A case study of cut point evaluations at early stages of clinical studies
- how to provide reliable interim ADA results -

Hisanori Hara, PK Sciences, Novartis Pharma AG
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ADA cut point determination and its challenge

- The cut points are determined using serum from healthy donors in the method validation in general.
- The cut points with healthy serum may not be relevant to the target patient population.
- Commercially available target disease serum may also not represent the patient population in the clinical study.
- In-study cut points with at least 50 pre-dose samples are recommended.

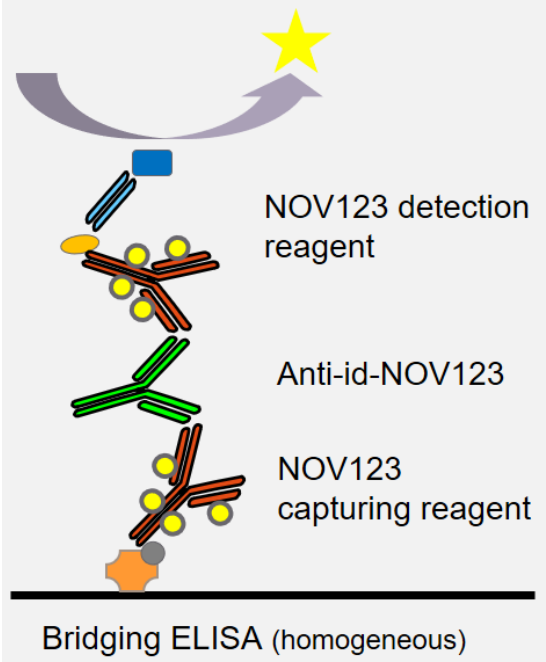
- Some clinical programs request interim ADA results at very early stage before having 50 pre-dose samples due to a concern on efficacy and AE.

  e.g. ADA was developed in all animals after the second dose in the GLP Tox study. It affected exposures of the drug.
  A preceding biologics project terminated partly due to ADA. etc

Outline of the project and the method

- Antibody drug conjugate (ADC) for an oncology program
- ADA by ELISA assay: homogenous bridging format
- Screening → confirmatory → titration

