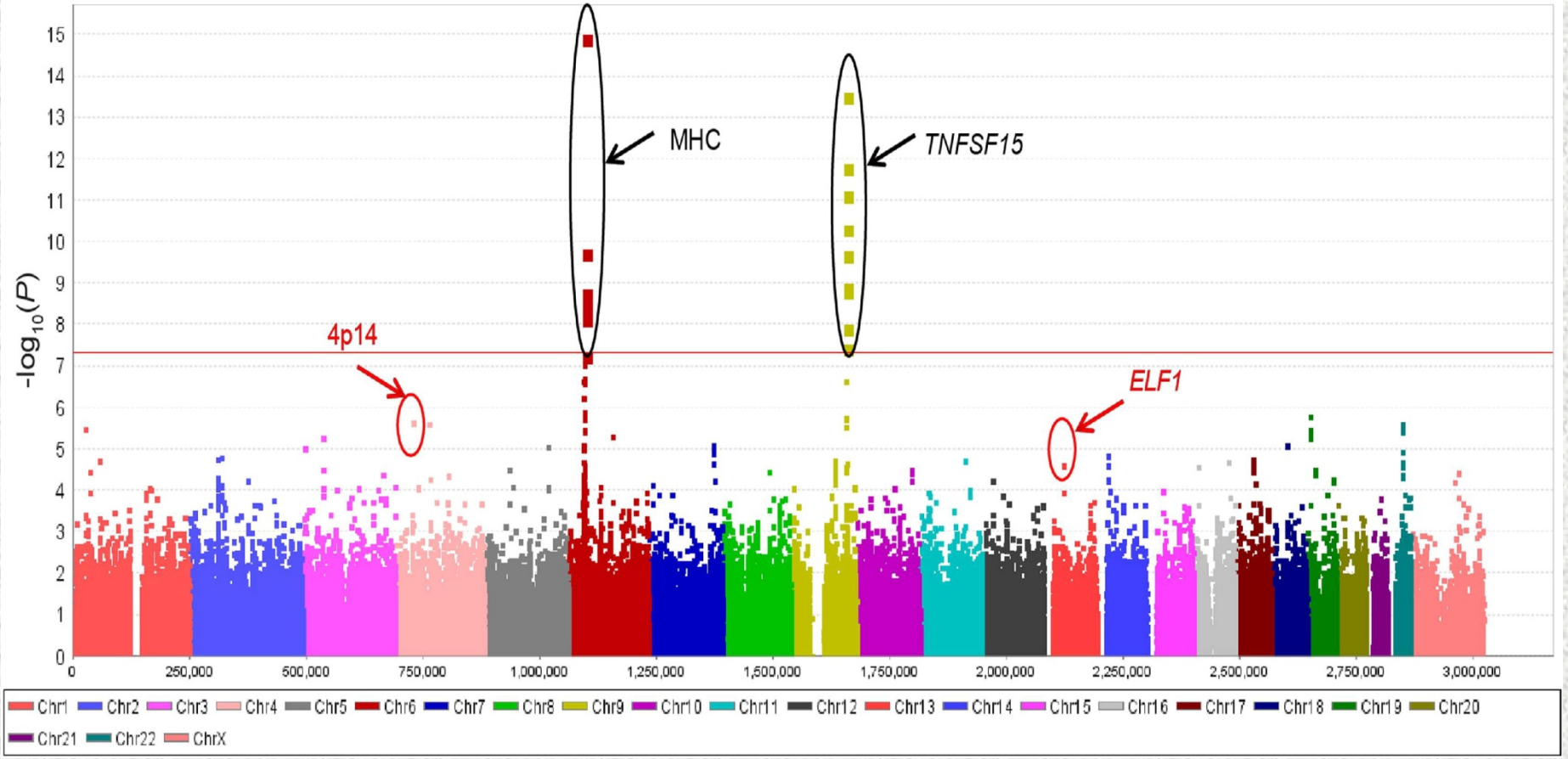
1. Provisional differences in response to biologics between Western and Asian populations.

2. Differences in protocols and results of clinical trials between Western countries and Japan (i.e. Adalimumab for Crohn's disease).

3. Problems in objective assessment of efficacy.

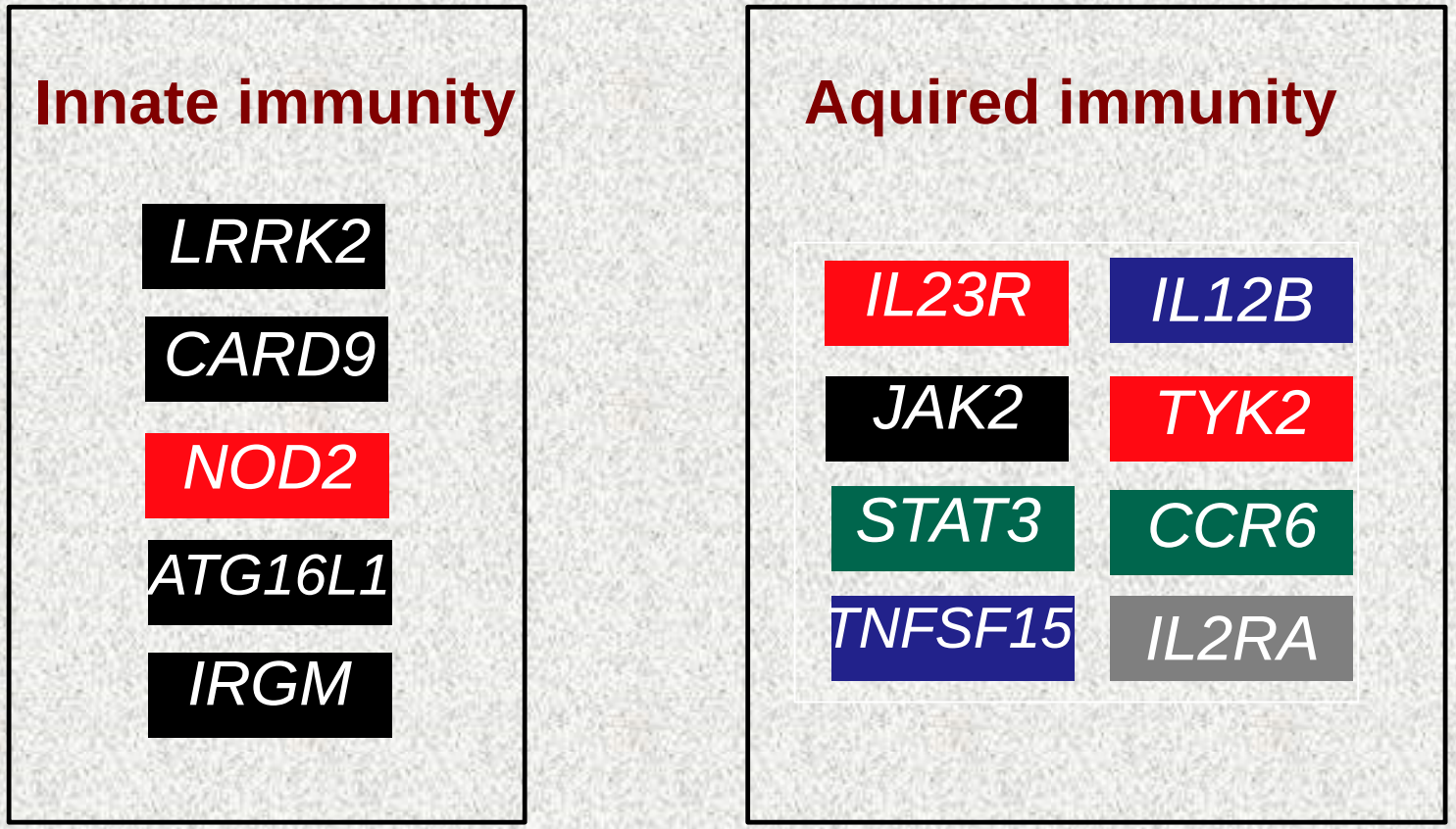
4. Problems in practical management of clinical trials (subject enrollment, global trials, *etc.*) including clinician-orientated clinical trials.

