#1012 Randomized phase III study of Taxane versus TS-1 as first-line treatment for metastatic breast cancer (SELECT BC)

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Comprehensive Support Project

Background

- The goals of treatment for metastatic breast cancer (MBC) are prolonging survival time and improvement of patients' quality of life (QoL).
- TS-1 is an orally active combination drug, based on biochemical modulation of 5-FU, containing tegafur, gimeracil and oteracil in a molar ratio of 1:0.4:1. It has been widely used as standard regimens in various cancers.
- Two Phase II studies of TS-1 in patients with MBC, including subjects who had received prior chemotherapy as well as those who had not, have been performed in Japan. The response rates were 42.0% and 40.7%, respectively, comparable to the response rates of taxane derivatives

Study design

Non-inferiority

Patients with HER2-negative MBC (N=618) Chemotherapy naïve for MBC

R

Taxane arm
- Docetaxel: 60-75 mg/m^2 q3 or 4w IV
- Paclitaxel: 175 mg/m^2 q3 or 4w IV
- Paclitaxel: 80-100 mg/m^2 q1, 3 out of 4w IV

repeated until PD or for at least 6 cycles

TS-1 arm
TS-1: orally bid, days, 1-28, q6w
Dose according to BSA
<1.25 m^2, 80 mg/d
≥ 1.25 to <1.5 m^2, 100 mg/d
≥ 1.5 m^2, 120 mg/d

repeated until PD or for at least 4 cycles

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

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

Study objectives

- To verify the non-inferiority of TS-1 in efficacy and toxicity to taxane as first-line chemotherapy for MBC
  - Primary endpoint: Overall Survival (OS)
  - Secondary endpoints: Time to Treatment Failure (TTF), Progression-free Survival (PFS), Adverse Events (AEs), Health-Related Quality of Life (HR-QoL): EQ-5D, EORTC QLQ-C30, PNQ, Cost-effectiveness
    (Detailed results of HR-QoL and Cost-effectiveness will be presented later.)

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 taxane derivatives or oral 5-FU > 24 weeks

Statistics

600 patients required
- Required death events per group: 190
- Expected median survival time: 24-28 months
- Two-sided alpha error: 0.05, Power: 80%
- Non-inferiority threshold HR: 1.333

CONSORT diagram

Patients enrolled（N=618）
Taxane (n=309) TS-1 (n=309)

From 258 institutions
Enrollment period: Oct 2006 - Jul 2010
Median follow up time: 34.6 months
Number of death events: 398

Eligible（n=608）
Taxane (n=301) TS-1 (n=307)

Ineligible（n=10）
Taxane (n=8) TS-1 (n=2)

FAS（n=592）
Taxane (n=286) TS-1 (n=306)
DTX (n=146) PTX (n=140)

No treatment（n=16）
Taxane (n=15) TS-1 (n=1)

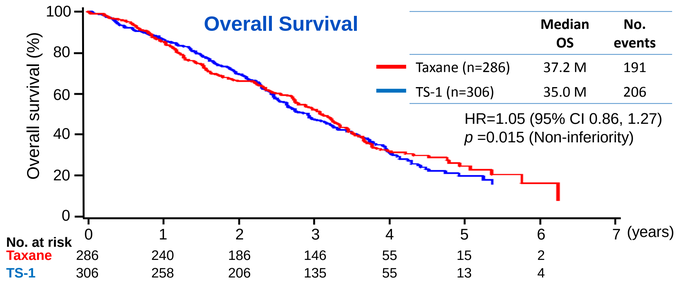
FAS：Full analysis Set, DTX: Docetaxel, PTX: Paclitaxel

Patients characteristics

		Taxane (n=286)	TS-1 (n=306)	*P* value
Median age, (range)		58.5 (21–75)	59.0 (29–75)	0.62
Hormone receptor	ER / PgR (+)	212 (74.1)	223 (72.9)	0.50
	ER and PgR (-)	71 (24.8)	76 (24.8)	
	Unknown	3 (1.0)	7 (2.3)	
Disease free interval	≤ 2 years	57 (19.9)	60 (19.6)	0.75
	2-5 years	98 (34.3)	103 (33.7)	
	≥ 5 years	86 (30.1)	94 (30.7)	
	Unknown	0 (0)	2 (0.7)	
	No surgery	45 (15.7)	47 (15.4)	
Liver metastasis	Yes	96 (33.6)	103 (33.7)	0.98
	No	190 (66.4)	203 (66.3)	
Prior oral 5-FU	Yes	39 (13.6)	35 (11.4)	0.42
	No	247 (86.4)	271 (88.6)	
Prior taxane	Yes	80 (28.0)	80 (26.1)	0.62
	No	206 (72.0)	226 (73.9)	
Prior endocrine therapy	Yes	170 (59.4)	169 (55.2)	0.30
	No	116 (40.6)	137 (44.8)	

Survival analysis (FAS)

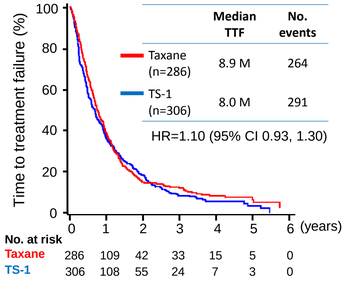
Overall Survival



	Median OS	No. events
Taxane (n=286)	37.2 M	191
TS-1 (n=306)	35.0 M	206

HR=1.05 (95% CI 0.86, 1.27)
p =0.015 (Non-inferiority)

