No. 516

Comprehensive Support Project

Phase III trial comparing AC (4) → taxane (4) with taxane (8) as adjuvant therapy for node-positive breast cancer: Results of N-SAS BC 02 trial (Japan)

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Background

- Doxorubicin and cyclophosphamide (AC) x 4 → paclitaxel x 4 is a standard regimen for postoperative chemotherapy.
- Rare but serious side effects (e.g., cardiac failure, secondary leukemia) are major concerns with AC.
- AC cannot be used in some patients.
- Relative efficacy of docetaxel to that of paclitaxel needs to be clarified.

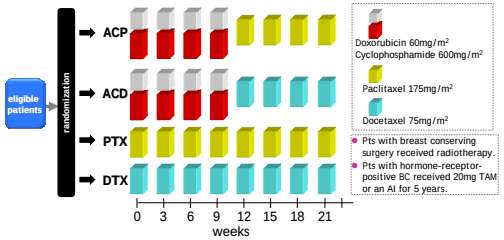
Objectives and Endpoints

- To verify whether **8 cycles of a taxane** is not inferior to **4 cycles of Doxorubicin /Cyclophosphamide (AC) followed by 4 cycles of a taxane** given every 3 weeks in terms of survival
- To compare disease-free survival and overall survival between **Docetaxel (75 mg/m²) (DTX)** and **Paclitaxel (175 mg/m²) (PTX)** given every 3 weeks

Exploratory Analyses

- To find subsets of patients who benefit from additional treatment with AC
- Subsets:
  - HER2 positive vs. HER2 negative or unknown
  - ER positive vs. ER negative

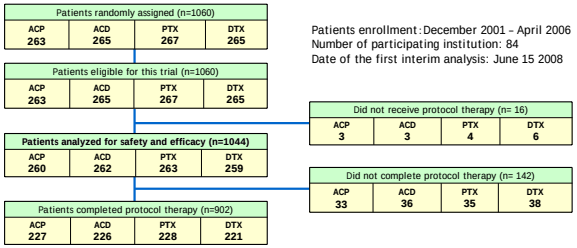
Study Design



Eligibility Criteria

1. Female patients with stage I to IIIA histologically confirmed adenocarcinoma of the breast
2. Histologically involved lymph nodes as confirmed by axillary lymph-node dissection or sentinel-node biopsy
3. Age 18 to 75 years
4. PS(ECOG) 0, 1
5. No prior chemotherapy or endocrine therapy
6. Adequate organ function
7. Written informed consent

Patient Disposition



Patients enrollment: December 2001 – April 2006
Number of participating institution: 84
Date of the first interim analysis: June 15 2008

Demographics and Baseline Characteristics

	ACP (n=260)	ACD (n=262)	PTX (n=263)	DTX (n=259)
Age (mean±sd)	52.8±8.3	52.7±9.5	52.4±8.7	51.9±8.6
Stage				
I	42	18	29	35
II A	95	115	102	103
II B	85	106	109	97
III A	38	23	23	24
Pathological tumor size				
< 3cm	168	167	167	165
≥ 3cm	92	95	96	94
Number of positive lymph node				
1 - 3	154	158	156	154
4 - 9	63	61	64	64
10 -	43	43	43	41

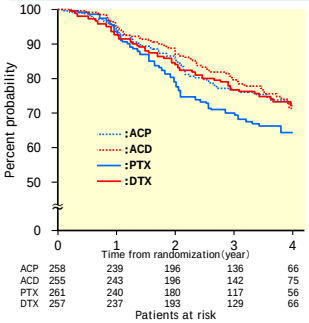
	ACP (n=260)	ACD (n=262)	PTX (n=263)	DTX (n=259)
Estrogen Receptor				
positive	147	144	147	144
negative	110	116	111	112
unknown	3	2	5	3
Progesterone Receptor				
positive	107	122	109	113
negative	149	138	147	142
unknown	4	2	5	4
Type of surgery				
Breast Conserving Surgery	121	121	122	121
Mastectomy	135	140	139	136
Others	4	1	2	2
HER2 (HercepTest®)				
0	85	77	91	90
1+	76	68	63	61
2+	24	26	29	27
3+	35	36	35	34
unknown	40	55	45	47