# Genome-wide Association Study of Japanese Patients with Crohn's Disease




*Yamasaki K, Matsumoto T, et al. Gastroenterology 2013*

# Comparison of Crohn's Disease-Associated Genes between Western and Japanese Population




Strong association in Jp

Weak association in Jp

No association in Jp

No SNP in Jp

Not enough power

*Hirano A, Matsumoto T, et al. Inflammatory Bowel Dis 2013*

# Major Clinical Trials for Adalimumab in Crohn's Disease

## Western countries

CLASSIC I

M02-403 Induction
Infliximab naïve

GAIN

M04-691 Induction
Infliximab failure

CHARM

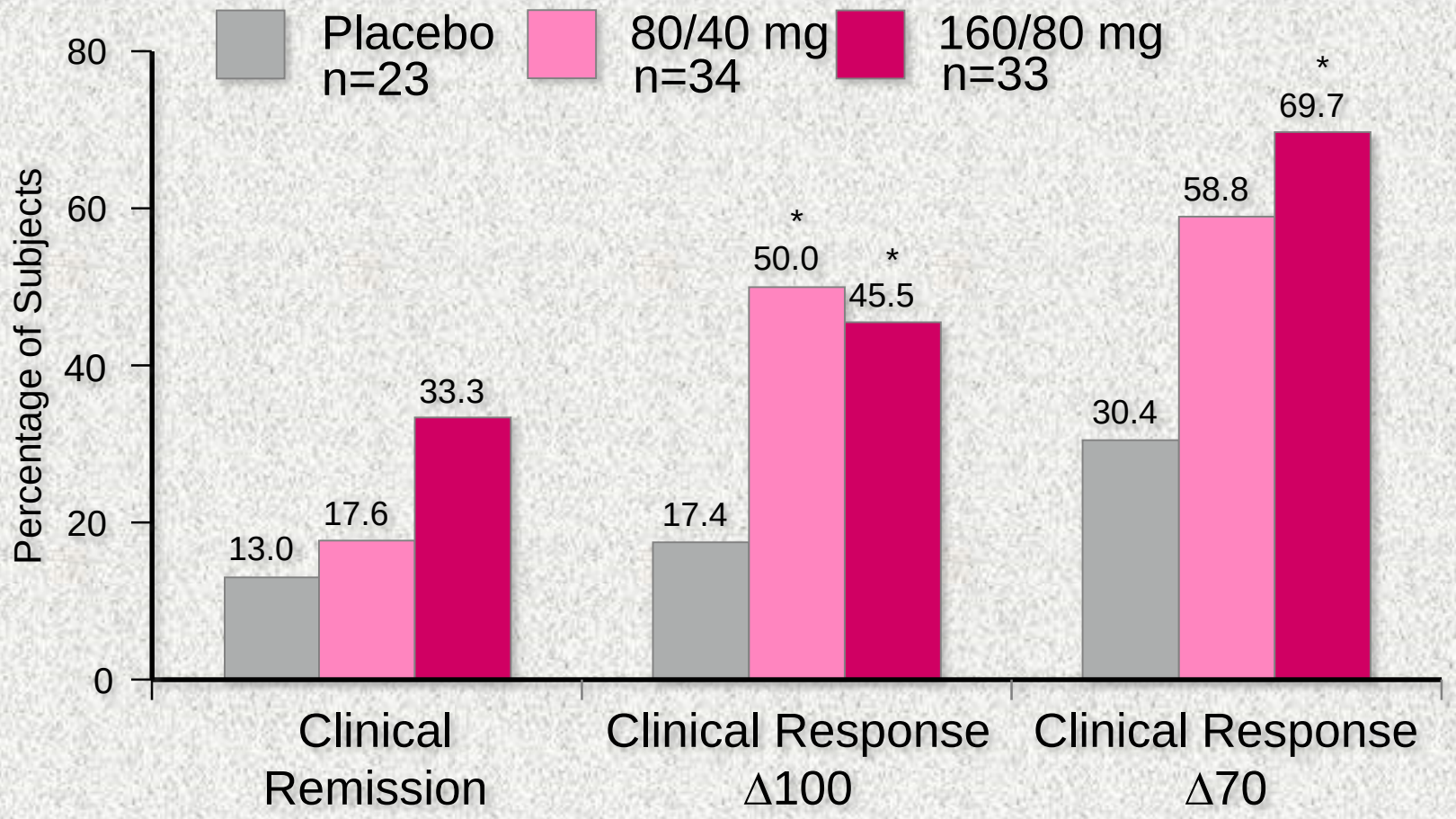
M02-404 Maintenance
Infliximab naïve + failure

## Japan

M04-729 Induction
Infliximab naïve + failure

M06-837 Maintenance

# Results of Induction Trial

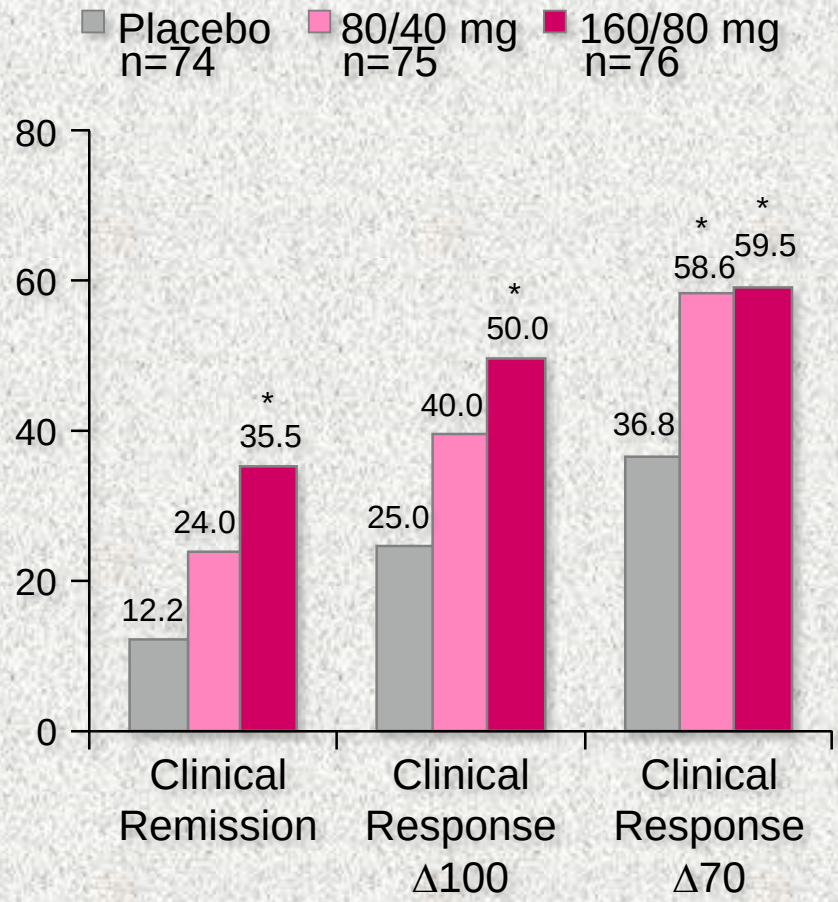



*p<0.05 vs. placebo (FAS population)

