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Single Day Event

Pertuzumab plus Trastuzumab for HER2-positive metastatic colorectal cancer: Comparison of the MyPathway trial with a real-world external control arm

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- The contents of this presentation represent the opinions of the individual presenters and do not represent the opinions or positions of the organization to which we belong

Contents

Background

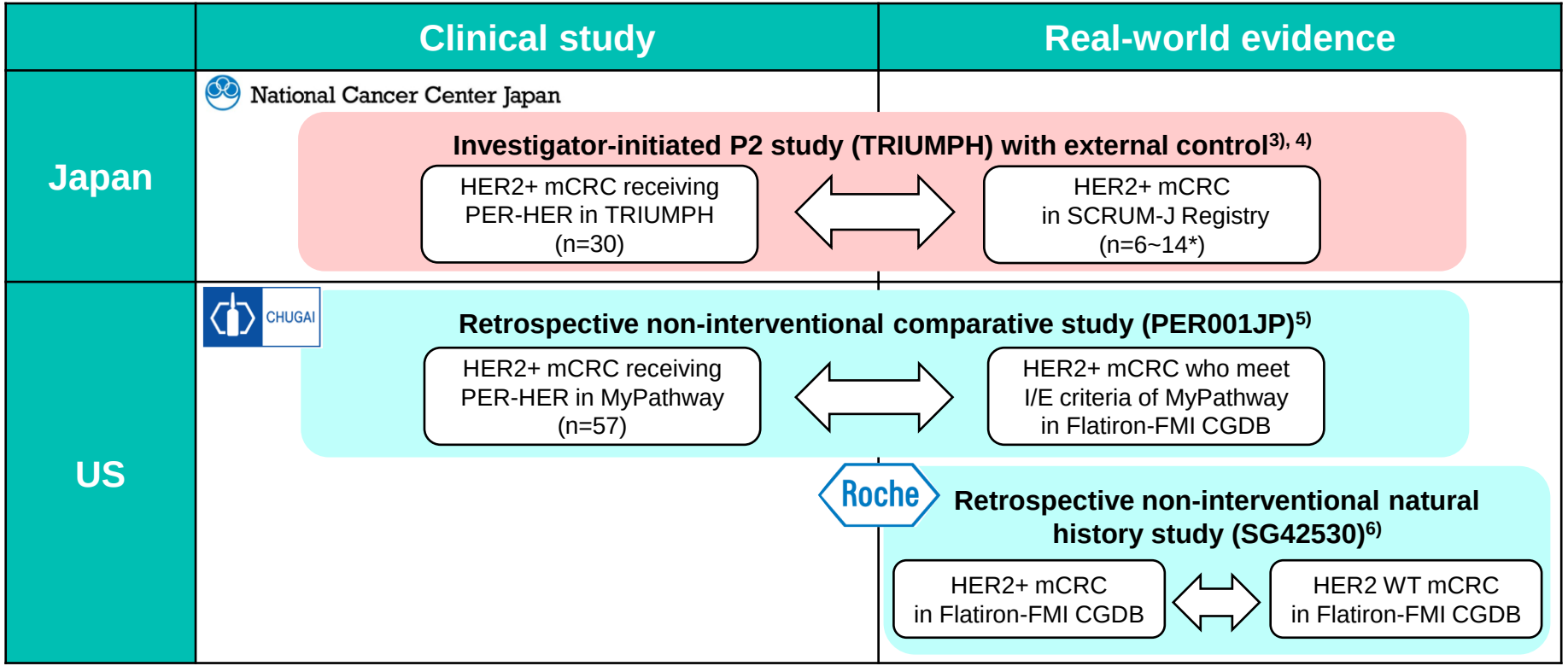
- Approximately 3~6% of patients with metastatic colorectal cancer (mCRC) are HER2 positive (HER2+)[1)]
- No standard therapy approved globally for HER2+ mCRC before 2022
  - National Comprehensive Cancer Network (NCCN) guideline has been listing pertuzumab + trastuzumab (PER-HER) based on the promising results for patients with treatment refractory HER2+ mCRC in single arm, multiple basket, phase IIa MyPathway study[2)]
- Investigator-initiated single arm phase II TRIUMPH study[3)] was conducted in Japan to obtain the approval of this combination therapy
- To contextualize results of single arm studies, external controls derived from real-world data (RWD) were used in the regulatory submission
  - SCRUM-Japan Registry for TRIUMPH study[4)]
  - Flatiron-FMI clinico-genomic database (CGDB) for MyPathway study[5)]

FMI: Foundation Medicine Inc.