  confirmatory with non-conjugated Ab
- MRD: 50
- Sensitivity: 60 ng/mL PC



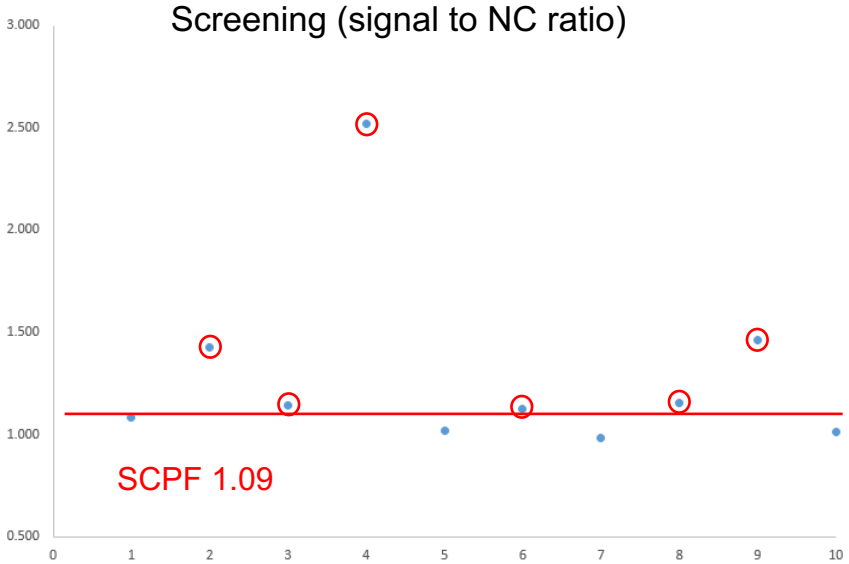
Cut points in the method validation

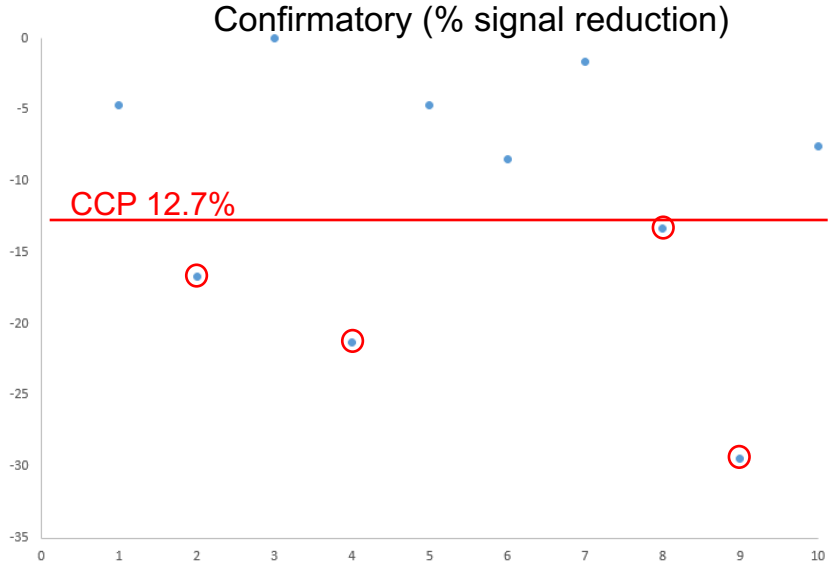
- 51 individual serum from healthy donors, n=6 repeated determinations eliminating analytical outliers, biological outliers, assessing distribution, selecting the model, parametric/non-parametric/robust parametric, according to the recommendation paper by Devanarayan V. et. al, 2017
- SCPF=1.09, CCP=12.7%, TCPF=1.16

- 10 commercial target cancer sera tested

Signals of commercial target cancer sera

(n=10)





7/10 screen positive 4/10 positive immunodepletion

-> Concern on too high false positive results in the clinical sample analysis which may give impact to the development strategy.

A strategy how to tackle the issue?

- How to provide more reliable (not too high or not too low false positive) results before having 50 pre-dose samples?
- How to set preliminary in-study cut points with limited number of pre-dose samples (and also with commercial target cancer sera)?

- How to reconcile preliminary ADA data (by cut points in validation or by preliminary in-study cut point) with data at the end of the study (in-study cut points at the end)?