*Watanabe M, et al. J Crohn's Colitis 2012*

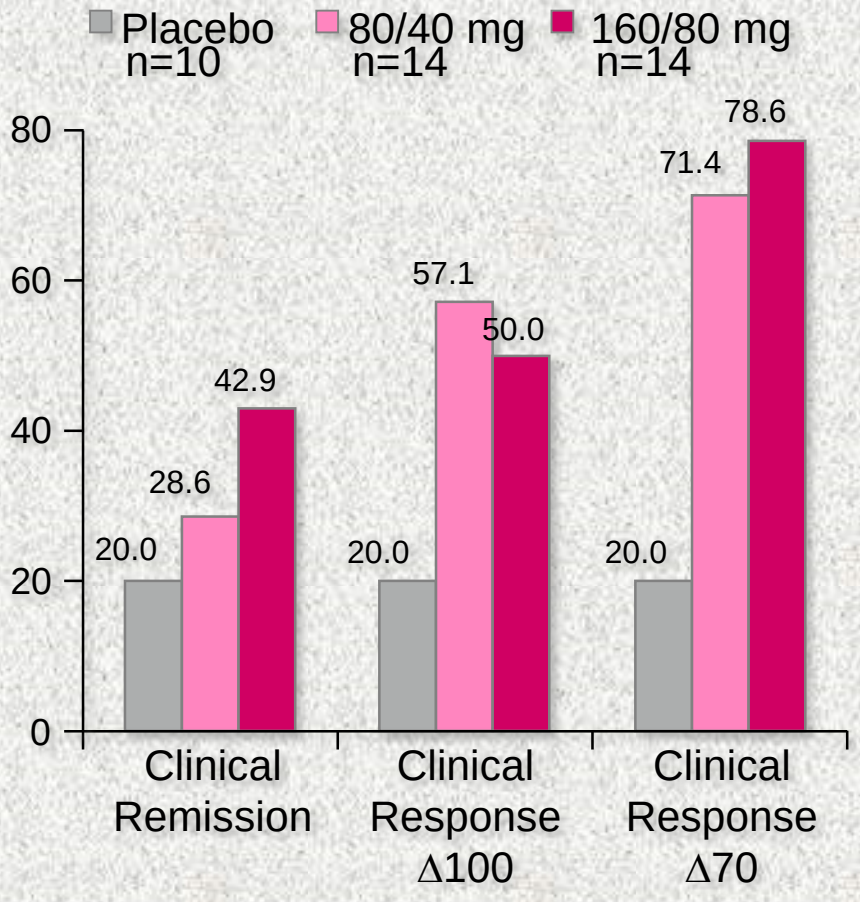
# Comparison between Induction Trials (Patients Naïve to Infliximab)

## Western area (CLASSIC I)




*p<0.05 vs. placebo (FAS population)

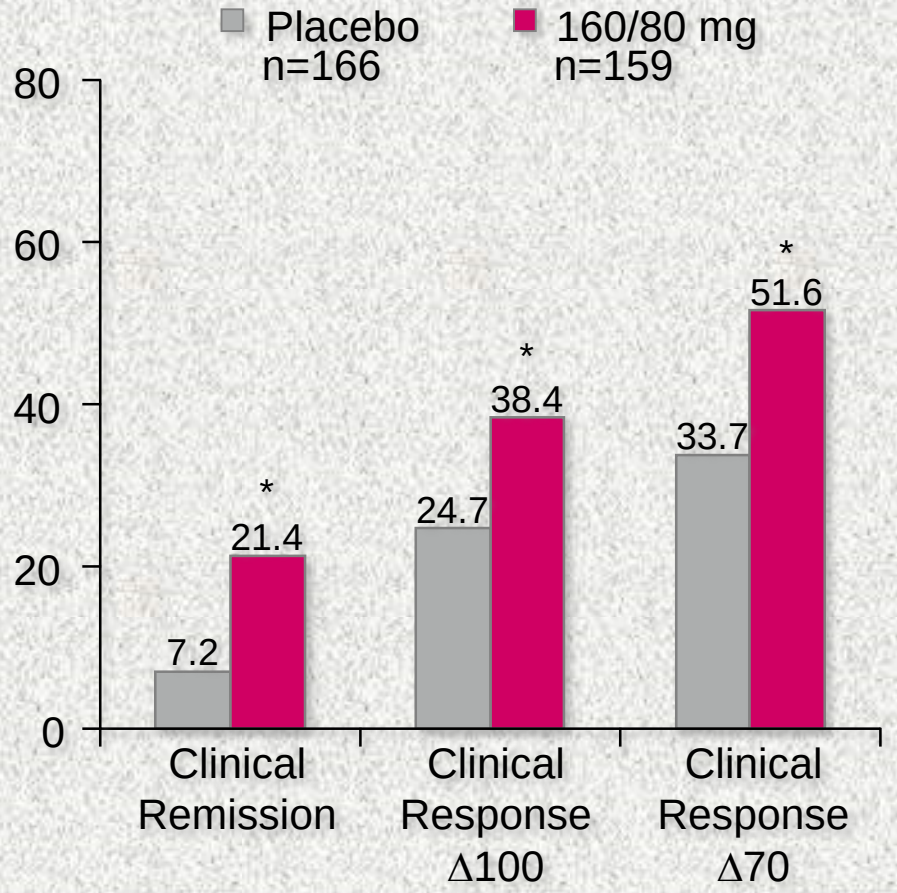
## Japan (M04-729)



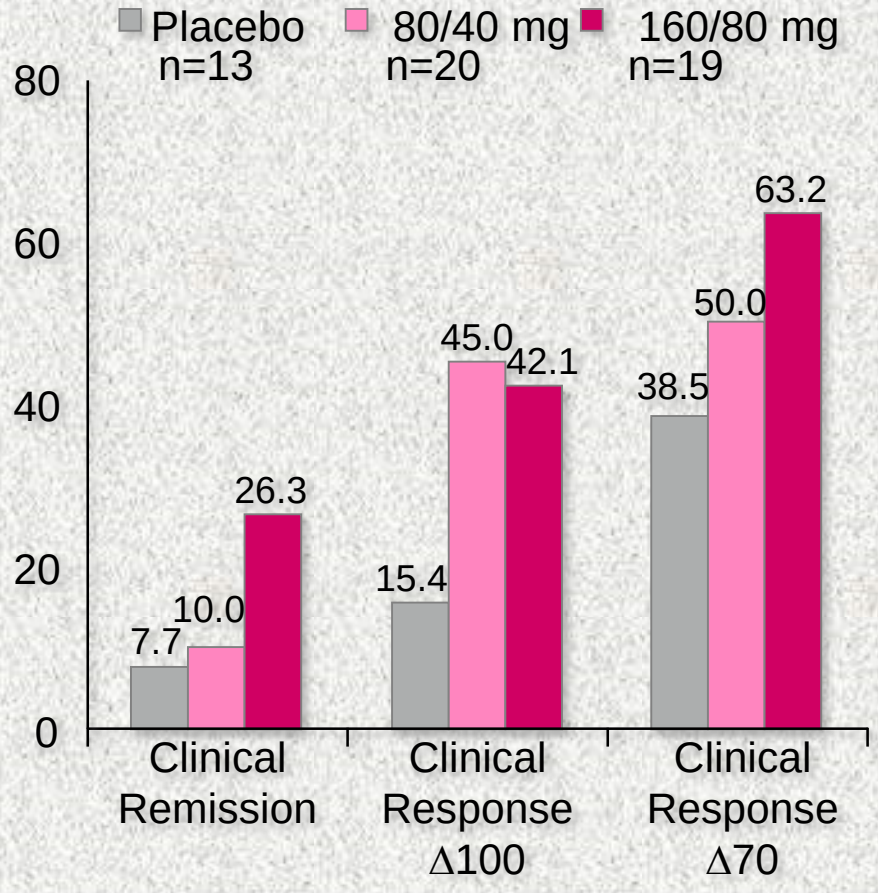

No statistical test was conducted.

