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Health-related quality of life in 2nd-line endocrine therapy for patients with acquired endocrine-resistant postmenopausal ER-positive, HER2-negative metastatic breast cancer: the HORSE-BC study

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Comprehensive Support Project For Oncological Research of Breast Cancer
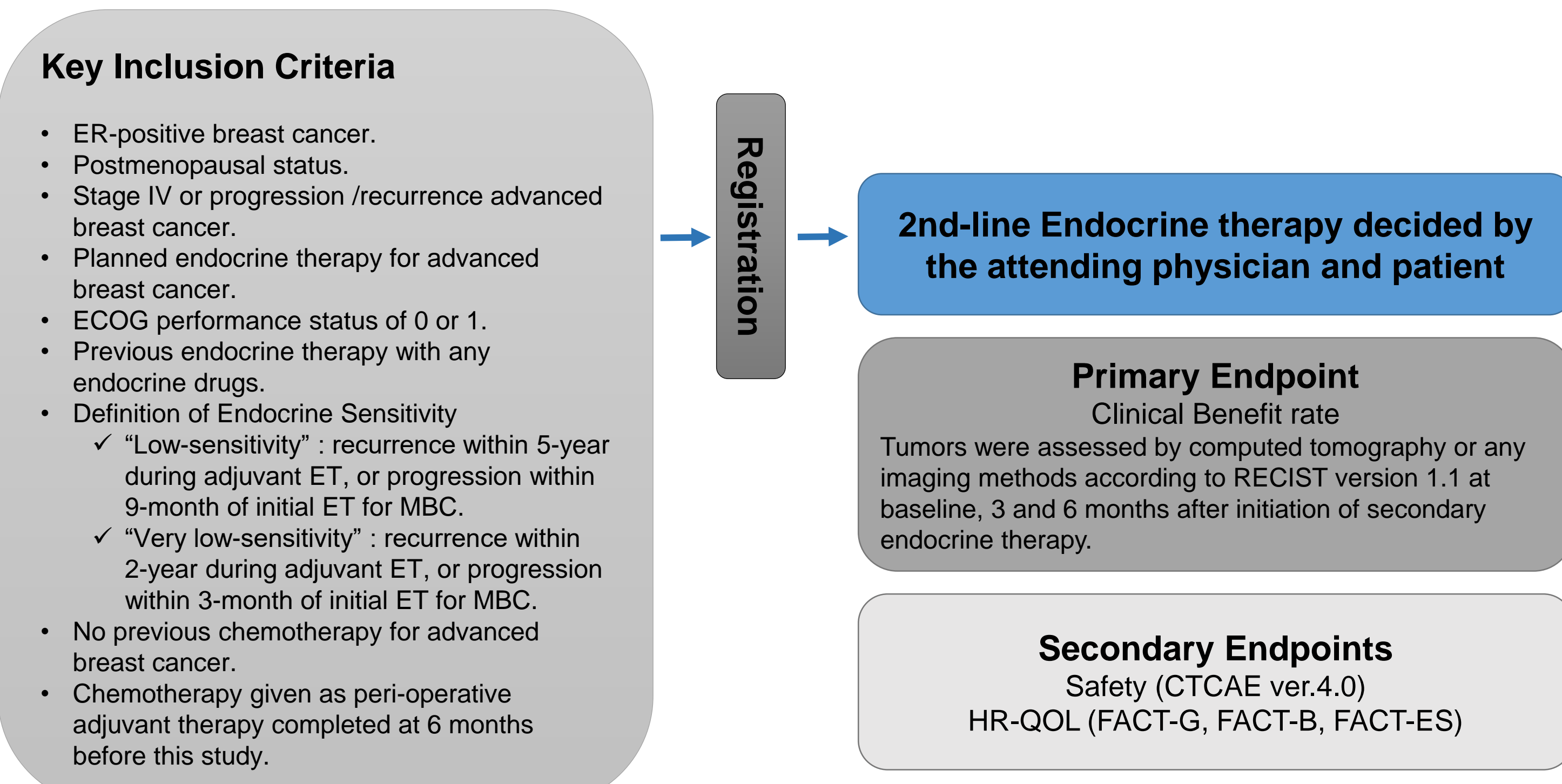
Background

- Maintaining health-related quality of life (HR-QOL) is one of the most important outcomes for metastatic breast cancer (MBC) patients.
- Endocrine therapy (ET) is often chosen as the upfront treatment option instead of chemotherapy for estrogen receptor-positive patients.
- HORSE-BC, a multicenter cohort study (UMIN ID: 000019556), previously demonstrated that 2nd-line ET for MBC patients with acquired endocrine resistance still provided a clinically meaningful benefit (presented by Araki at SABCS 2018).
- The HR-QOL in the HORSE-BC was investigated in this study.