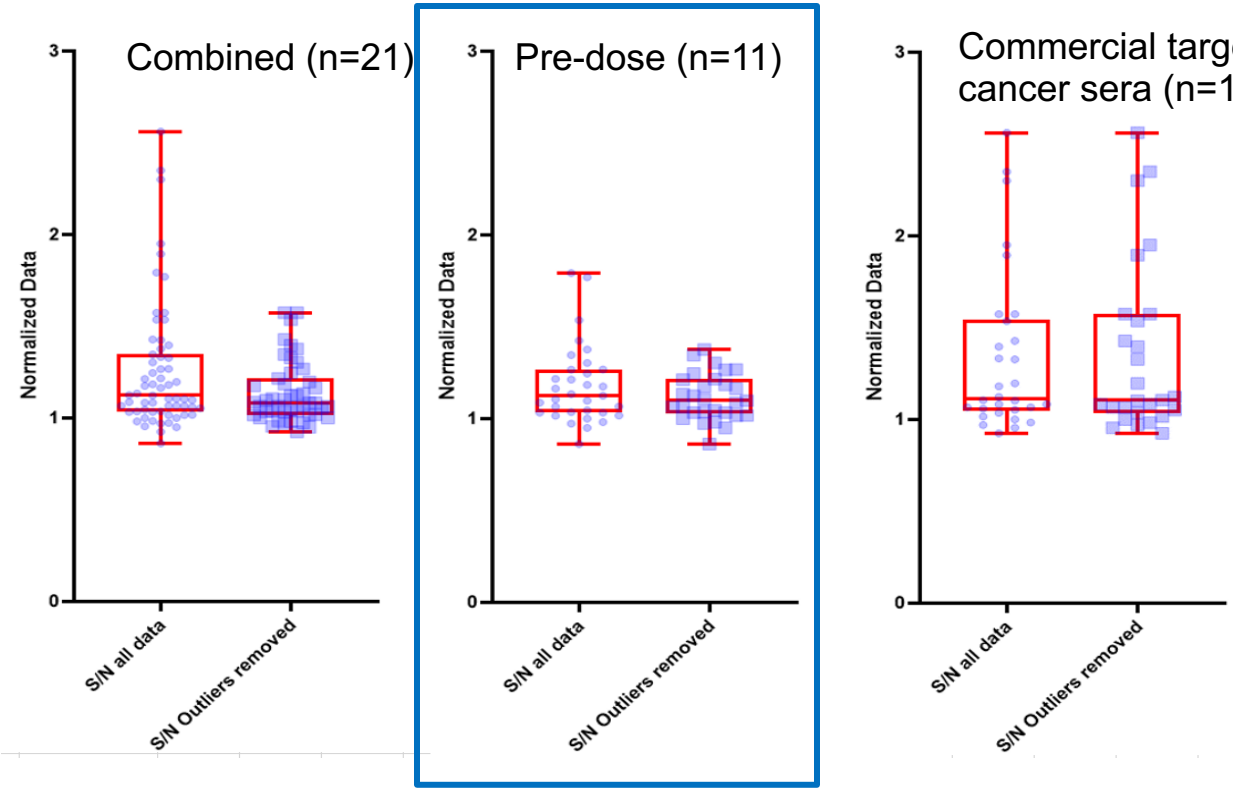
In-study cut points at early stage

- Analyze all available pre-dose samples (≥10), 3 (or more) times
- Analyze the commercial target cancer sera (≥10), 3 (or more) times
- Compare the distribution of the signal to NC ratio among the two groups
  - If they are similar, combine them.
  - If not, use only pre-dose samples.

Number of results vs Relevant data for in-study cut point

- After excluding analytical and biological outliers, the distributions of the commercial target cancer sera (n=10) and patient pre-dose samples (n=11) were compared to determine if the two patient populations are comparable.
- Levene's test for the equality of variances between the two groups and the ANOVA f-test for equality of means between the two groups were performed.

Preliminary in-study cut point assessment

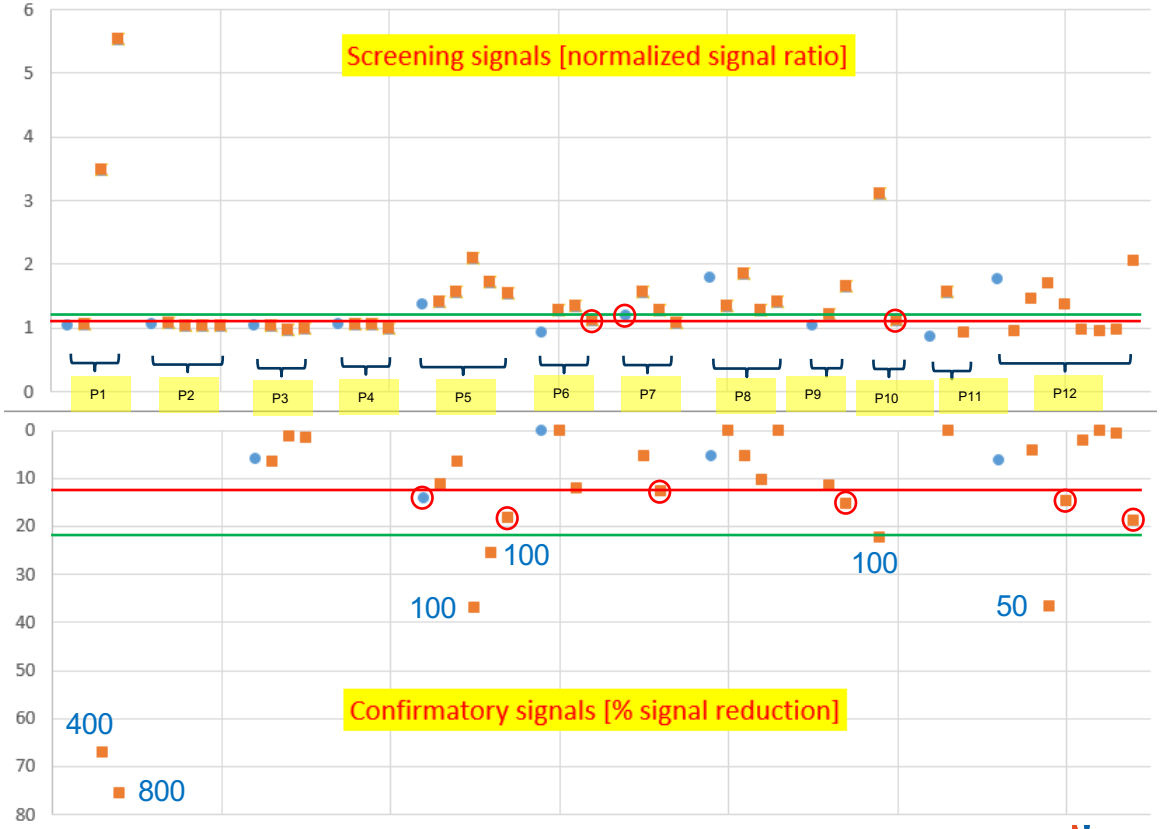


Recommendation by statistician:

- Evidence of a slight difference in both means and variances between two groups ($P \leq 0.05$ for both the ANOVA f-test and Levene's tests).
- All further calculations were performed using the patient pre-dose samples.