Filing Package

Evaluation data

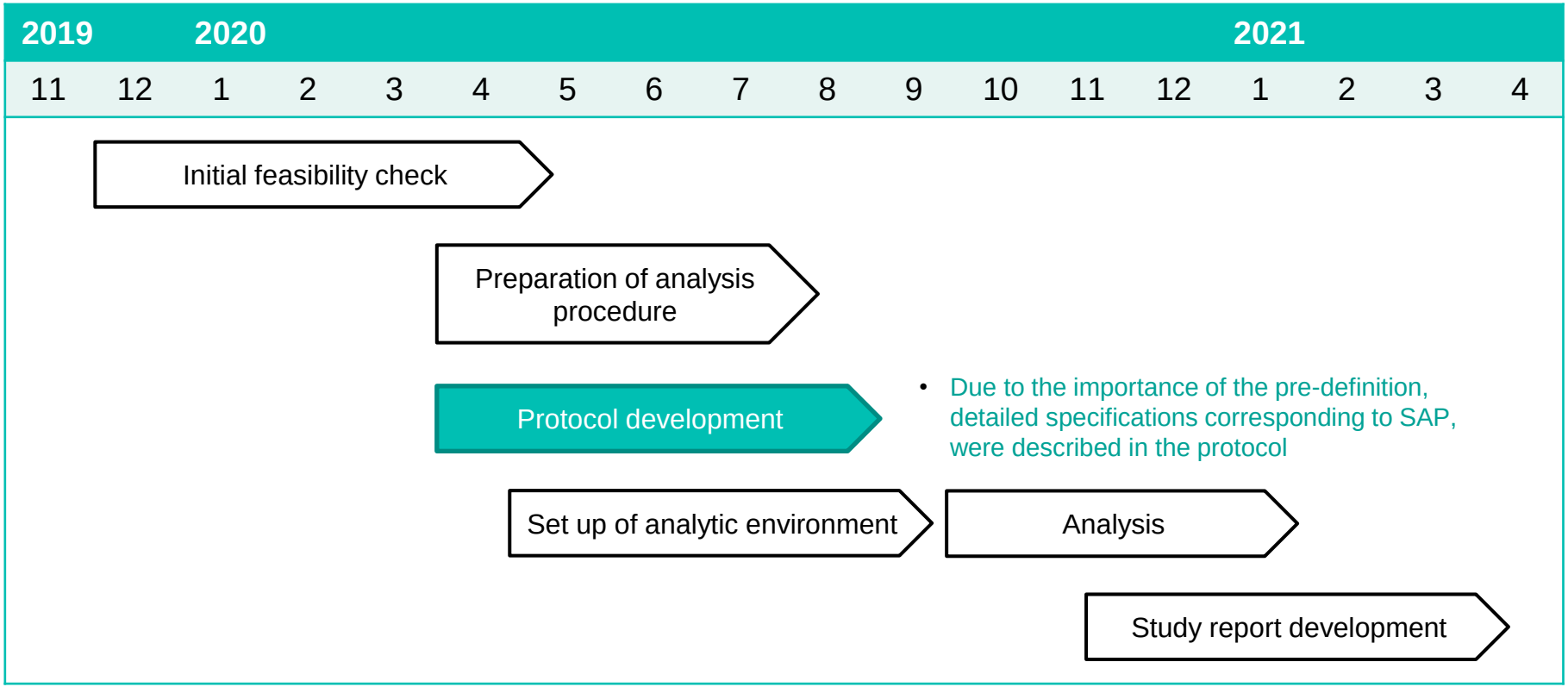
Reference data



I/E: Inclusion / Exclusion, WT: wild-type

*PMDA did not agree to include 8 patients with opt-out consent in evaluation data because efficacy data were collected in a retrospective manner for these patients