# Comparison between Induction Trials (Patients with Prior Use of Infliximab)

## Western area (GAIN)



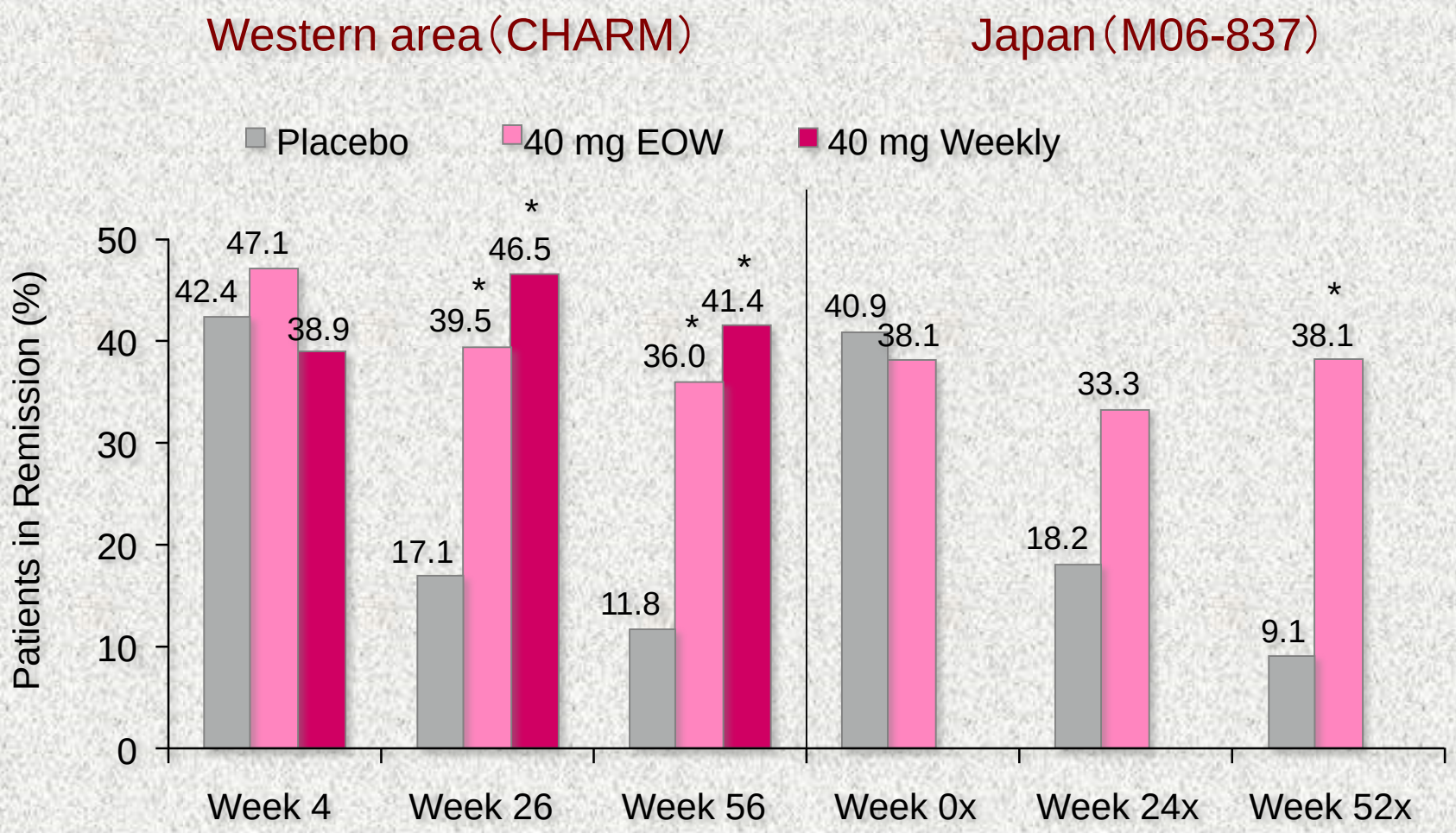

## Japan (M04-729)




*p<0.05 vs. placebo (FAS population)

No statistical test was conducted.

# Comparison between Maintenance Trials




NRI ( Non-responder imputation)
*p<0.05 vs. placebo (FAS population)

# Current measures of Crohn's disease activity

## Clinical activity

- **CDAI** Crohn's disease activity index developed by the NCCDS
- **HBI** Harvey–Bradshaw simple index

## Endoscopic activity

- **CDEIS** Crohn's disease endoscopic index of severity developed and validated by the GETAID for ileocolonic or colonic disease
- **SES-CD** Simplified version of CDEIS
- **Rutgeerts** **Score** dedicated to endoscopic post-operative recurrence in the neoterminal ileum after ileocolonic anastomosis

## Histologic activity

- **D'Haens, Geboes, et al.** Scoring system for histological abnormalities in Crohn's disease mucosal biopsy specimens

*Sandborn WJ, et al. Gastroenterology 2002*

# Simple endoscopic score for Crohn's disease (SES-CD)

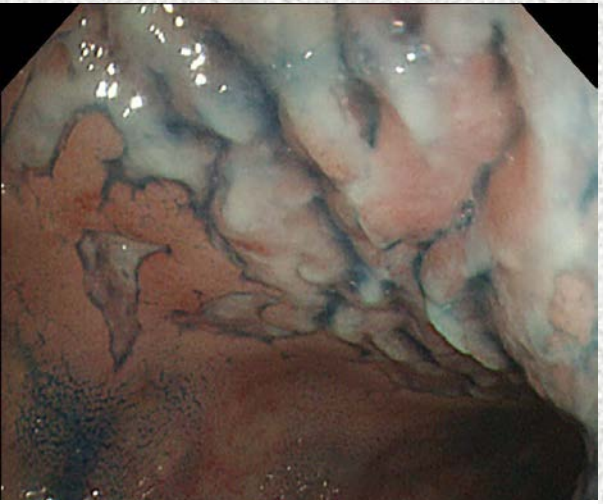
| | I | A | T | D•S | R | total |
|---|---|---|---|---|---|---|
| Size of ulcer | | | | | | |
| Extent of | | | | | | |

Even though simplified,
1. It is extremely complicated to calculate, and
2. It does not take jejunal and ileal lesions into account.