Study Objectives

- To evaluate HR-QOL and the endocrine symptoms found in the endocrine less-sensitive MBC patients during second line ET.
- To investigate the minimally important differences (MIDs) of FACT-ES score.
- To investigate the correlation between the clinical benefit and HR-QOL.

Methods

Figure 1. Study Design

Key Inclusion Criteria
- ER-positive breast cancer.
- Postmenopausal status.
- Stage IV or progression /recurrence advanced breast cancer.
- Planned endocrine therapy for advanced breast cancer.
- ECOG performance status of 0 or 1.
- Previous endocrine therapy with any endocrine drugs.
- Definition of Endocrine Sensitivity
  - ✓ "Low-sensitivity" : recurrence within 5-year during adjuvant ET, or progression within 9-month of initial ET for MBC.
  - ✓ "Very low-sensitivity" : recurrence within 2-year during adjuvant ET, or progression within 3-month of initial ET for MBC.
- No previous chemotherapy for advanced breast cancer.
- Chemotherapy given as peri-operative adjuvant therapy completed at 6 months before this study.

Registration → **2nd-line Endocrine therapy decided by the attending physician and patient**

Primary Endpoint
Clinical Benefit rate
Tumors were assessed by computed tomography or any imaging methods according to RECIST version 1.1 at baseline, 3 and 6 months after initiation of secondary endocrine therapy.

Secondary Endpoints
Safety (CTCAE ver.4.0)
HR-QOL (FACT-G, FACT-B, FACT-ES)

HR-QOL Assessment

- HR-QOL was assessed at baseline, 1 month, and 3 months after initiation of 2nd-line ET using the Japanese version of the Functional Assessment of Cancer Therapy (FACT)-General (G), Breast (B) and FACT-Endocrine Symptom (ES).
- The FACT-B is a 36-item questionnaire that measures general HR-QOL associated with cancer using 27 items in FACT-G [7 for physical well-being (PWB), 7 for social and family well-being (SFWB), 6 for emotional well-being (EWB), and 7 for functional well-being (FWB)] and has 9 more items on the breast cancer subscale (BCS) that are more specific to women with breast cancer.
- The ES was designed for use with the FACT-B and comprises 18 items, with a maximum possible score of 72.
- The FACT-B Trial Outcome Index (TOI) scores is the sum of scores from PWB, FWB, and BCS. A total of 23 items contribute to the FACT-B TOI, resulting in a maximum possible score of 92. The FACT-ES TOI is the sum of scores from PWB, FWB, and ES of which the maximum score is 108. TOI is often used as the main outcome index of HR-QOL.
- Each item or question on the FACT-B and ES has response choices ranging from 0 ("not at all") to 4 ("very much") and the higher scores indicate a better HR-QOL.

Subjective Significant Questionnaire (SSQ)

- Six questions corresponding to PWB, SFWB, EWB, FWB, ES, and ES-total score in order to identify the MIDs.
- SSQs are the seven grade Likert scale and written as follows:
  Since you decided to participate in this study,
  A) your physical condition is…
  B) your social or relationship with your familial people are…
  C) your anxious things are….
  D) your social activities are….
  E) your menopausal symptoms are…..
  F) your general health status is….
- The choices after each question are as follows:
  1, very much better; 2, moderately better; 3, a little better; 4, about the same; 5, a little worse; 6, moderately worse; 7, very much worse

Analyses

- The means and standard deviations (SDs) of scores for FACT-G, FACT-B and FACT-ES at the time of enrollment and after 1 and 3 months of 2nd-line ET were calculated.
- MIDs based on the Distribution Method
  - ✓ 1/3 and1/2 SDs were defined as the small and moderate MIDs for the distribution based method (Eton et al., J Clin Epidemiol, 2004).
  - ✓ The standard error of measurement (SEM) for the HR-QOL scores was calculated across all time points. The SEM is used as the minimal detectable change and was approximately equal to the MID (Wyrwich et al., Med Care, 1999).
  - ✓ The SEM was computed as $\sigma_x (1-\text{rel}_x)^{1/2}$, where σ_x is the SD of the scale and rel_x is the reliability (internal consistency) of the scale.
  - ✓ Cronbach alpha coefficients were calculated as the internal consistency of the scale.
- MIDs based on the Anchor Method
  - ✓ Differences of the change in HR-QOL between categories in six questions of the SSQs (Osoba et al., J Clin Oncol, 1998) were calculated for the anchor based method (Eton et al., J Clin Epidemiol, 2004).
- Missing values were systematically deleted and not included in the analyses.

