EMA workshop on the investigation of subgroups in confirmatory clinical trials

The investigation of subgroups in confirmatory clinical trials
- The PMDA Perspective -

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Use of subgroup analysis

- General understanding
  - Be cautious not to over-interpret subgroup results.
    - There are several issues such as multiplicity issues, false positive rate, imbalance of baseline characteristics between groups, selection bias, small sample size.
  - Statistical analysis results will not directly lead to the restriction or recommendation for usage.
    - Biological and clinical plausibility should be discussed.
  - Subgroup analysis is a part of the investigation for providing further information of the investigational drug.
  - Subgroup analysis should not be used for rescue of failed studies.

In clinical trial consultations

- Reviewers will provides advices on
  - Relationship between inclusion/exclusion criteria and expected indication
  - Avoiding easy selection of the subgroup which shows favorable results as the target population in the future development
  - Existence of biologically/clinically plausible subgroup which will show different trend in efficacy and/or safety
  - Necessity of stratified randomization
  - Pre-specification of important subgroup analysis or consideration of subgroup analysis as a part of the primary analysis

In new drug review

- After reviewing the overall (positive) results, the impact of factors is reviewed.
  - Especially relationship between particular factors and safety of the drug, as a results, benefit risk balance in particular subgroup
- In practice, relationship between below two aspects is considered, when focusing on subgroup.
  - Results of all subjects/results of subgroups/biological and clinical plausibility of subgroup results

  - Usage restriction/providing information on labeling/well characterization of the investigational drug

Subgroups in MRCT

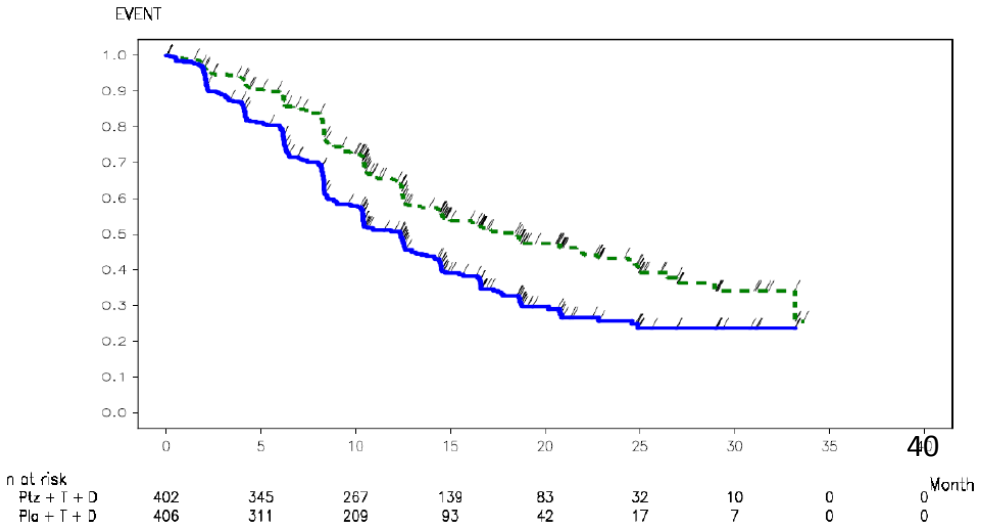
- Regarding multi-regional clinical trial (MRCT), region/country will be one of the key factors at the designing and evaluation stages.
  - PMDA issued the guidance and reference cases for this issue.
- The primary evaluation is based on the analysis of all subjects data, but it is expected to be explained …
  - Possible intrinsic and extrinsic factors influence the drug efficacy and/or safety
  - Plausibility of regional difference
  - Consistency between the results of all subjects and that of subgroup (ex. Japanese subjects)
- Evaluation of regional subgroup includes all the issues of subgroup analysis and will be difficult in some cases.