Study Timeline of PER001JP



SAP: statistical analysis plan

Health Authority Interactions before Filing

Pre-meeting

- No negative feedback from PMDA on proposed data package including RWE

Pre-submission Consultation

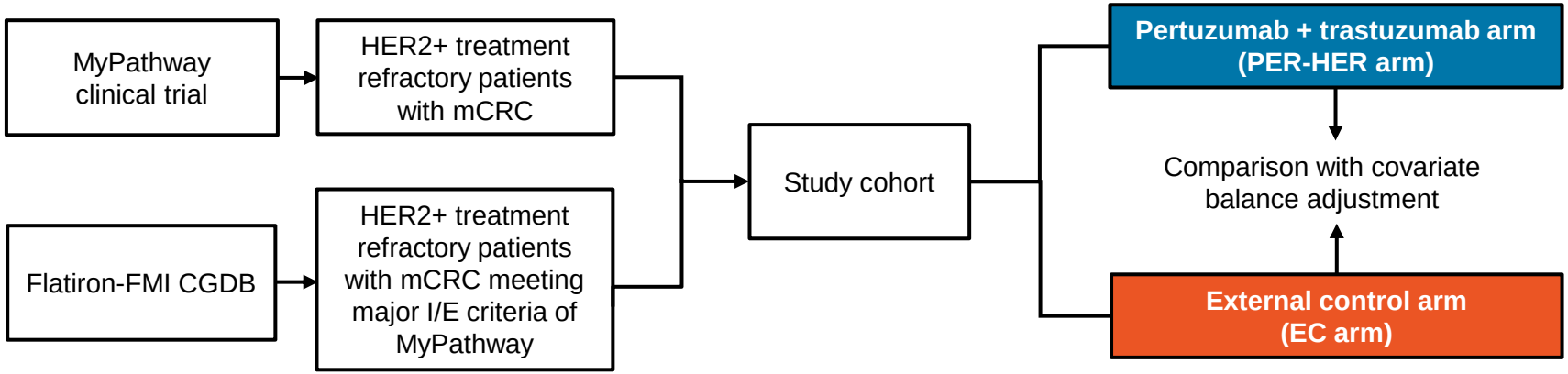
- PMDA agreed with proposed data package including RWE
- Several suggestions received including I/E criteria, importance of transparency in patient selection and discussion of limitation

Ad-hoc Consultation

- Finalized protocol was submitted to PMDA before analysis
- Several feedback on protocol were received

Study Design of PER001JP

- A non-interventional study comparing overall survival (OS) in patients with HER2+ mCRC treated with PER-HER combination therapy in MyPathway study, with OS in those receiving routine clinical care in a real-world external control arm
  - **PER-HER arm** : Patients with HER2+ mCRC who were treated with PER-HER in MyPathway study
  - **EC arm** : Patients with HER2+ mCRC who received routine clinical care



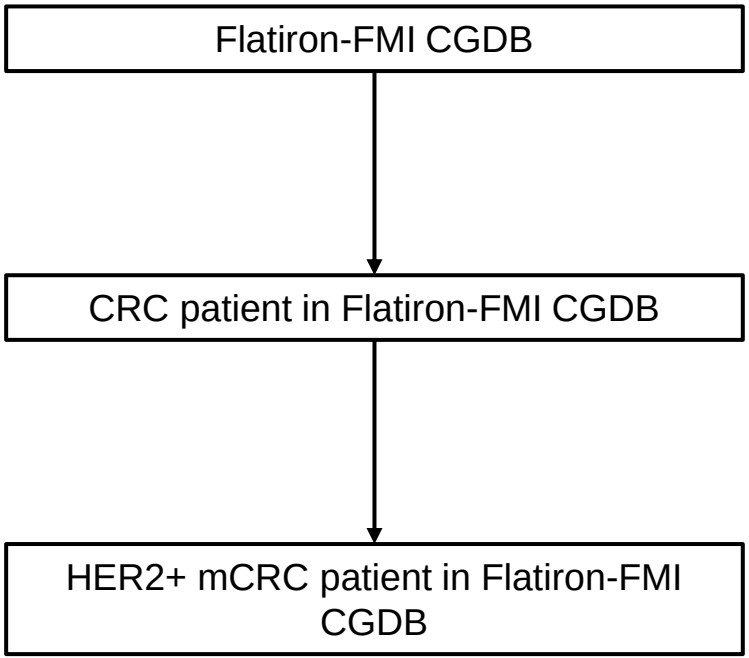
Flatiron-FMI CGDB

- Retrospective longitudinal clinical data were derived from electronic health record (EHR) data in the FH database (Flatiron Health, New York, NY) compromising patient-level information from structured (eg, laboratory values, prescribed treatments) and unstructured data (eg, biomarker reports) collected via technology-enabled chart abstraction from physicians' notes and other clinical documents
- The de-identified data originated from approximately 280 US cancer clinics (~800 sites of care, primarily community-based cancer centers)
- The CGDB includes patients from the FH database who underwent comprehensive genomic profiling (CGP) by FMI (Foundation Medicine, Cambridge, MA), and provides de-identified patient-level genomic data linked by deterministic matching, including specimen features (eg, tumor mutation burden, tumor purity), alteration-level details (eg, genomic position, reference and alternate alleles), and targeted therapeutic options reported to the clinician at the time of testing[6)]