Results

Table 1. Patients characteristics at baseline (n=47)

		Value
Age, years		
	Mean (SD)	65.7 (9.0)
	Median (range)	66 (41-88)
ECOG PS		
	0	39 (83.0%)
	1	7 (14.9%)
	2	1 (2.1%)
2nd line Endocrine Treatment		
	Letrozole	1 (2.0%)
	Tamoxifen	3 (6.1%)
	Tremelone	1 (2.1%)
	Fulvestrant	39 (83.0%)
Martial Status		
	Married or with partner	23 (48.9%)
	Never Married	5 (10.6%)
	Separated or divorced	11 (23.4%)
	Widowed	8 (17.0%)
Highest level of education		
	Compulsory school education	5 (10.6%)
	High school	31 (66.0%)
	university level or above	10 (21.3%)
	missing	1 (2.1%)
Employment status before diagnosis of breast cancer		
	Full time	18 (38.3%)
	Part time	7 (14.9%)
	Homemaker	15 (31.9%)
	Volunteer	1 (2.1%)
	Retired	4 (8.5%)
	Unemployed	2 (4.3%)

		Value
Employment status at baseline		
	Full time	4 (8.5%)
	Part time	10 (21.3%)
	Homemaker	15 (31.9%)
	Volunteer	1 (2.1%)
	Retired	3 (6.4%)
	Unemployed	14 (29.8%)
Annual household income		
	3,000,000 yen or less	23 (48.9%)
	3,000,000-5,000,000 yen	10 (21.3%)
	5,000,000-10,000,000	6 (12.8%)
	10,000,000 yen or more	2 (4.3%)
	missing	6 (12.8%)
Living situation (multiple answers allowed)		
	Alone	13 (27.7%)
	With husband	20 (42.6%)
	With children	12 (25.5%)
	With parents	4 (8.5%)
	Other	4 (8.5%)
Comorbidity (multiple answers allowed)		
	Nothing	15 (31.9%)
	Hypertension	16 (34.0%)
	Diabetes Mellitus	6 (12.8%)
	Hyperlipidemia	7 (14.9%)
	Other	12 (25.5%)
	missing	1 (2.1%)

Table 2. HRQOL scores after 1 month and 3 months of 2nd line ET   (*n=44 for FACT-B TOI and ES TOI at 1month)

Variable	Baseline (n=47) Mean (SD)	After 1 month (n=43*) Mean (SD)	After 3 months(n=43*) Mean (SD)
FACT-G total score (range: 0 -108)	75.11 (14.68)	74.94 (13.83)	74.59 (16.15)
FACT-B total score (range: 0 -148)	97.71 (16.91)	97.81 (15.72)	97.36 (18.64)
FACT-B TOI (range: 0 - 96)	64.13 (11.64)	64.64 (11.28)	63.57 (12.80)
FACT-ES total score (range: 0 - 180)	138.00 (17.75)	136.08 (16.74)	137.41 (19.99)
FACT-ES TOI (range: 0 - 128)	104.43 (12.75)	104.68 (13.04)	103.63 (14.53)