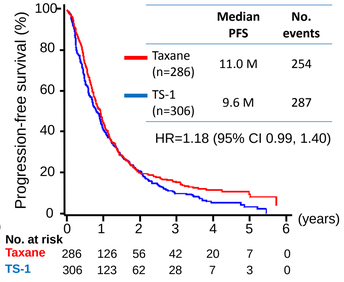
Time to Treatment Failure



	Median TTF	No. events
Taxane (n=286)	8.9 M	264
TS-1 (n=306)	8.0 M	291

HR=1.10 (95% CI 0.93, 1.30)

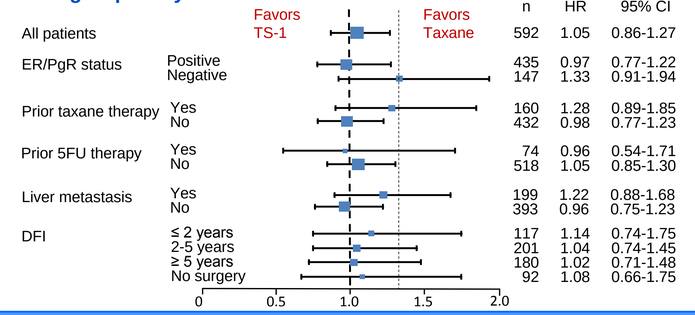
Progression-free Survival



	Median PFS	No. events
Taxane (n=286)	11.0 M	254
TS-1 (n=306)	9.6 M	287

HR=1.18 (95% CI 0.99, 1.40)

Subgroup analysis of Overall Survival



		n	HR	95% CI
All patients		592	1.05	0.86-1.27
ER/PgR status	Positive	435	0.97	0.77-1.22
	Negative	147	1.33	0.91-1.94
Prior taxane therapy	Yes	160	1.28	0.89-1.85
	No	432	0.98	0.77-1.23
Prior 5FU therapy	Yes	74	0.96	0.54-1.71
	No	518	1.05	0.85-1.30
Liver metastasis	Yes	199	1.22	0.88-1.68
	No	393	0.96	0.75-1.23
DFI	≤ 2 years	117	1.14	0.74-1.75
	2-5 years	201	1.04	0.74-1.45
	≥ 5 years	180	1.02	0.71-1.48
	No surgery	92	1.08	0.66-1.75

Adverse Events

Events	Taxane: n, (%) Any	Grade≥3	TS-1: n, (%) Any	Grade≥3
No. of pts	n =290		n =307	
Leukopenia	78 (28.9)	7 (2.6)	136 (45.3)	3 (1.0)
Neutropenia	64 (25.3)	9 (3.6)	126 (43.0)	20 (6.8)
Thrombocytopenia	13 (4.8)	9 (3.6)	108 (35.9)	4 (1.3)
Hemoglobin	164 (60.7)	5 (1.9)	156 (52.3)	4 (1.3)
ALT	71 (26.4)	2 (0.7)	139 (51.3)	0 (0)
Bilirubin	12 (4.5)	1 (0.4)	127 (47.0)	2 (0.7)
Fatigue	153 (53.7)	12 (4.2)	125 (41.1)	10 (3.3)
Alopecia	220 (77.5)	-	15 (4.9)	-
Edema	111 (38.9)	12 (4.2)	26 (8.5)	1 (0.3)
Sensory neuropathy	143 (50.2)	9 (3.2)	29 (9.5)	1 (0.3)
Arthralgia	62 (21.8)	0 (0.0)	22 (7.2)	1 (0.3)
Myalgia	64 (22.5)	1 (0.4)	33 (10.8)	0 (0.0)
Allergy	23 (8.1)	4 (1.4)	12 (3.9)	0 (0.0)
Febrile neutropenia	10 (3.5)	10 (3.5)	6 (2.0)	6 (1.9)
Diarrhea	57 (29.1)	4 (1.4)	103 (33.8)	8 (2.6)
Mucositis	45 (15.8)	0 (0.0)	79 (25.8)	4 (1.3)
Nausea	66 (23.2)	3 (1.1)	100 (32.9)	4 (1.3)
Vomiting	29 (10.2)	2 (0.7)	33 (10.8)	3 (1.0)
Anorexia	88 (30.9)	4 (1.4)	114 (37.4)	8 (2.6)

Summary

- SELECT BC is the first phase III study to evaluate the efficacy of TS-1 for patients with HER2 negative MBC.
- SELECT BC demonstrated non-inferiority of TS-1 in OS to taxane as first-line chemotherapy for MBC.
  Median OS: TS-1 35.0 M vs Taxane 37.2 M (HR=1.05: 95% CI 0.86-1.27; *p*=0.015).
  Median TTF: TS-1 8.0 M vs Taxane 8.9 M (HR=1.10: 95% CI 0.93-1.30).
- TS-1 were less toxic than Taxane, except GI toxicity. Alopecia, edema and sensory neuropathy were much less frequent in TS-1 arm.

Conclusions

- TS-1 can be considered as a new standard treatment option of the first-line chemotherapy for MBC patients, particularly who want to avoid hair loss or neuropathy.

Acknowledgement

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