Flatiron-FMI CGDB

https://flatiron.com/real-world-evidence/clinico-genomic-database-cgdb

Extraction of Patients with HER2+ mCRC from CGDB



Extraction criteria*

- Diagnosed with CRC (ICD-9 153-4.x or ICD-10 C18-21x)
- Flatiron chart-confirmed diagnosis of CRC
- FMI test on tumor sample from CRC

  etc.

- Evidence of stage IV or recurrent metastatic CRC diagnosis
- FMI test with quality control status
- HER2+ identified with FMI test

  etc.

*Detailed extraction criteria are provided in the literature[5)]

Inclusion / Exclusion criteria

MyPathway inclusion criteria	Apply for EC arm
≥18 years of age	Apply
Histologically documented metastatic colorectal cancer	Apply
Molecular testing results from CLIA-certified laboratories demonstrating HER2 amplification by NGS or by CISH/FISH testing or HER2-activation mutation.	Apply
Participants who have received standard first-line therapy for metastatic colorectal cancer and in whom a trial of targeted therapy is considered the best available treatment option	Apply
No previous treatment with the specific assigned study drug or any other drug sharing the same target	Apply
ECOG PS score of 0, 1, or 2	Apply[a]
Adequate hematologic function	Apply[a]
Adequate renal and liver function	Apply[a]
LVEF >50% or above the lower limit of the institutional normal range (whichever is lower)	Apply[a]
Written informed consent; able to comply with study; life expectancy ≥12 weeks; measurable or evaluable disease by RECIST v1.1; use of contraception methods or abstinence (if applicable); availability of an archival or new pre-treatment tissue sample (if molecular testing was not performed by FMI)	Not applicable

MyPathway exclusion criteria	Apply for EC arm
Hematologic malignancies	Apply
Active or untreated brain metastases	Apply
History of carcinomatous meningitis	Apply
Uncontrolled concurrent malignancy	Apply
Previous treatment with any HER2-targeted therapy	Apply
Any significant cardiovascular events within 6 months prior to study entry	Apply
Pulmonary embolism within 30 days prior to study entry	Apply
History or presence of clinically significant ventricular or atrial dysrhythmia > Grade 2 per NCI CTCAE v4.0	Apply[b]
Concurrent administration of any other anti-cancer therapy; pregnant or breastfeeding women (including intending to become pregnant during the study); any other severe acute or chronic medical or psychiatric condition or laboratory abnormality; psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol	Not applicable

[a] Patients with missing ECOG PS or relevant laboratory values were included.
[b] Patients with evidence of ventricular or atrial dysrhythmia regardless of Grade per NCI CTCAE were excluded.

CLIA: Clinical Laboratory Improvement Amendments, CISH: Chromogenic In Situ Hybridization, FISH: Fluorescence In Situ Hybridization, CTCAE: Common Terminology Criteria for Adverse Events, ECOG PS: Eastern Cooperative Oncology Group performance status, LVEF: left ventricular ejection fraction, NCI: National Cancer Institute, NGS: next-generation sequencing, RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1

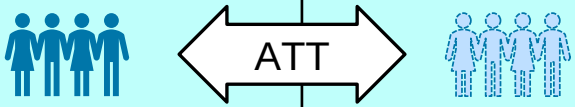
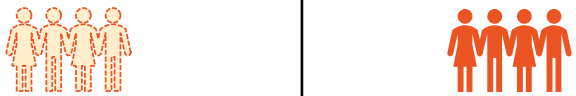
Data Cut-off Date

- PER-HER arm
  - Data cut-off of August 1, 2017

- EC arm
  - Data collected between January 1, 2011, and December 31, 2019

Causal Inference

- Comparison of the treatment effect in patients who received PER-HER with the effect in case of receiving routine clinical care in the MyPathway population
- Assuming that identifiability condition holds, propensity score will be used for deriving the pseudo-population, in which the average causal treatment effect can be estimated without confounding
  - Average treatment effect on treat（ATT）

	PER-HER treated	PER-HER non-treated
PER-HER arm (MyPathway, $Z = 1$)		
EC arm (CGDB, $Z = 0$)		