Table 3. MIDs by Distribution-based method

	Alpha	1/3SD	1/2SD	SEM
FACT-G total score (PWB+SWB+EWB+FWB)				
Baseline	0.85	4.89	7.34	5.69
1 mo	0.84	4.61	6.92	5.53
3 mo	0.90	5.38	8.08	5.11
Baseline to 1 mo	-	3.53	5.30	
Baseline to 3 mo	-	2.57	3.88	
Mean		4.20	6.30	5.44
FACT-B total score (FACT-G + BCS)				
Baseline	0.85	5.63	8.46	6.55
1 mo	0.84	5.24	7.86	6.29
3 mo	0.89	6.21	9.32	6.18
Baseline to 1 mo	-	3.36	5.05	
Baseline to 3 mo	-	2.68	4.02	
Mean		4.63	6.94	6.34
FACT-B TOI (PWB+FWB+BCS)				
Baseline	0.82	3.88	5.82	4.94
1 mo	0.83	3.76	5.64	4.65
3 mo	0.86	4.27	6.40	4.79
Baseline to 1 mo	-	1.92	2.88	
Baseline to 3 mo	-	2.37	3.55	
Mean		3.34	4.86	4.79
FACT-ES total score (FACT-G + ES)				
Baseline	0.84	5.91	8.88	7.10
1 mo	0.85	5.58	8.37	6.48
3 mo	0.90	6.66	10.00	6.32
Baseline to 1 mo	-	3.71	5.57	
Baseline to 3 mo	-	3.23	4.85	
Mean		5.02	7.53	6.63
FACT-ES TOI (PWB+FWB+ES)				
Baseline	0.82	4.25	6.38	5.41
1 mo	0.85	4.35	6.52	5.05
3 mo	0.88	4.84	7.27	5.03
Baseline to 1 mo	-	2.27	3.41	
Baseline to 3 mo	-	2.91	4.37	
Mean		3.72	5.59	5.16

Table 4a. MID of PWB by Anchor-based method

	Change in PWB Mean	SD	Diff
Change in SSQ (A) at 1 month			
Improved (n= 9)	1.61	4.83	
Stable (n= 29)	-0.30	2.59	
Declined (n=5)	-4.60	3.65	
(Improved↔Stable)			1.91
(Stable↔Declined)			4.30
Change in SSQ (A) at 3 months			
Improved (n=9)	3.11	3.48	
Stable (n=27)	-0.68	2.51	
Declined (n=3)	-0.67	0.58	
(Improved↔Stable)			3.79
(Stable↔Declined)			-0.01

Table 4b. MID of SFWB by Anchor-based method

	Change in SFWB Mean	SD	Diff
Change in SSQ (B) at 1 month			
Improved (n=8)	7.74	7.11	
Stable (n=34)	-3.18	9.62	
Declined (n=0)	NE	NE	
(Improved↔Stable)			10.92
(Stable↔Declined)			NE
Change in SSQ (B) at 3 months			
Improved (n=8)	5.60	7.02	
Stable (n=32)	0.22	7.41	
Declined (n=0)	NE	NE	
(Improved↔Stable)			5.38
(Stable↔Declined)			NE

Table 4c. MID of EWB by Anchor-based method

	Change in EWB Mean	SD	Diff
Change in SSQ (C) at 1 month			
Improved (n=9)	0.89	1.90	
Stable (n=29)	0.12	2.33	
Declined (n=5)	-2.40	4.98	
(Improved↔Stable)			0.77
(Stable↔Declined)			2.52
Change in SSQ (C) at 3 months			
Improved (n=9)	0.00	3.35	
Stable (n=26)	1.35	3.19	
Declined (n=5)	1.00	3.39	
(Improved↔Stable)			-1.35
(Stable↔Declined)			0.35

Table 4d. MID of FWB by Anchor-based method

	Change in FWB Mean	SD	Diff
Change in SSQ (D) at 1 month			
Improved (n=2)	3.00	1.41	
Stable (n=39)	0.67	3.34	
Declined (n=1)	-5.00	NE	
(Improved↔Stable)			2.33
(Stable↔Declined)			5.67
Change in SSQ (D) at 3 months			
Improved (n=2)	3.5	2.12	
Stable (n=37)	0.24	3.73	
Declined (n=0)	NE	NE	
(Improved↔Stable)			3.26
(Stable↔Declined)			NE

Table 4e. MID of ES by Anchor-based method

	Change in ES Mean	SD	Diff
Change in SSQ (E) at 1 month			
Improved (n=2)	3.00	4.24	
Stable (n=38)	-0.36	4.6	
Declined (n=2)	-2.5	6.36	
(Improved↔Stable)			3.36
(Stable↔Declined)			2.14
Change in SSQ (E) at 3 months			
Improved (n=2)	1.50	2.12	
Stable (n=35)	0.19	6.49	
Declined (n=2)	-1.00	4.24	
(Improved↔Stable)			1.31
(Stable↔Declined)			1.19
Change in SSQ (E) (pooled)			
Improved (n=4)	2.25		
Stable (n=73)	-0.09		
Declined (n=4)	-1.75		
(Improved↔Stable)			2.34
(Stable↔Declined)			1.66

