P1-14-07

Randomized phase III study of anthracycline-containing regimens versus S-1 as first-line chemotherapy for metastatic breast cancer (SELECT BC-CONFIRM) - A combined analysis of two randomized phase III studies（SELECT BC-CONFIRM and SELECT BC）-

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Comprehensive Support Project

Background

- Anthracycline-containing regimens and taxane have been standard as the first-line chemotherapy for metastatic breast cancer (MBC).
- We conducted SELECT BC (randomized phase 3 study of taxane versus S-1 as first-line treatment for MBC) for evaluating the efficacy of S-1 for patients with HER2-negative MBC from 2006 to 2010 in Japan. This study demonstrated non-inferiority of S-1 in overall survival (OS) (median OS was 37.2 months in taxanes group and 35.0 months in S-1 group (HR 1.05, 95% CI 0.86–1.27, p=0.015)), and superiority in health-related quality of life (HRQOL) to taxanes. S-1 was also shown as less toxic than taxane (Lancet Oncol 2016; 17: 90-98).
- S-1 might provide clinical benefit as first-line treatment for patients with HER2-negative MBC.
- To confirm this suggestion, we have conducted further study (randomized phase 3 study of anthracycline-containing regimens versus S-1 as first-line treatment for HER2-negative MBC: SELECT BC-CONFIRM) from 2011 to present, and a combined analysis of two randomized studies (SELECT-BC CONFIRM and SELECT-BC).

Study objectives

- To verify the non-inferiority of S-1 in efficacy and toxicity to anthracycline containing regimen as first-line chemotherapy for MBC.
- To confirm the hypothesis that S-1 treatment is not inferior to the standard therapy (taxanes / anthracycline) for HER2-negative MBC according to a combined analysis of two randomized studies (SELECT-BC CONFIRM and SELECT-BC).

Study design

Non-inferiority

Patients with HER2-negative MBC (N=230) Chemotherapy naïve for MBC

R

Anthracycline-containing arm

AC: 40-60 mg/m², 400-600 mg/m² q3 or 4w IV
EC: 60-90 mg/m², 400-600 mg/m² q3 or 4w IV
FAC: 500 mg/m², 40-60 mg/m², 500 mg/m² q3 or 4w IV
FEC: 500 mg/m², 60-100 mg/m², 500 mg/m² q3 or 4w IV

A:Doxorubicin, E:Epirubicin, C:Cyclophosphamide, F:5-FU

repeated until PD or for at least 6 cycles

S-1 arm

S-1: orally bid, days, 1-28, q6w
Dose according to BSA
<1.25 m², 80 mg/d
≥ 1.25 to <1.5 m², 100 mg/d
≥ 1.5 m², 120 mg/d

repeated until PD or for at least 4 cycles

Stratification factors
- Liver metastasis
- Hormone receptor
- Prior anthracycline,taxane or oral 5-FU
- DFI
- Institution

2nd line regimen was limited to an approved standard drug such as unused anthracycline, taxane, S-1 (for only anthracycline arm), vinorelbine, gemcitabine, CMF, capecitabine, irinotecan, eribulin, and bevacizumab.

Key eligibility criteria

- Female and aged between 20 and 75 years
- PS 0 or 1 (ECOG scale)
- Histologically confirmed HER2 negative
- Endocrine resistant breast cancer
- Never received cytotoxic chemotherapy for MBC
- Prior (neo) adjuvant use of anthracycline, taxane or oral 5-FU > 24 weeks

Statistics

200 patients required
- Required death events per group: 172
- Expected median survival time: almost 24months
- Bayesian posterior probability not exceeding the threshold of 1.33: 90%

Consort diagram

Patients enrolled（N=230）

Anthracycline (n=115)	S-1 (n=115)

Eligible（n=222）

Anthracycline (n=109)	S-1 (n=113)

Ineligible（n=8）

Anthracycline (n=6)	S-1 (n=2)

FAS（n=222）

Anthracycline (n=109)	S-1 (n=113)

From 52 institutions
Enrollment period: June 2011 - December 2013
Median follow up time: 33.7 months
Number of death events: 164

Anthracycline : Anthracycline containing regimen
S-1: Tegafur - Gimeracil - Oteracil potassium

FAS：Full Analysis Set

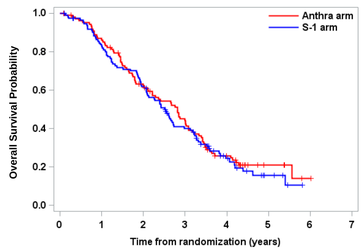
Patients characteristics

		Anthracycline (n=109)	S-1 (n=113)	*P* value
Median age, (range)		61.0 (32–75)	59.0 (31–75)	**0.041**
Hormone receptor	ER / PgR (+)	87 (78.9)	92 (81.4)	**0.45**
	ER and PgR (-)	19 (17.4)	14 (12.4)	
	Unknown	3 (2.8)	7 (6.2)	
Liver metastasis	Yes	46 (42.2)	47 (41.6)	**1.00**
	No	63 (57.8)	66 (58.4)	
Prior anthracycline	Yes	37 (33.9)	37 (32.7)	**0.89**
	No	72 (66.1)	76 (67.3)	
Prior taxane	Yes	30 (27.5)	31 (27.4)	**1.00**
	No	79 (72.5)	82 (72.6)	
Prior oral 5-FU	Yes	14 (12.8)	12 (10.6)	**0.68**
	No	95 (87.2)	101 (89.4)	
Disease free interval	< 2 years	16 (14.7)	14 (12.4)	**0.94**
	2-5 years	26 (23.9)	30 (26.5)	
	≥ 5 years	42 (38.5)	42 (37.2)	
	Unknown	0 (0)	0 (0)	
	No surgery	25 (22.9)	27 (23.9)	