Pseudo Population

- Standardized mortality ratio weighting (SMRW) from propensity score was used to derive a pseudo population
- Stabilized weights were applied for each arm

$$W_{ATT} = Z + \frac{e}{1-e} \cdot \frac{1-p}{p}(1-Z)$$

  - PER-HER arm ($\boldsymbol{Z = 1}$) : 1
  - EC arm ($\boldsymbol{Z = 0}$) : $(e/p) \times \{(1-p)/(1-e)\}$

e : Propensity score for PER-HER arm
p : Ratio of PER-HER arm to the overall population

- Truncation of weights at the 99th percentile over 1st percentile was performed

Primary Analysis

- In the post-weighting population, multivariate Cox proportional hazards (PH) models were used for estimation of the hazard ratio (HR) in the primary analysis
- The Kaplan-Meier method was used to estimate OS distribution

- Hereinafter, the model for the estimation of propensity score is referred to as “propensity score model” and the model for the estimation of HR as “outcome model”

Analysis Procedure and Primary Endpoint

- Analyses will be conducted in a stepwise manner

1. Estimation of propensity score

- Analysis population: Post-weighting population
  - Comparison of the treatment effect in patients who received PER-HER with the effect in case of receiving routine clinical care in the MyPathway population

2. Estimation of outcome

- Primary endpoint: OS
  - PER-HER arm :Time from the date of initiation of PER-HER to death
  - EC arm :Time from the date of initiation of index treatment to death

Points to Consider

- Definition of treatment refractory
- Handling of immortal time bias and multiple index date
- Development of propensity score model and outcome model
- Estimation of variance for HR
- Remapping of variables
- Evaluation of robustness of primary analysis

Treatment Refractory Setting

- The definition of treatment refractory from the I/E criteria of MyPathway study can be divided into the following two aspects

  – Patients who have received standard first-line therapy for metastatic colorectal cancer

  Application of 2L+

  +

  – And in whom a trial of targeted therapy is considered as the best available treatment option

  Physician's judgement

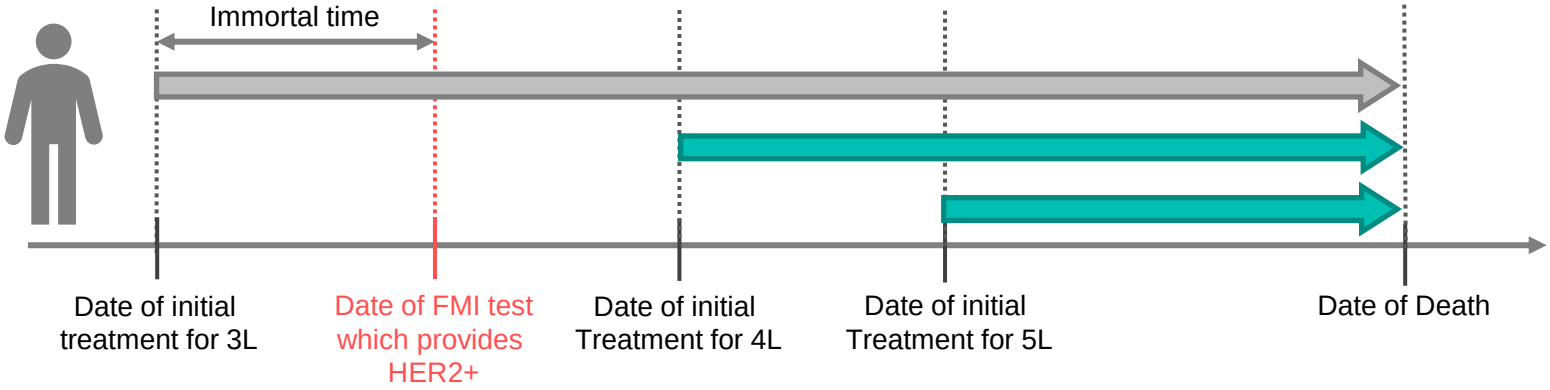
→ To take physicians judgment into account for the treatment refractory setting, we defined that patients who have received 3 or more line of therapy (3L+) are considered as treatment refractory patients in EC arm

Definition of Index Date for EC arm

- To take immortal time bias into account, the index date was defined as the date of initiation of treatment after the first FMI test providing confirmation of HER2+ status
  - There was no specific treatment line for EC arm, thus, multiple index dates may exist for patients who received multiple treatments in the refractory setting

→ The method with multiple index date showed well performed rather than using the unique index date via Monte Carlo simulation in terms of precision and bias[8)]