Case 1. pertuzumab

- Indication: HER2 positive inoperable or recurrent breast cancer
- Trial design: Randomized, double-blinded, parallel-group study
  - Comparison groups
    - Pertuzumab + trastuzumab + docetaxel
    - Plasebo + trastuzumab + docetaxel
  - Stratification factors: pretreatment, region
  - Primary endpoint: PFS(IRF)
  - Secondary endpoints: OS, PFS, response rate

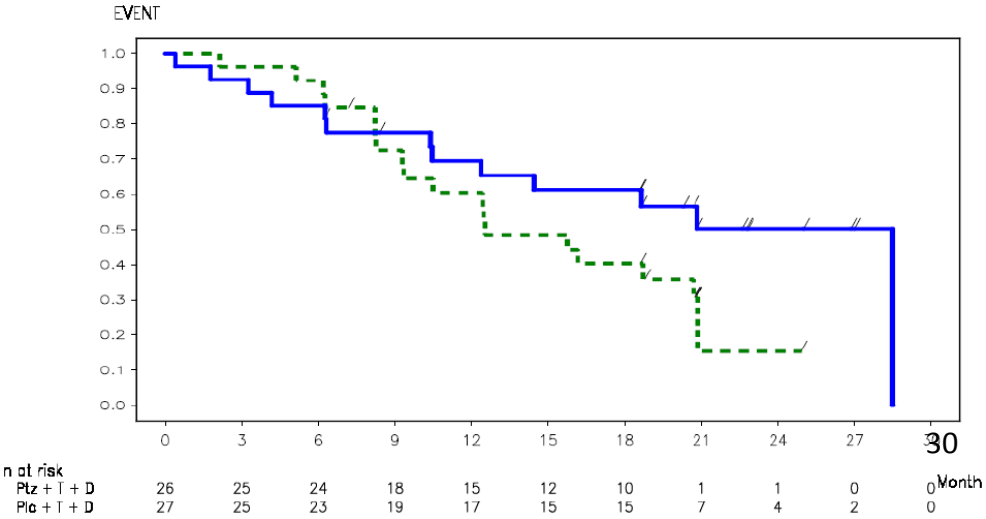
All subjects

	pertuzumab	placebo
N	402	406
Event(%)	119(47.5)	242 (59.6)
Median survival [95%CI]	18.5 [14.6, 22.8]	12.4 [10.4, 13.2]
HR [95%CI]	0.62 [0.51, 0.75]	
P-value	<0.0001	



Japanese subgroup

	pertuzumab	placebo
N	26	27
Event(%)	18 (69.2)	13 (48.1)
Median survival [95%CI]	12.5 [9.3, 20.7]	28.5 [12.4, 28.5]
HR [95%CI]	1.92 [0.91, 4.04]	
P-value	0.0871	



http://www.info.pmda.go.jp/shinyaku/P201300075/450045000_22500AMX01001000_A100_1.pdf

Case 2. umeclidinium/vilanterol

- LAMA/LABA combination drug
- Indication: Chronic obstructive pulmonary disease (COPD)
- Two MRCTs including Japanese subjects for two different doses of UMEC
  - Trial design (comparison groups)
    - UMEC high dose trial: 125/25µg, UMEC125µg, VI25µg, Placebo
    - UMEC low dose trial: 62.5/25µg, UMEC62.5µg, VI25µg, Placebo
- Primary endpoint: trough EFV1 change from baseline at 24w

Results of the trial with high dose UMEC

All subjects

Group	125/25µg	UMEC125µg	VI25µg	Placebo
Baseline	1.257±0.481 (402)	1.299±0.488 (406)	1.279±0.487 (403)	1.259±0.473 (274)
24w	1.503±0.524 (324)	1.469±0.516 (312)	1.418±0.520 (300)	1.337±0.504 (183)
Change from BL	0.214±0.222 (323)	0.139±0.212 (312)	0.100±0.223 (299)	-0.024±0.226 (182)
Column vs Placebo diff. [95%CI], p-value	0.238 [0.200, 0.276] P<0.001	0.160 [0.122, 0.198] P<0.001	0.124 [0.086, 0.162] P<0.001	-
125/25µg vs Column diff. [95%CI], p-value	-	0.079 [0.046. 0.112] P<0.001	0.114 [0.081, 0.148] P<0.001	-