Survival analysis (FAS)

Data through October 31, 2017

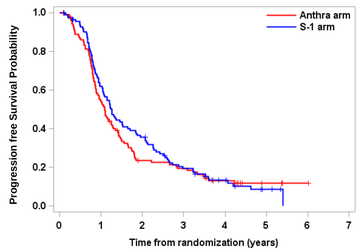
Overall survival



	Median OS	No. events
Anthracycline (n=109)	33.7m	81
S-1 (n=113)	30.1m	85

HR=1.09 (95% CI 0.80, 1.48)

Progression free survival

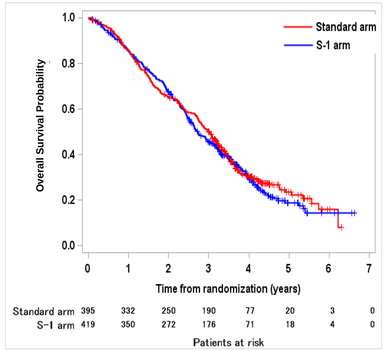


	Median OS	No. events
Anthracycline (n=109)	13.1m	92
S-1 (n=113)	15.2m	98

HR=0.90 (95% CI 0.68, 1.20)

Combined analysis （SELECT BC-CONFIRM and SELECT BC）

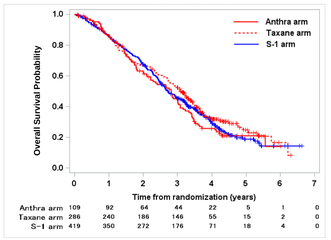
Overall survival



	Median OS	No. events
Standard (n=395)	**36.3m**	**272**
S-1 (n=419)	**32.7m**	**291**

HR=1.06 (95% CI 0.90, 1.25)
***p* =0.0062 (Non-inferiority)**

Overall survival



Adverse events

Events	Anthracycline: n, (%) Any	Grade≥3	S-1: n, (%) Any	Grade≥3	*P* value
No. of pts	n =109		n =113		
Hemoglobin	70 (64.1)	8 (7.3)	65 (57.5)	4 (3.5)	0.0856
Leukopenia	53 (48.5)	9 (8.2)	55 (48.6)	4 (3.5)	0.6145
Neutropenia	35 (32.0)	10 (9.1)	50 (44.3)	9 (8.0)	0.1096
Thrombocytopenia	9 (8.2)	1 (0.9)	38 (33.6)	1 (0.9)	<.0001
Febrile neutropenia	11 (10.1)	11 (10.1)	1 (0.9)	1 (0.9)	0.0026
Fever	24 (21.1)	1 (0.9)	15 (13.3)	0 (0.0)	0.053
Fatigue	65 (59.6)	6 (5.5)	58 (51.4)	7 (6.2)	0.4775
Alopecia	85 (78.0)	-	3 (2.7)	-	<.0001
Allergy	2 (1.8)	0 (0.0)	7 (6.2)	0 (0.0)	0.0503
Diarrhea	15 (13.7)	1 (0.9)	47 (41.6)	9 (8.0)	<.0001
Mucositis	43 (39.4)	2 (1.8)	34 (30.1)	0 (0.0)	0.1481
Nausea	63 (55.9)	3 (2.8)	60 (53.2)	2 (1.8)	0.9191
Vomiting	24 (22.0)	4 (3.7)	21 (18.6)	0 (0.0)	0.5156
Anorexia	62 (56.8)	2 (1.8)	64 (56.7)	8 (7.1)	0.2350
Edema	9 (10.1)	0 (0.0)	6 (5.3)	0 (0.0)	0.3926
Motor neuropathy	2 (1.8)	0 (0.0)	2 (1.8)	1 (0.9)	0.5779
Sensory neuropathy	15 (13.7)	0 (0.0)	15 (13.2)	1 (0.9)	0.6211
Arthralgia	8 (7.3)	1 (0.9)	10 (8.9)	0 (0.0)	0.9043
Myalgia	11 (10.1)	1 (0.9)	6 (5.3)	0 (0.0)	0.1142

Summary

- The results of SELECT BC-CONFIRM were combined with SELECT BC, to confirm the hypothesis that S-1 treatment is not inferior to the standard therapy (taxanes / anthracycline) for HER2 negative MBC.
- A combined analysis of two randomized studies showed that HR was 1.06, 95%CI 0.90-1.25, and p=0.0062 between the standard therapy group and S-1 group with data through October 31, 2017.
- In addition, the Bayesian posterior probability for which HR would be less than 1.333 was about 99.53%.

Conclusions

- A combined analysis of **SELECT BC-CONFIRM** and **SELECT BC** clearly demonstrated that OS with S-1 was not inferior to that with the standard therapy in patients receiving first-line treatment for HER2 negative MBC.
- S-1 could become a standard therapy for this patients population.

Acknowledgement

- To all of the patients who participated in SELECT BC-CONFIRM and SELECT BC, and their families.
- To the investigators and research coordinators at the 52 and 258 institutions, and CSPOR.

This study was funded by the Comprehensive Support Project (CSP) of the Public Health Research Foundation. The research fund was provided to CSP by Taiho Pharmaceutical Co., Ltd. under the study contract.

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Clinical Registration Information: UMIN (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000006465) Study ID: UMIN000005449