Obtained in-study cut points: SCPF 1.20, CCP 21%

Preliminary results in the clinical study



P1 Each patient

Pre-dose sample

Post-dose sample

50 Titer value

Potential positive sample by validation cut points

SCPF 1.20, in-study — 26 positive screen

SCPF 1.09, validation — 29 positive screen

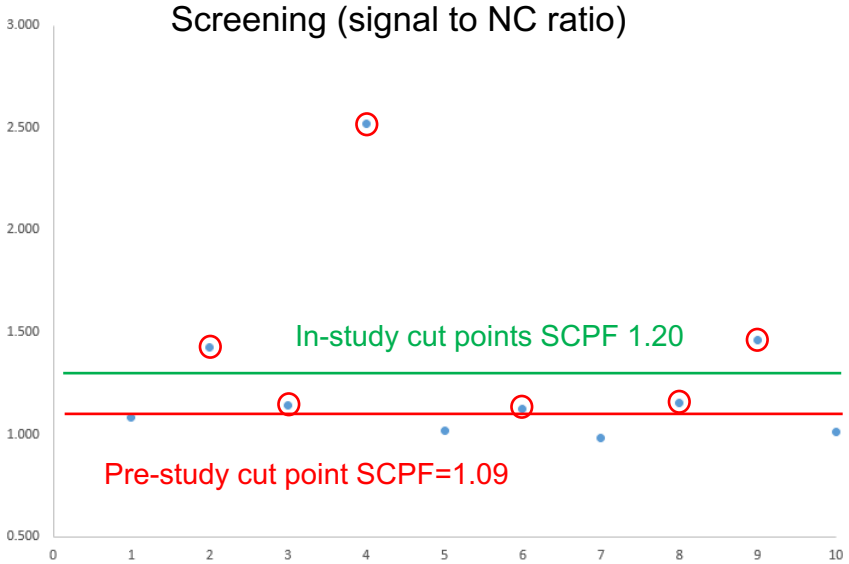
CCP 12.7%, validation — 12 positive immunodepletion

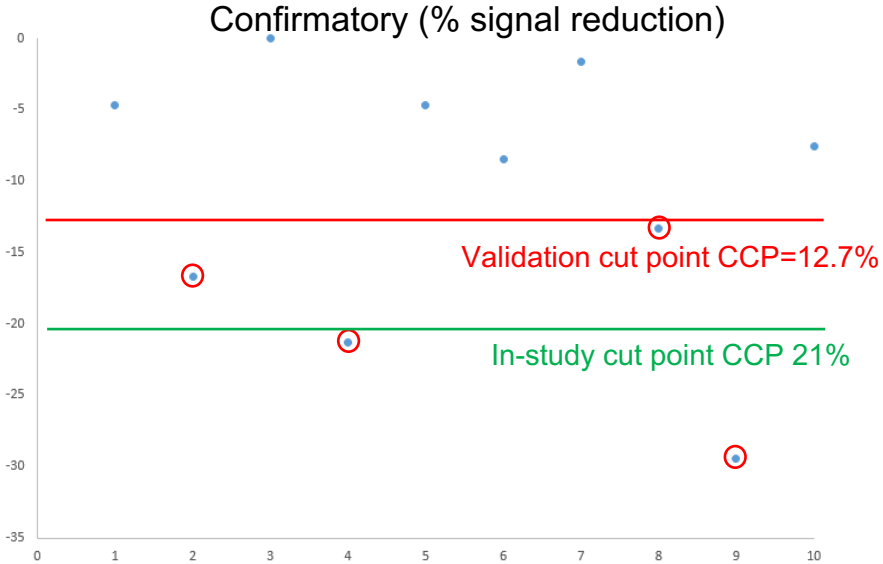
CCP 21%, in-study — 6 positive immunodepletion

Cut points from validation
-> positive immunodepletion increase
from 6 (11.3%) to 12 (22.6%)

Commercial target cancer sera with two cut points

Even though the group is slightly different from the pre-dose samples, the disease sera should be closer to the patient population than healthy sera.





screening positive 7 -> 3, confirmatory positive 4 -> 2

It looks more reasonable?

Summary and future plan

In order to provide more reliable interim ADA data at early stage of the clinical study,

- Set a procedure for in-study cut points with limited number of pre-dose (n=11) and commercial sera (n=10)
- If the two groups were judged comparable by the mean and variance of each group, the data of commercial cancer sera could be added.
- Selected only pre-dose sera by the statistical analysis
- Established a preliminary in-study cut point
- Started the sample analysis with the in-study cut points

- Carefully monitoring the progress of the study with potential safety and efficacy issues
- Reconciling the preliminary in-study cut points by assessing false positive rate at the end (or close to the end) of the study
- Reestablish in-study cut points if needed

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Q&A