  - In the PER001JP study, multiple index dates were included in the analysis if the index dates were eligible according to the prespecified criteria



Pre-specified Propensity Score Model

- Four prespecified models for estimating propensity score were pre-planned
- The first model considered to be stable was used for the primary analysis

Variables	Full model	Full excluding ECOG PS	Intermediate	Minimum
Age	Apply	Apply	Apply	NOT applicable
ECOG PS	Apply	NOT applicable	NOT applicable	NOT applicable
Tumor site	Apply	Apply	Apply	Apply
Number of previous treatment regimens	Apply	Apply	Apply	Apply
Time from metastatic diagnosis to index date	Apply	Apply	Apply	Apply
KRAS status	Apply	Apply	Apply	Apply
NRAS status	Apply	Apply	NOT applicable	NOT applicable
RAS/RAF status	Apply	Apply	NOT applicable	NOT applicable
Previous anti EGFR exposure	Apply	Apply	Apply	Apply
Liver metastases	Apply	Apply	NOT applicable	NOT applicable
Lung metastases	Apply	Apply	NOT applicable	NOT applicable

Propensity Score Model and Outcome Model

- Propensity score model:
  - Propensity score was estimated using logistic regression for the selected model with treatment assignment as the dependent variable
- Outcome model:
  - Multivariate Cox PH models, which included the covariates defined for the minimum model for estimating propensity score, were used

Estimation of Variance for HR

- To estimate the variance for HR, bootstrapping was applied to account for the entire source of the variability due to complex estimation process for HR

- Procedure of estimating the bootstrap variance:
  1. Generate bootstrap sampling with replacement per patient
  2. Per bootstrap samples, a pseudo-population weighted by the stabilized SMRW will be constructed using the logistic model, and the HR of the treatment group will be estimated using the multivariate Cox PH model
  3. The 2.5% tile and 97.5% tile in the sample distribution obtained were used as the 95%CI based on the bootstrap method