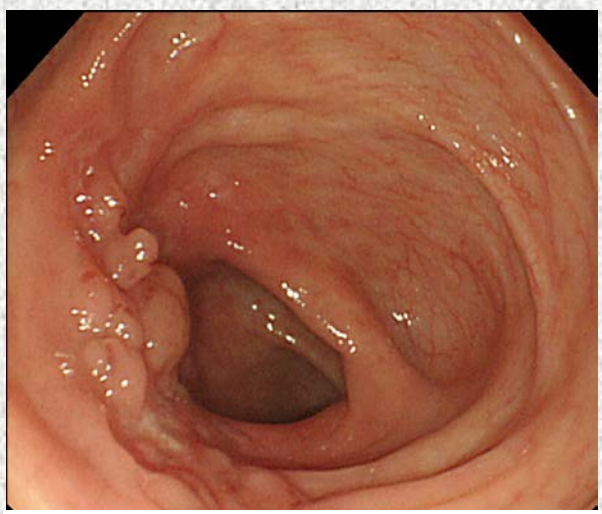
Size of ulcer
0; none 1; 0.1~0.5cm 2; 0.5cm~2cm 3; >2cm
Extent of ulcerative surface
0; nine 1; <10% 2; 10~30% 3; >30%
Extent of affected surface
0; none 1; <50% 2; 50~75% 3; >75%
Narrowing
0; none 1; single 2; multiple 3; scope not pass through

*Daperno M et al. Gastrointest Endosc 2004*

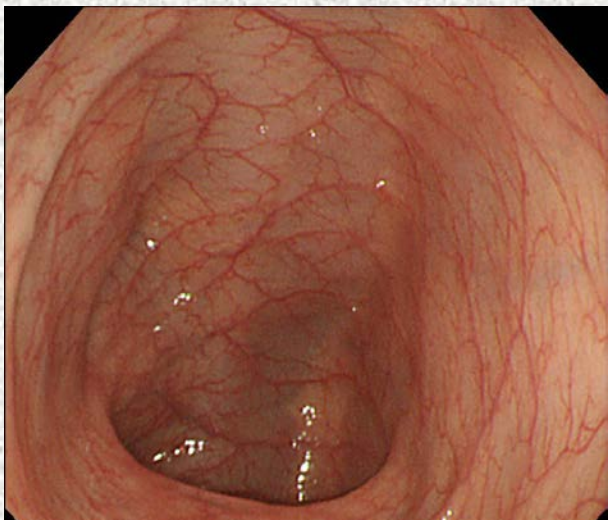
# Example of SES-CD



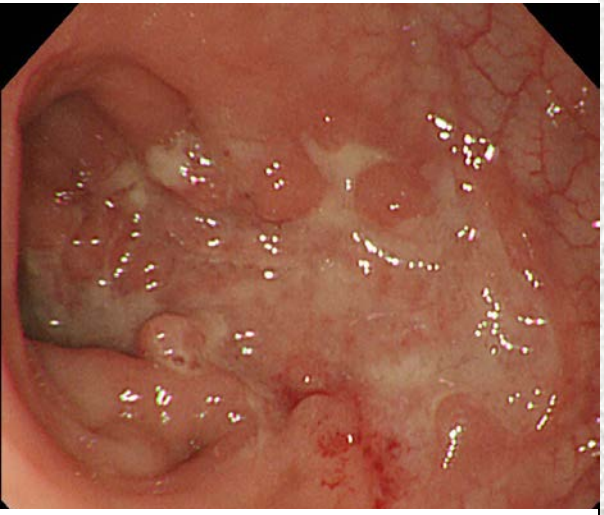
I: 3+2+1+0=6



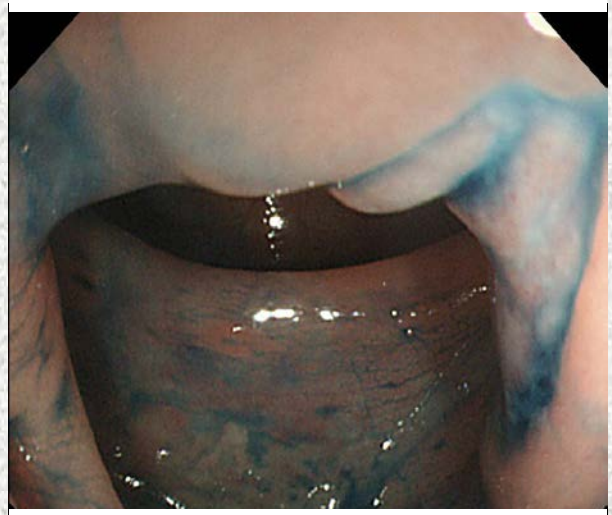
A: 2+1+1+0=4



T: 0+0+0+0=0



D/S: 3+2+1+0=6



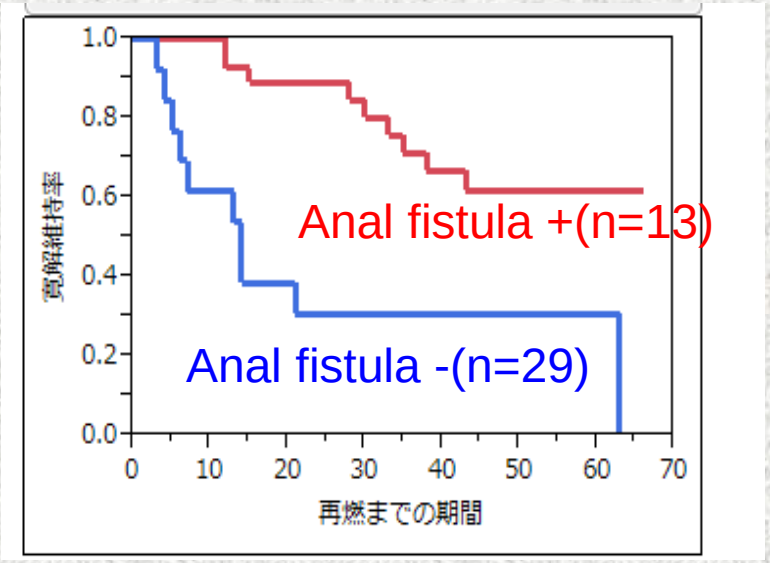
R: 2+1+1+0=4

SES-CD=20

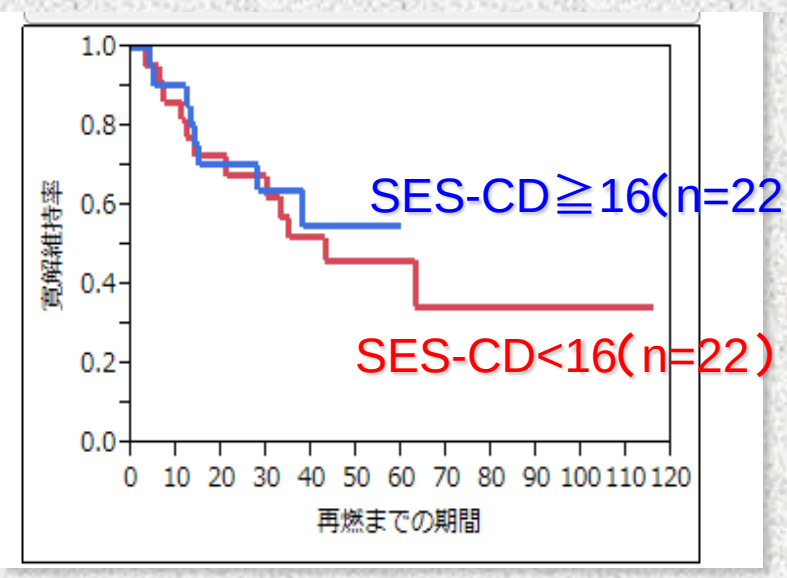
# Is SES-CD predictive of clinical course of CD under infliximab?

Subjects: 44 patients with Crohn's disease.
Methods: The association between SES-CD and loss of response to infliximab was retrospectively investigated.