Table 4f. MID of FACT-ES by Anchor-based method

	Change in FACT-ES Mean	SD	Diff
Change in SSQ (overall QOL) at 1 month			
Improved (n=10)	2.68	10.20	
Stable (n=27)	-1.88	10.46	
Declined (n=4)	-9.45	12.16	
(Improved↔Stable)			4.56
(Stable↔Declined)			7.57
Change in SSQ (overall QOL) at 3 months			
Improved (n=9)	-1.05	9.26	
Stable (n=27)	1.65	10	
Declined (n=2)	1.33	4.71	
(Improved↔Stable)			-2.70
(Stable↔Declined)			0.32
Change in SSQ (overall QOL) (pooled)			
Improved (n=19)	0.91		
Stable (n=54)	-0.12		
Declined (n=6)	-5.86		
(Improved↔Stable)			1.03
(Stable↔Declined)			5.74

Figure 2. FACT-ES mean score changes from baseline

Clinical benefit +: n=20, +1.50 (1 month); n=22, +2.39 (3 months)
Clinical benefit -: n=23, -3.75 (1 month); n=21, -1.79 (3 months)
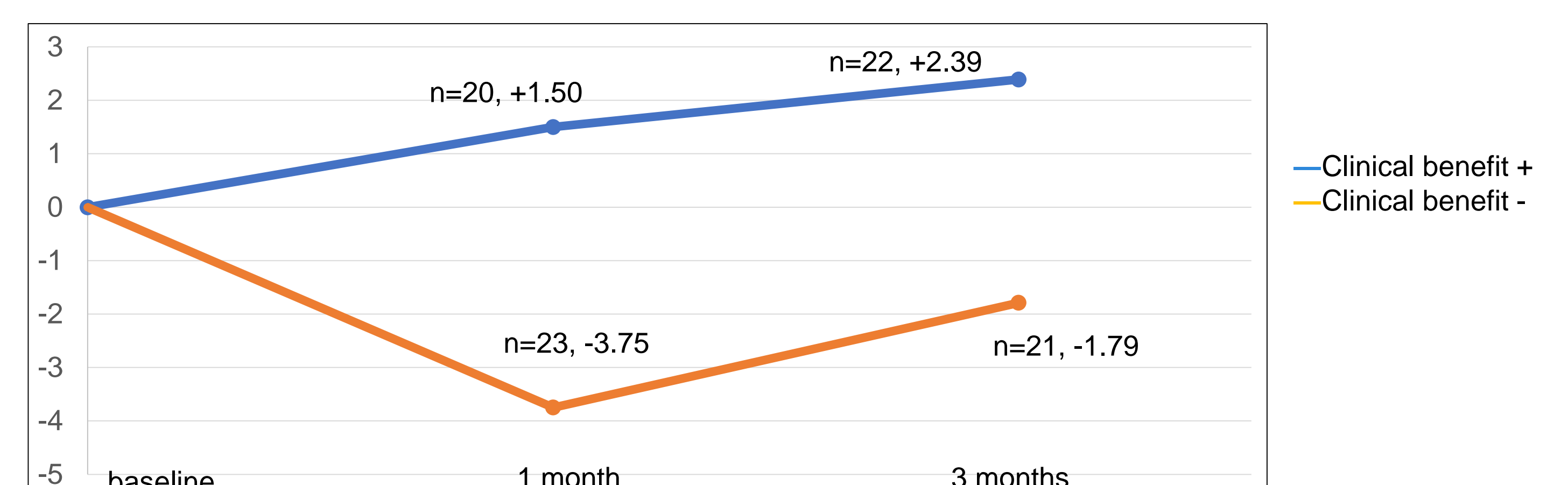
Conclusions

- MIDs of FACT-G and FACT-B from the distribution-based method were almost the same as the previous report (Eton et al., J Clin Epidemiol, 2004).
- MID in FACT-ES scores were inconsistent between the distribution-based method and the anchor-based method in this population.
- Regarding the deterioration, a 5-8 point decline may be the MIDs of FACT-ES score from the results of the pooled anchor-based method and the distribution-based method.
- Maintaining HR-QOL within 3 months as determined by FACT-ES may be correlated with a clinical benefit in patients with acquired endocrine-resistant MBC treated with ET.

Acknowledgment