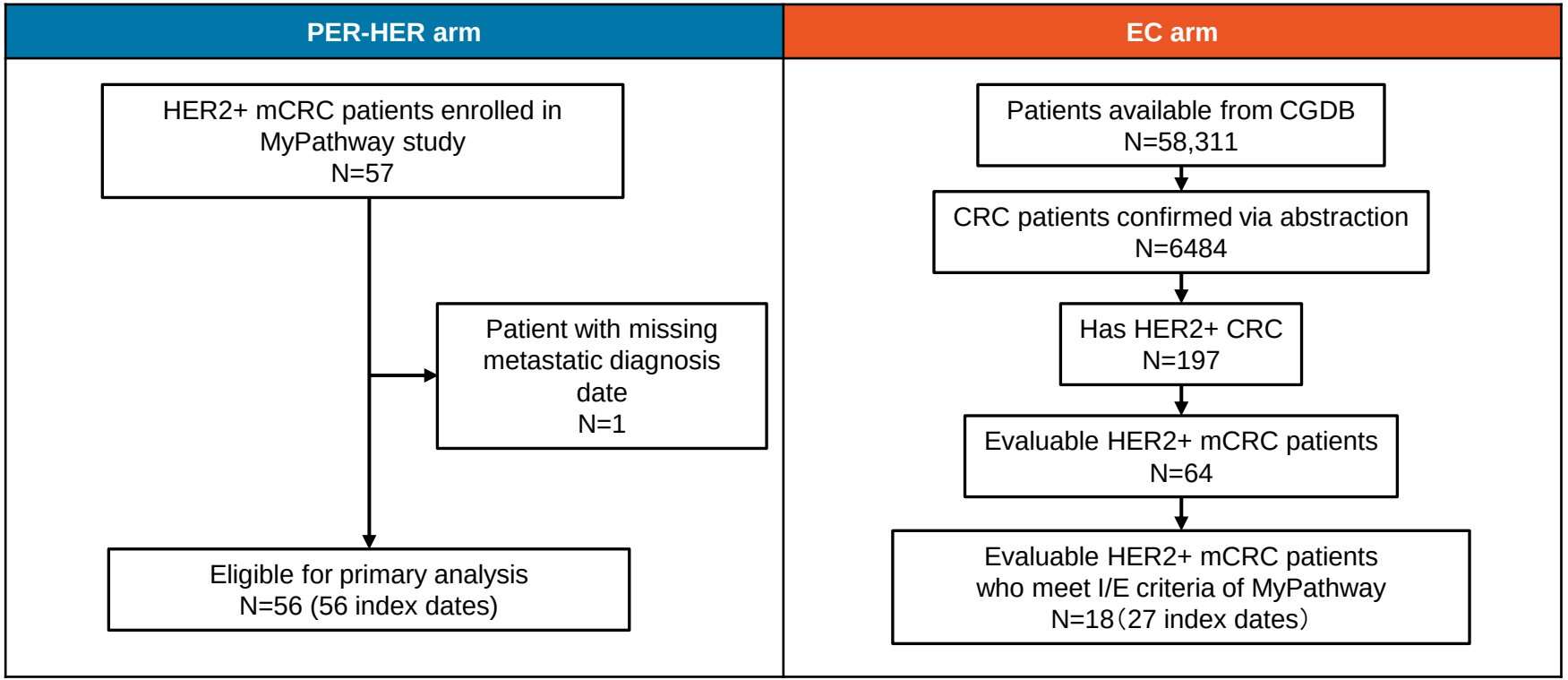
Re-mapping of variables

- As the data sets came from the different data sources, it was necessary to understand how data are entered into each data set and re-map the variables when needed

Sensitivity Analyses

Analysis method	Note	Pre-planned?
Analysis without any truncation	*For analysis using risk set adjustment approach, an approach in which index dates before the first FMI test providing confirmation of HER2+ status were considered eligible for analysis on the condition that these index dates were included in the risk set only after the first FMI test	Y
Complete case analysis for ECOG PS		
Analysis using the minimum model		
Analysis using repeated measure logistic regression model		
Analysis using risk set adjustment approach*		
Use the earliest index treatment date as index date		
Analysis of the HER2+ patient confirmed by NGS test in the PER-HER arm		
Use the latest index treatment date as index date	Added as an analysis corresponding to the analysis using the earliest treatment date	Post-hoc
Analysis using the intermediate excluding biomarker model	Added as an analysis excluding KRAS from the propensity score and outcome model	Post-hoc

Overview of Patient Attrition Diagram*



*Detailed patient attrition diagrams are provided in the literature[5)]

Selection of Propensity Score Model

- According to the pre-specified method, the primary propensity score model was determined to be the intermediate model without accessing outcome data

Variables	Full model	Full excluding ECOG PS	Intermediate	Minimum
Age	Apply	Apply	Apply	NOT applicable
ECOG PS	Apply	NOT applicable	NOT applicable	NOT applicable
Tumor site	Apply	Apply	Apply	Apply
Number of previous treatment regimens	Apply	Apply	Apply	Apply
Time from metastatic diagnosis to index date	Apply	Apply	Apply	Apply
KRAS status	Apply	Apply	Apply	Apply
NRAS status	Apply	Apply	NOT applicable	NOT applicable
RAS/RAF status	Apply	Apply	NOT applicable	NOT applicable
Previous anti EGFR exposure	Apply	Apply	Apply	Apply
Liver metastases	Apply	Apply	NOT applicable	NOT applicable
Lung metastases	Apply	Apply	NOT applicable	NOT applicable

Demographic and Baseline Characteristics[a]

- Most post-weighting characteristics were balanced better than those in the pre-weighting population; however, SMDs for some variables, such as time from initial metastatic diagnosis to index date and number of previous metastatic treatment regimens, had larger post-weighting SMDs

Characteristic, n (%)	Pre-weighting population			Post-weighting population			Included in the primary PS model
	PER-HER arm (n=56)	EC arm (n=27)[b]	SMD	PER-HER arm (n=56.00)	EC arm (n=22.85)	SMD	
Age, mean (SD)	56.1 (13.0)	57.3 (10.0)	0.104	56.12 (12.96)	55.99 (11.10)	0.011	✓
Sex, female	28 (50.0)	14 (51.9)	0.037	28.0 (50.0)	10.3 (45.3)	0.095	
Race, white[c]	45 (80.4)	13 (50.0)	0.689	45.0 (80.4)	9.1 (42.6)	0.870	
ECOG Performance Status, 0	20 (35.7)	8 (29.6)	1.244	20.0 (35.7)	4.8 (20.9)	1.258	
Year of index date, 2019	0	16 (59.3)	2.725	0	14.7 (64.4)	2.906	
mCRC diagnosis to index date, mean (SD), mo	31.1 (23.5)	27.8 (11.5)	0.180	31.10 (23.49)	24.85 (11.62)	0.337	✓
Tumor site, left side	22 (39.3)	12 (44.4)	0.411	22.0 (39.3)	8.0 (34.8)	0.354	✓
HER2 status (NGS), amplification	41 (73.2)	27 (100.0)	0.855	41.0 (73.2)	22.9 (100.0)	0.855	
No. of previous metastatic treatment regimens, <4	32 (57.1)	19 (70.4)	0.278	32.0 (57.1)	17.2 (75.2)	0.389	✓
KRAS status, mutation	13 (23.2)	5 (18.5)	0.116	13.0 (23.2)	3.9 (17.2)	0.150	✓
Previous anti-EGFR therapy, cetuximab only	17 (30.4)	11 (40.7)	0.492	17.0 (30.4)	7.7 (33.6)	0.149	✓
Liver metastases	42 (75.0)	24 (88.9)	0.367	42.0 (75.0)	20.2 (88.5)	0.356	
Lung metastases	42 (75.0)	19 (70.4)	0.104	42.0 (75.0)	13.9 (61.0)	0.303	