Anal fistula (p=0.001)

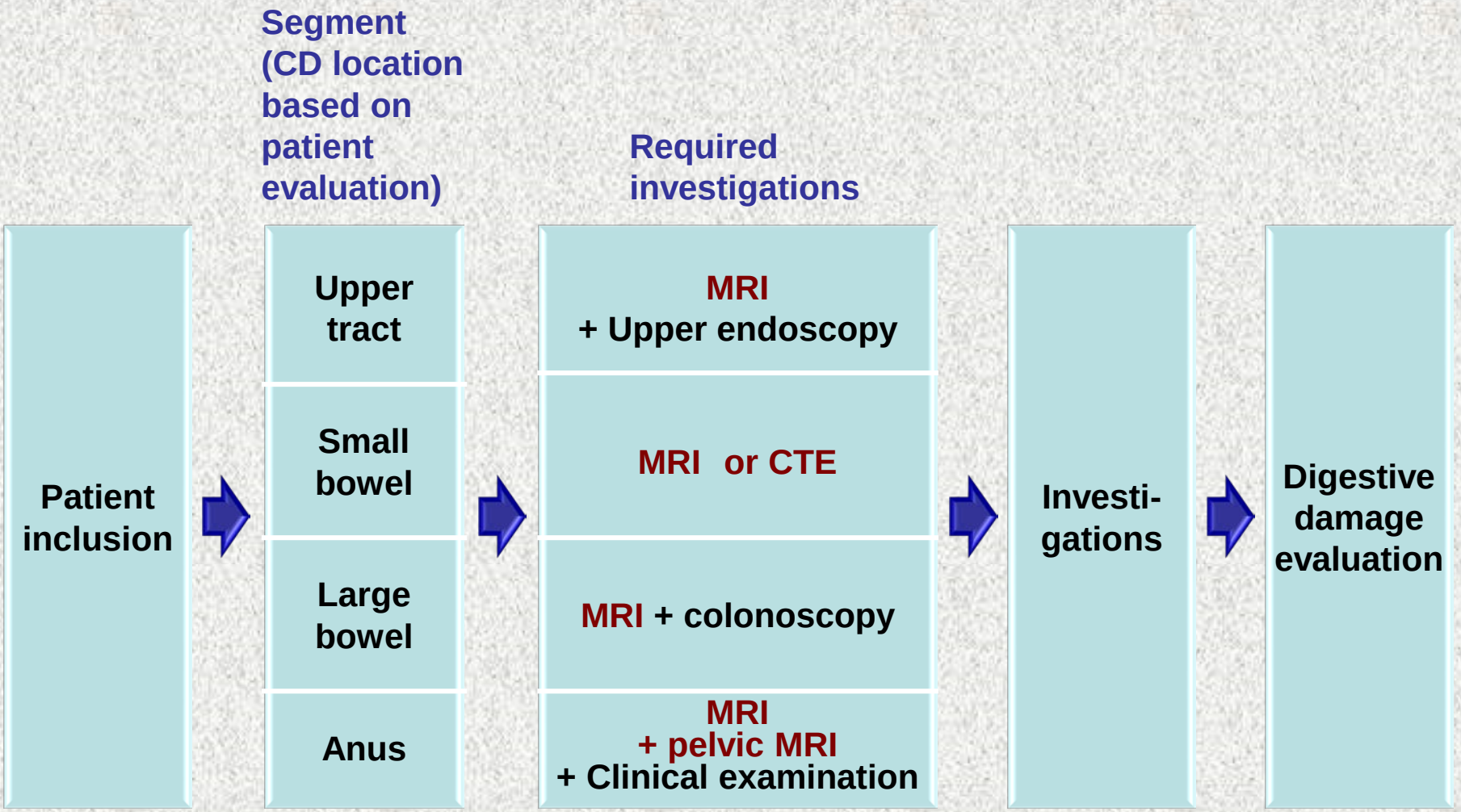



SES-CD (n.s.)




*Fuyuno Y, Matsumoto T, et al.: Dig Endosc (under submission)*

# The Lémann score for the assessment of digestive damage in Crohn's disease




*Pariente B et al. Inflamm Bowel Dis 2011*

# Lémann Score: small bowel example

## Severity assessment for each 20 cm segment

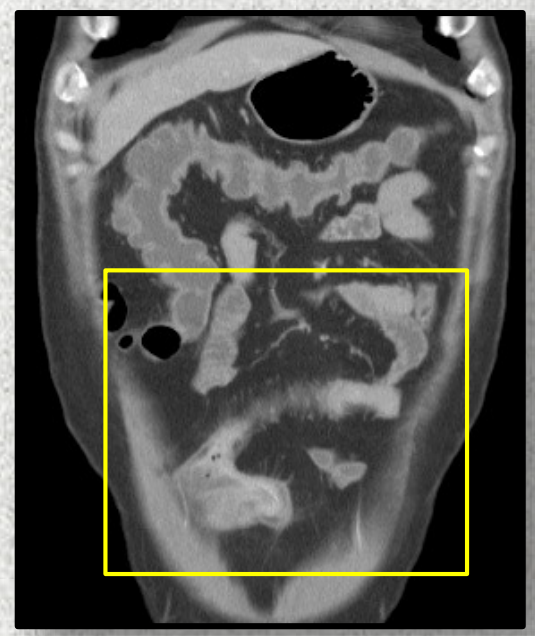
| Grade | Stricturing lesions (0–3) | Penetrating lesions (0–3) | History of surgery or other interventional procedure (0–3) |
|---|---|---|---|
| Null (0) | Normal | Normal | No procedure |
| Mild (1) | Wall thickening <3 mm without pre-stenotic dilatation | - | Endoscopic dilatation |
| Moderate (2) | Wall thickening ≥3 mm without pre-stenotic dilatation | Transmural fissure with increased density in perienteric fat | By-pass diversion Stricturoplasty |
| Severe (3) | Stricture with pre-stenotic dilatation | Abscess or fistula | Resection |

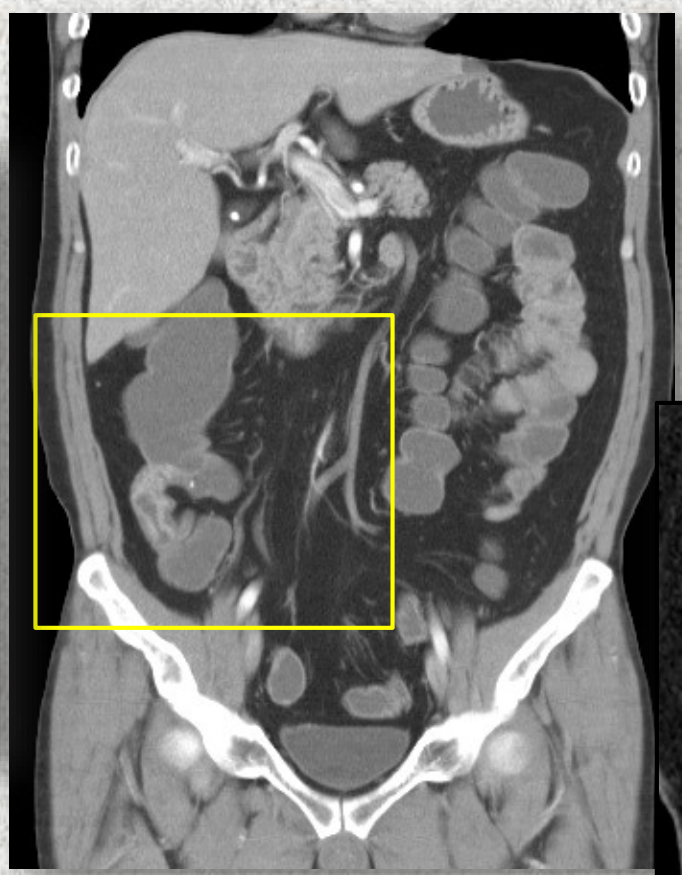
# Procedures for CT enterography

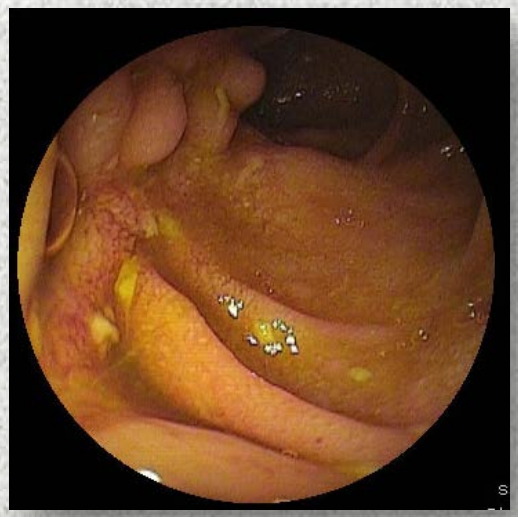
- By multidetector CT (MDCT), patients undergo CT examination in supine and prone positions.
- Positive or neutral contrast agent is administered transorally (enterography) or through duodenal tube (enteroclysis) for adequate luminal distension. Intravenous contrast material is administered for cases of positive contrat agent in the GI tract.
- Images are usually assessed under multiplanar reconstruction (MPR).

