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Final Analysis of a Prospective Observational Study to Evaluate the Impact of Comprehensive Genome Profiling on Treatment Decision Making in Metastatic or Recurrent Breast Cancer in Japan: JBCRG-C07 REIWA Study

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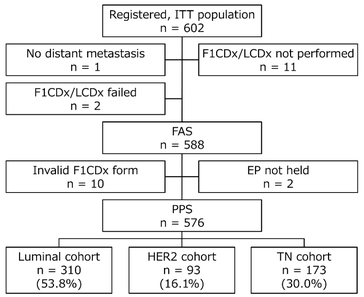
Introduction

- The Comprehensive Genome Profiling (CGP) has been covered by insurance in Japan since July 2019 for patients who have completed or are expected to complete standard treatment.
- We conducted a study (JBCRG-C07 (REIWA study), UMIN000038065) to determine the proportion of patients with stage IV or recurrent breast cancer (BC) who have received matched therapy (MT) identified by gene panel testing since January 2020.
- Forty-three major Japanese hospitals participated in this study, and 602 cases were enrolled.
- We report the final analysis of treatment access rates for MT and the present results of survival analysis.

Methods

- Patients with stage IV or recurrent BC who had completed or were expected to complete standard therapy were eligible.
- Patients who consented to undergo the FoundationOne® CDx (F1CDx) or FoundationOne® Liquid CDx (F1LCDx) cancer gene panel tests were enrolled prospectively.

Figure 1: Patient flow diagram



Primary endpoints:

The proportion of patients who received MT for their genomic alterations after undergoing F1CDx or F1LCDx in the population where MT was available, and the proportion of patients who participated in the recommended clinical trials.

Key secondary endpoints:

Overall survival, detection rate of actionable genetic alterations, and the percentage of patients for whom MT for actionable genetic alterations was available under the Japanese healthcare system (including those used for other cancers).

Results

Table 1: Patient characteristics

n = 576		Total		F1CDx		F1LCDx	
		No.	%	No.	%	No.	%
Sex	Female	574	99.7	488	99.6	86	100
	Male	2	0.3	2	0.4	0	0
Age (y)	Median	56		56		59	
	Range	26.0–91.0		26.0–91.0		31.0–85.0	
	<50	172	29.9	156	31.8	16	18.6
	≧50	404	70.1	334	68.2	70	81.4
	<30	2	0.3	2	0.4	0	0
	30–39	31	5.4	30	6.1	1	1.2
	40–49	139	24.1	124	25.3	15	17.4
	50–59	170	29.5	142	29	28	32.6
	60–69	145	25.2	115	23.5	30	34.9
	≧70	89	15.5	77	15.7	12	14
Cancer status	Recurrence	427	74.1	359	73.3	68	79.1
	De-novo stage IV	148	25.7	130	26.5	18	20.9
	Distant recurrence after refusal of surgery	1	0.2	1	0.2	0	0
Number of pretreatment regimens	Median: Total	3		3		5	
	0 regimen	29	5	29	5.9	0	0
	1 regimen	105	18.2	99	20.2	6	7
	2 regimens	81	14.1	73	15	8	9.3
	3 regimens	82	14.2	63	13	19	22.1
	≥4 regimens	279	48.4	226	46.1	53	61.6
	(≥10 regimens)	36	6.3	29	5.9	7	8.1
Median number of pretreatment regimens by subtype	Luminal	5		4		6	
	HER2	4		4		6	
	TN	2		2		3	
Specimens submitted for F1CDx	Primary breast sites	286	58.4	286	58.4	—	—
	Biopsies from metastatic sites	204	41.6	204	41.6	—	—
Submitted metastatic sites	Distant lymph nodes	51	25	51	25	—	—
	Skin	39	19.1	39	19.1	—	—
	Liver	38	18.6	38	18.6	—	—
	Lung	21	10.3	21	10.3	—	—
	Soft tissue	15	7.4	15	7.4	—	—
	Local lesion	14	6.9	14	6.9	—	—
	Brain	4	2	4	2	—	—
	Bone	3	1.5	3	1.5	—	—
	Pleura	3	1.5	3	1.5	—	—
	Others	16	7.8	16	7.8	—	—

Figure 2: Oncoprint plot visualizing detected gene alterations.