[a] Baseline patient demographics and clinical characteristics were used as recorded prior to and closest to the index date.
[b] Number of eligible index dates from 18 patients.
[c] There was one patient (one index date) with missing value in EC arm.
SMD: standardized mean difference, PS: propensity score

Primary Analysis and Sensitivity Analyses

- Although CIs were wide due to small sample size and several limitations existed, the totality of evidence from this study suggested that PER-HER could have a potential benefit in OS in this population

Analysis	Multivariable model HR (bootstrap 95% CI)
Primary analysis	**0.729 (0.184, 3.900)**
Sensitivity analyses[a]	
Analysis without any truncation	0.729 (0.184, 3.912)
Analysis of patient with HER2+ status confirmed by NGS test in PER-HER arm	0.623 (0.083, 4.152)
Use the earliest treatment date as index date	0.817 (0.143, 6.689)
Use the latest treatment date as index date	0.456 (0.092, 3.145)
Analysis excluding KRAS status from propensity score model	0.607 (0.206, 2.835)
Analysis using risk set adjustment approach[b]	0.653 (0.248, 1.920)

[a] Sensitivity analyses with complete case analysis for ECOG PS and using repeated measure logistic regression model were not performed.
[b] A total of 53 index dates from 28 patients in the EC arm were included in this sensitivity analysis.
CI: confidence interval

Limitations

Missing of ECOG PS	• Although ECOG PS is one of the key prognostic factors, it is often not available in real-world data sets as it is not routinely collected in clinical practice • In this sense, the potential imbalance in ECOG PS distribution might have affected the OS comparison
Biomarker testing method	• There were differences in the selection of HER2-positive patients between the PER-HER and EC arms • The sensitivity analysis using patients confirmed to have HER2+ by the NGS testing in the PER-HER arm (42 of 57 patient) was consistent with the primary analysis, suggesting that biomarker testing methods might not have had a major impact on the interpretation of our findings
Calendar time bias	• Because the EC arm was from a later calendar time, these patients would have been more likely to have taken advantage of available treatment advances for CRC
Definition of Line of Therapy (LOT)	• The definition of LOTs in each arm might have not been fully aligned. In MyPathway, LOTs were not systematically defined and were left up to the investigator's discretion • There was no guarantee that the LOTs defined in MyPathway would be the same as those from FH
Treatment refractory setting	• Because the determination of whether the study drug is the best available option was left up to the investigator and was impossible to define in MyPathway, eligibility criteria for the EC arm were decided on the basis of the treatment algorithm for mCRC to only include patients who had received ≥ 2 previous metastatic LOTs
Covariate	• Potential prognostic factors, including unmeasured factors that were not included in the propensity score model or outcome model as covariates, might not have been well balanced between the arms

Summary and Learnings

- The supportive evidence generated from non-interventional study using Flatiron-FMI CGDB were included in the submission package for the first time
  - The PER001JP study is also the first non-interventional study using CGDB planned and conducted by Chugai in collaboration with Roche/Genentech

- Chugai's opinion that the evidence from PER001JP support the approval was included in the assessment report
  - It is unclear, however, how the evidence contributed to PMDA's decision as they did not provide their opinion in the assessment report

- Interpretation of findings from single-arm trial for regulatory and clinical decision making can be supported by contextual information from EC arm derived from RWD sources
  - Evidence generation activities using RWD can provide valuable complementary information, particularly in cases when a randomized controlled trial is not feasible

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