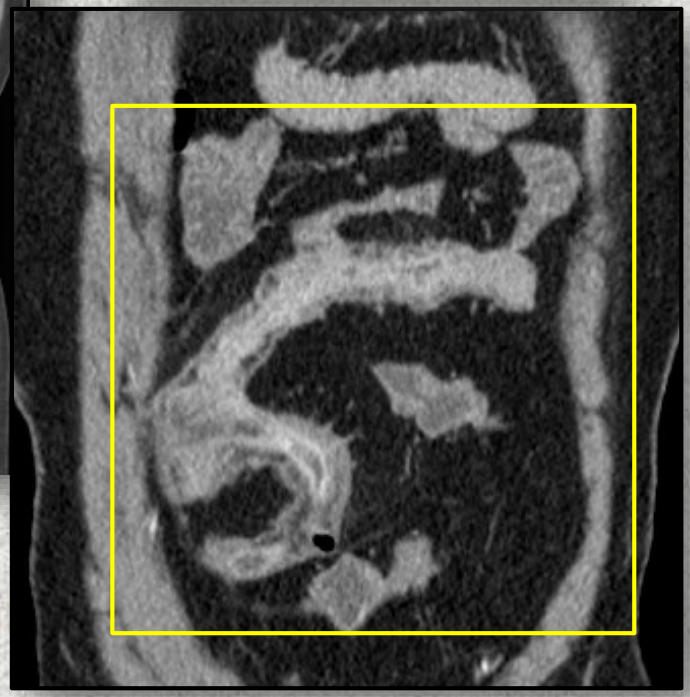
*Hara AK, et al. Abdominal Imaging 2008*