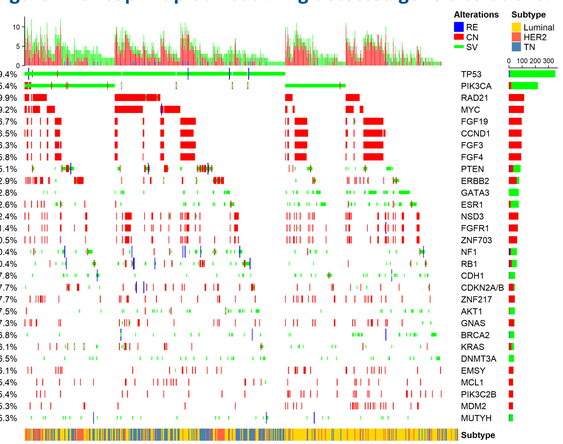
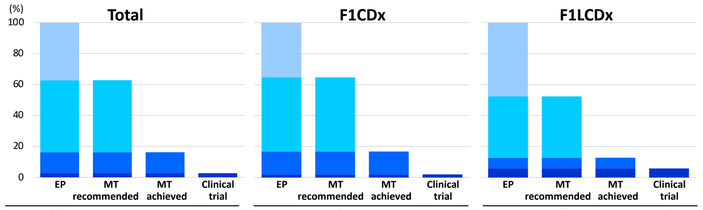


Figure 3: The proportion of patients who had matched therapy (MT) and participated in the recommended clinical trials.



		Total				F1CDx				F1LCDx			
		EP	MT recommended	MT achieved	Clinical trial	EP	MT recommended	MT achieved	Clinical trial	EP	MT recommended	MT achieved	Clinical trial
n	576		362	93	15	490	317	82	10	86	45	11	5
%			62.8	16.1	2.6		64.7	16.7	2.0		52.3	12.8	5.8

✓ A total of 82 patients (16.7%) received matched therapy based on F1CDx, and 11 patients (12.8%) received matched therapy based on F1LCDx.

Table 2: Matched therapies administered outside of clinical trials.

Matched therapy	Alteration	n (82)	%
Immune checkpoint inhibitor		**26**	**31.7**
ICI	TMB high	23	28.0
ICI	MSI high	2	2.4
ICI	MSI high, TMB high	1	1.2
ICI	*CD274* amp, *PDCD1* amp	1	1.2
mTOR inhibitor		**19**	**23.2**
EVE	*PIK3CA* mut	17	20.7
EVE	*PTEN* loss	1	1.2
EVE	*PTEN* loss, *PIK3CA* mut	1	1.2
Anti-HER2 therapy		**14**	**17.1**
T-DXd	*ERBB2* amp	5	6.1
Tmab	*ERBB2* amp	4	4.9
LAP	*ERBB2* amp	2	2.4
LAP	*ERBB3* mut	2	2.4
T-DM1	*ERBB2* amp	2	2.4
T-DXd	*ERBB2* mut	2	2.4
Tmab+Pmab	*ERBB2* amp	2	2.4
T-DXd	*ERBB3* mut	1	1.2
Tmab+LAP	*ERBB2* amp	1	1.2

Matched therapy	Alteration	n (82)	%
PARP inhibitor		**12**	**14.6**
PARP inhibitor	*BRCA2* mut	8	9.8
PARP inhibitor	*BRCA1* mut	3	3.7
PARP inhibitor	*PALB2* mut	1	1.2
AKT inhibitor		**7**	**8.5**
CAPI	*PIK3CA* mut	5	6.1
CAPI	*AKT1* mut	1	1.2
CAPI	*PTEN* mut	1	1.2
CDK4/6 inhibitor		**3**	**3.7**
CDK4/6i	*CCND1* amp	3	3.7
NTRK inhibitor		**2**	**2.4**
Entrectinib	*NTRK1* fusion	1	1.2
Entrectinib	*NTRK3-ETV* fusion	1	1.2
Larotrectinib	*NTRK3-ETV* fusion	1	1.2
Larotrectinib	*NTRK1* fusion	1	1.2
SERD		**1**	**1.2**
FUL	*ESR1* mut	1	1.2
Other		**2**	**2.4**
Tmab+Taxan+CBDCA	Genomic instability	2	2.4

Note: Among the 93 patients who received matched therapies (MT), four received MT both within and outside clinical trials, and another four patients received two types of MT addressing different actionable gene alterations. In addition, some patients received MT with different regimens within the same type.