Japanese subgroup

Group	125/25µg	UMEC125µg	VI25µg	Placebo
Baseline	0.947±0.400 (19)	0.981±0.312 (21)	0.926±0.335 (21)	1.038±0.214 (13)
24w	1.093±0.398 (16)	1.104±0.329 (18)	1.030±0.316 (13)	1.111±0.165 (7)
Change from BL	0.138±0.185 (16)	0.139±0.141 (18)	0.071±0.177 (13)	-0.11±0.152 (7)
Column vs Placebo diff. [95%CI]	0.174 [-0.008, 0.356]	0.188 [0.009, 0.366]	0.131 [-0.053, 0.315]	-
125/25µg vs Column diff. [95%CI]	-	-0.014 [-0.160. 0.131]	0.043 [-0.109, 0.195]	-

Results of the trial with low dose UMEC

All subjects

Group	62.5/25μg	UMEC62.5μg	VI25μg	Placebo
Baseline	1.282±0.556 (413)	1.199±0.488 (417)	1.247±0.485 (421)	1.200±0.469 (280)
24w	1.461±0.557 (330)	1.357±0.516 (322)	1.358±0.492 (317)	1.226±0.475 (201)
Change from BL	0.164±0.246 (330)	0.123±0.225 (322)	0.083±0.234 (317)	0.004±0.230 (201)
Column vs Placebo diff. [95%CI], p-value	0.167[0.128, 0.207] P<0.001	0.115 [0.076, 0.155] P<0.001	0.072 [0.032, 0.112] P<0.001	-
62.5/25μg vs Column diff. [95%CI], p-value	-	0.052 [0.017. 0.087] P=004	0.095 [0.060, 0.130] P<0.001	-

Japanese subgroup

Group	62.5/25μg	UMEC62.5μg	VI25μg	Placebo
Baseline	0.890±0.328 (20)	1.118±0.349 (18)	1.094±0.450 (18)	1.204±0.508 (12)
24w	1.079±0.342 (19)	1.329±0.453 (13)	1.184±0.509 (18)	1.286±0.564 (8)
Change from BL	0.201±0.153 (19)	0.205±0.144 (13)	0.091±0.170 (18)	-0.006±0.140 (8)
Column vs Placebo diff. [95%CI]	0.201 [0.013, 0.388]	0.215 [0.018, 0.412]	0.114 [-0.067, 0.241]	-
62.5/25μg vs Column diff. [95%CI]	-	-0.014 [-0.177. 0.149]	0.087 [-0.067, 0.241]	-

Discussion about the two cases

- In both cases, primary analysis of overall subjects is statistically significant.
- Pertuzumab
  - The reason was not suggested by model-based analysis, and investigations of heterogeneity between countries and influences of prognostic factors
  - Statistically significant result of OS in all subjects was shown.
- Umeclidinium/vilanterol
  - No interaction are shown between factors and efficacy.
  - There is a possibility of influence of discontinuation, but not clear.
  - On the other hand, clinical usefulness of LAMA/LABA has been established.

Subgroups in MRCT

- Prior consideration on possible factors and interpretation of the difference between subgroup and all subjects are important.
  - There may be the discrepancy of hypothesis between sponsor and regulator.
- Evaluation based on the Interaction between region and drug effects seems to have a limitation because of the sample size for each region.
- Although the definition of “consistency” is unclear, evaluation only of the point estimates in subgroup compared to that in all subjects is not sufficient for explaining the consistency.
  - Using all available information is recommended.

Comments on the draft guideline

- The draft guideline provides comprehensive explanations for fundamental issue.
  - The document includes most of the points that many regulatory reviewers have to consider and interpret in many different.
- There will be interest in the practice of this guideline for reviewing complex design clinical trials
  - Combination with related issues, such as trial design with confirmatory analysis with pre-specified subgroups, complex study design with biomarkers

Comments on the draft guideline

- 6.5. Scenario 3
  - Basically additional confirmatory trial should be conducted.
  - There may be the situation with high medical/social needs and also with the problem of the feasibility of additional confirmatory trial, but that will be very rare and exceptional case.
  - Further investigation in post-marketing phase will be needed.
- Question
  - It is a little difficult to imagine which trends in the data can lead to the conclusion that the factor is not of interest when the test of interaction is significant. Examples or any comments will be appreciated.

Thank you for your attention!

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  - http://www.pmda.go.jp/english/index.html