# CTE findings of active CD





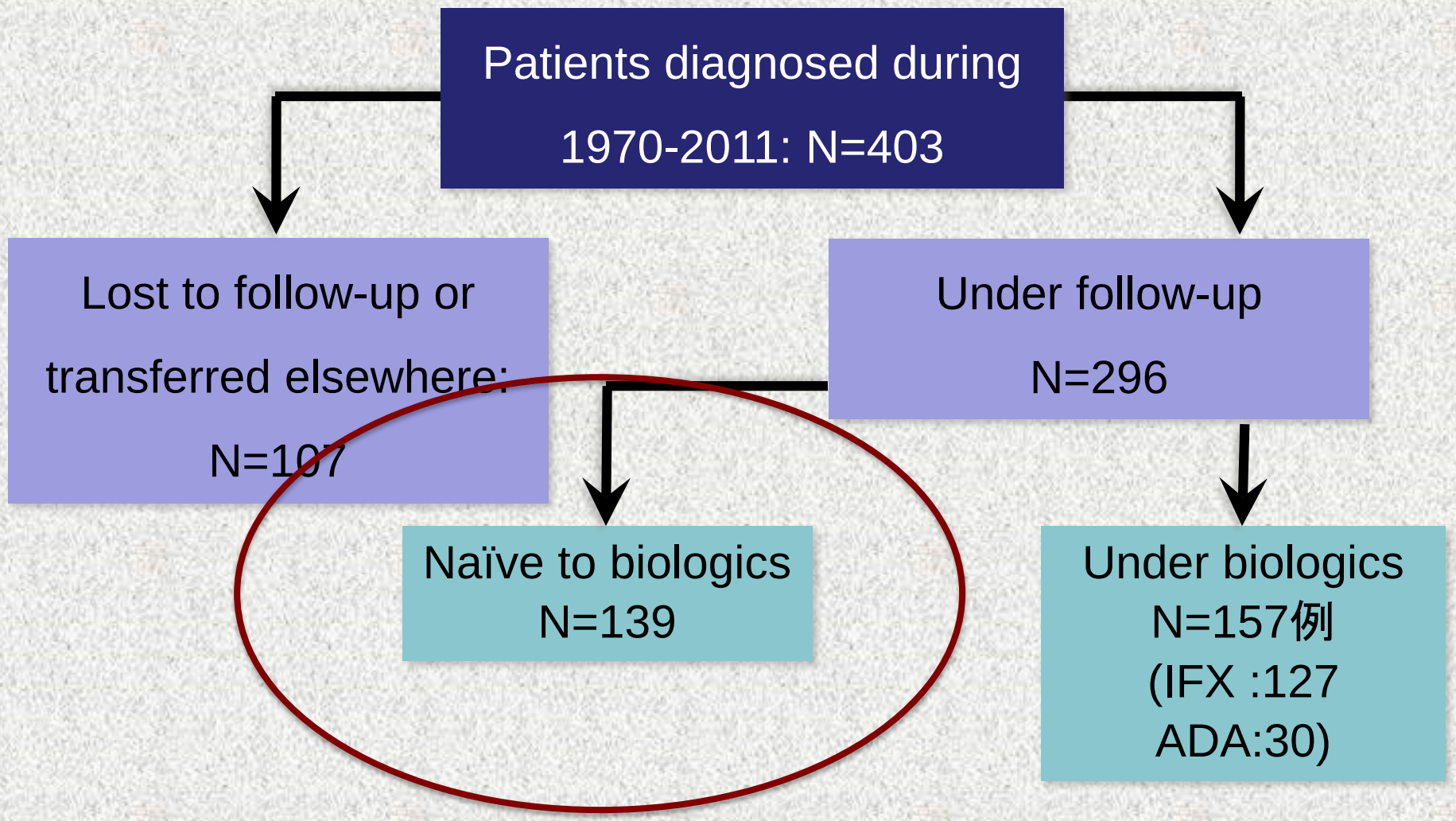




Mural hyperenhancement
Mural stratification
Comb sign

*Takeuchi K, et al: Stomach Intestine 2012*

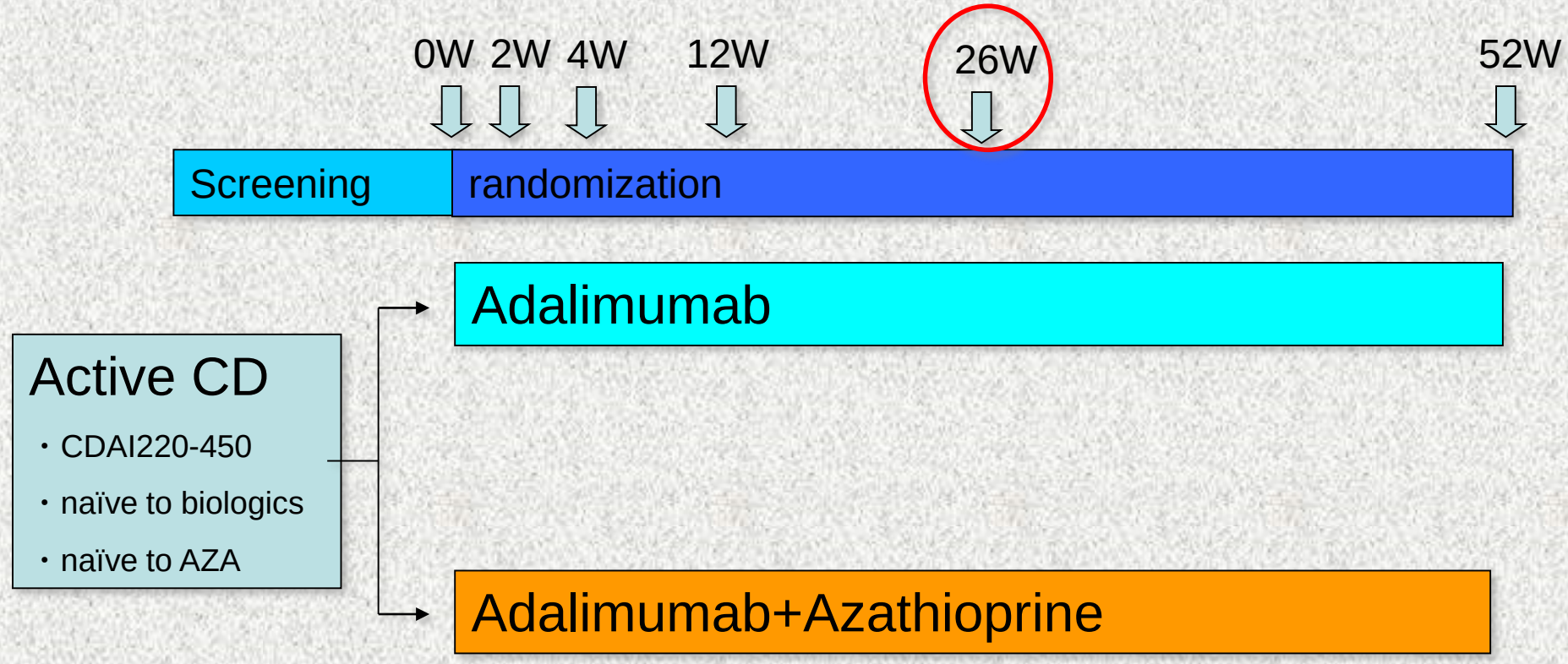
# Number of Patients with CD at Kyushu University Hospital



# Clinician-oriented Clinical Trial for Crohn's disease

Aim: To evaluate the efficacy of simultaneous AZA for active CD under ADA.

Study protocol: Multicenter, open-labelled, prospective study.



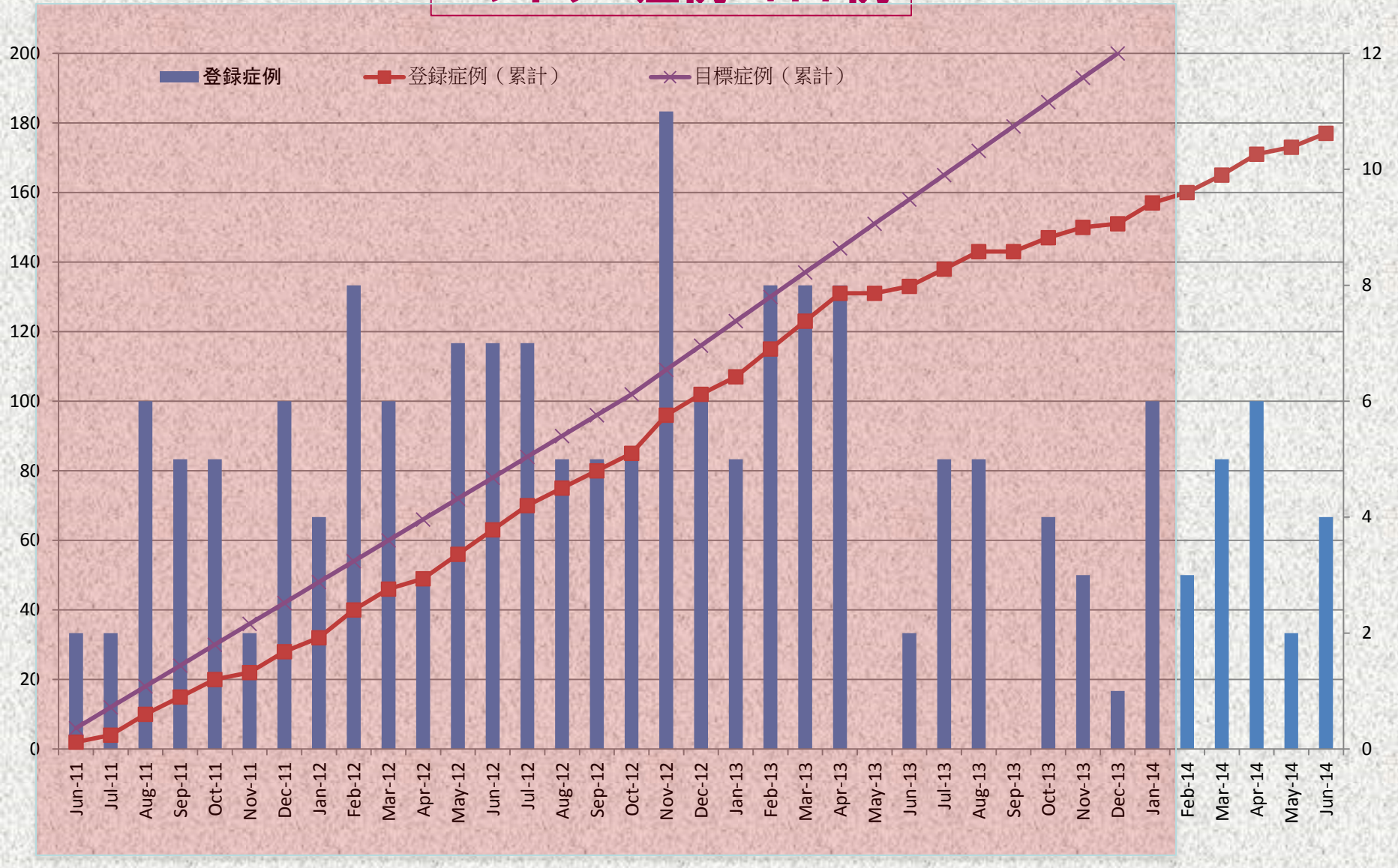

Primary endpoint: Remission rate at 26 wks.

Hypothesis: The combination of AZA and ADA is superior to ADA by an 15 points increase in remission rate.

Sample size: 100 patients in each arm.

# 症例の登録状況（最終）

**エントリー症例：177例**



# …and finally, Comments from Bedside -Claims from Clinical Research Associates-

## Dose-escalation study of ADA for Crohn's disease

- Inclusion and exclusion criteria are difficult to interpret.
- A certain proportion of candidates could not be enrolled because of minor lack in clinical demographics.
- Primary endpoint (efficacy at 8 wks) does not seem to be appropriate.

## Induction and maintenance trial of ustekinumab

- Extremely strict regulation and overload under global protocol.
- This was especially the case for dropouts.
- Both analogue and electronic CRFs were required.

## In general

- Many candidates could not be enrolled because of enteral nutrition.
- Strict regulation under global protocol does not seem to conform to the clinical management of CD in Japan.
- IVRS does not seem to be appropriate for the clinical trial.

# Conclusion

There seems to be following problems in clinical trials for Crohn's disease in Japan.

1. Effects of biologics may be different between Western and Asian populations.
2. Assessment of disease activity may not be objective.
3. There are difficulties in the assessment of actual intestinal damages.
4. Less number of CD patients in Japan disturbs the enrollment of study subjects.
5. Regulations in inclusion and exclusion are complicated.