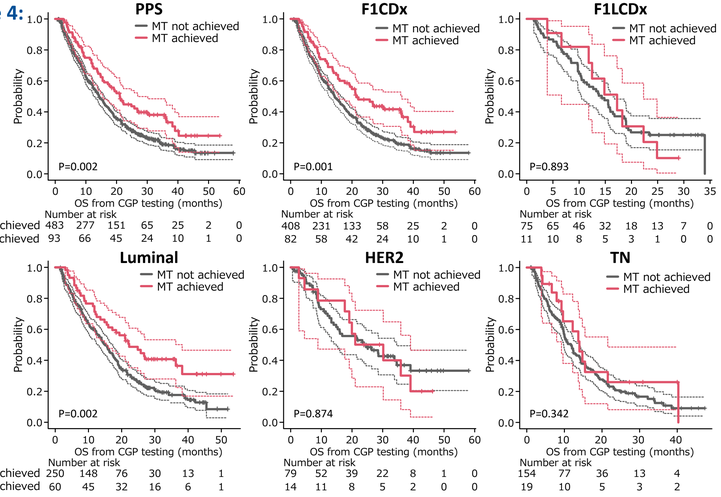
Table 3: Cases enrolled in clinical trials of molecularly matched targeted therapies.

No.	Age	Subtype	Alteration	Matched therapy
1	48	HER2	*ERBB2* amp	HER2-TKI
2	64	Luminal	*ERBB2* mut	HER2-TKI
3	69	Luminal	*ERBB2* mut	HER2-TKI
4	62	Luminal	*ERBB2* mut	HER2-TKI
5	52	Luminal	*ERBB2* mut	HER2-TKI
6	50	Luminal	*ERBB2* mut	HER2-TKI
7	68	TN	*ERBB2* mut	HER2-TKI
8	49	Luminal	*BRCA2* mut	PARP inhibitor
9	71	TN	*BRCA2* mut, *CHEK2* mut, *ATM* mut	PARP inhibitor +transporter inhibitor
10	45	TN	*BRAF* V600E	BRAF inhibitor + MEK inhibitor
11	64	TN	*BRAF* V600E	BRAF inhibitor + MEK inhibitor
12	38	Luminal	*FGF3/4/19* amp	FGFR TKI + ICI
13	58	Luminal	*FGFR1* rearrangement	FGFR TKI
14	47	Luminal	TMB high	ICI
15	45	TN	*TP53* mut	KIF18A inhibitor

Table 4: Reasons for selecting F1LCDx.

N=86	No.	%
Long-term storage of tissue (FFPE Tissue storage period in this group: median: 7 years (3-29))	43	50
Due to difficulty in obtaining tissue samples by biopsy (e.g. Small amount of tissue)	28	32.6
Because tissue specimen was obtained but difficult to analyze	21	24.4
F1LCDx provides a better understanding of the current genetic alteration status	7	8.1
Because the clinical advantages of Liquid were judged to be greater	0	0
Other	5	5.8

Figure 4: OS



Summary

- Among the 576 patients in the per-protocol set, 490 underwent F1CDx and 86 underwent F1LCDx. The median age was 56 years, and 25.7% of patients had de-novo stage IV disease.
- The median number of pretreatment regimens before testing was five in the luminal subtype (n = 310), two in the triple-negative subtype (n = 173), and four in the HER2-positive subtype (n = 93). MT was recommended for 362 patients (62.8%) and administered to 93 patients (16.1%).
- The primary endpoint—the proportion of patients receiving MT among those for whom MT was recommended—was 25.7% (93/362).
- The most frequently administered MT within clinical trials was HER2 tyrosine kinase inhibitor therapy for ERBB2-mutated luminal breast cancer, whereas the most common off-trial MTs were immune checkpoint inhibitors (31.7%) primarily for TMB-high tumors and mTOR inhibitors (23.2%) primarily for tumors harboring PIK3CA mutations.
- During the follow-up period (median, 13.5 months), 412 deaths (71.5%) occurred. OS was significantly longer in the MT group than in the non-MT group (median 21.1 vs. 14.4 months; HR 0.651, 95% CI 0.494–0.857; P = 0.002).
- Subtype-specific analysis showed a significant OS benefit in the luminal subtype (22.3 vs. 15.1 months; HR 0.565, 95% CI 0.396–0.809; P = 0.002), whereas no significant benefit was observed in the triple-negative (14.0 vs. 11.8 months; HR 0.758, 95% CI 0.428–1.345; P = 0.342) or HER2-positive subtype (25.6 vs. 23.9 months; HR 1.057, 95% CI 0.530–2.107; P = 0.874).

Conclusion

- Among patients with stage IV or recurrent BC who were recommended for targeted therapy through CGP, approximately one-quarter received MT and demonstrated an improved OS.
- An OS benefit was observed in the luminal subtype but not in the triple-negative or HER2-positive subtypes, highlighting the need for effective MT options and expanded early line clinical trials for these groups in Japan.

Conflict of interest

- This study was supported by Chugai Pharmaceutical Co., Ltd.

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