Grade 3-4 Adverse Events (%)

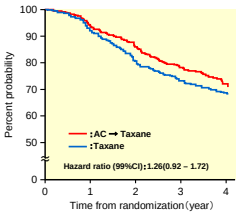
	ACP	ACD	PTX	DTX
Neutropenia	**17**	**18**	**2**	**6**
Leukopenia	3	5	0	2
Thrombocytopenia	0	0	0	0
Anemia	0	0	0	0
Febrile neutropenia	**5**	**11**	**0**	**8**
Elevated AST or ALT	2	1	2	0
Elevated bilirubin	0	0	0	0
Edema	**0**	**1**	**0**	**11**
Pleural effusion	0	0	0	0
Ascites	0	0	0	0
Body weight gain	0	0	0	0
Hair loss	0	0	0	0
Phlebitis (injection site)	0	0	0	0
Nail change	0	0	0	0

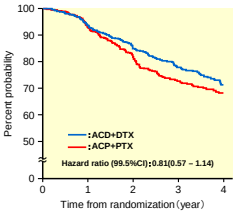
	ACP	ACD	PTX	DTX
Stomatitis	1	1	0	0
Nausea	**5**	**3**	**0**	**1**
Vomiting	**3**	**3**	**0**	**1**
Constipation	1	1	0	0
Diarrhea	0	1	0	2
Urinary urgency	0	0	0	0
Hematuria	0	0	0	0
Fatigue	3	3	2	2
Lacrimation	0	0	0	0
Rash, desquamation	2	1	0	1
Sensory neuropathy	**4**	**0**	**6**	**4**
Motor neuropathy	2	1	1	1
Joint pain (arthralgia)	6	4	8	2
Muscle pain (myalgia)	4	3	5	1

Disease-free Survival

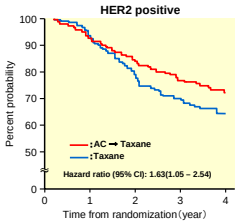


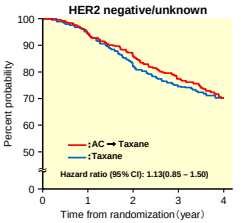
Summary of events (disease-free survival)	ACP	ACD	PTX	DTX
No. of pts	258	255	261	257
Hypothesis 1: A taxane alone is not inferior to AC + a taxane				
Hazard ratio (AC + a taxane as standard)			1.26	
99% CI			0.92 - 1.72	
90% CI			1.03 - 1.53	
p value			0.67	
Hypothesis 2: Whether PTX or DTX is more effective				
Hazard ratio (PTX as standard)			0.81	
99.5% CI			0.57 - 1.14	
95% CI			0.64 - 1.03	
p value			0.08	



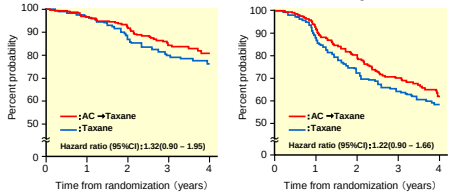


AC→Taxane vs Taxane subset according to HER2





AC→Taxane vs Taxane subset according to ER



Statistical Consideration

Hypothesis 1: 8 cycles of a taxane is not inferior to 4 cycles of AC followed by 4 cycles of a taxane.

Hypothesis 2: One of the taxanes is superior or equivalent to the other.

Planned N = 1200 (based on planned events (≥320) in hypothesis 1.

α = 0.05; 1-sided test (non-inferiority); power (1- β) = 0.80.

Summary

- **Taxane (×8)** is not demonstrated to be inferior to **AC (×4) → a taxane(×4)** in the study group as a whole in terms of DFS.
- **Docetaxel (75 mg/m²)** is superior to **Paclitaxel (175 mg/m²)** when given every 3 weeks in terms DFS.
- In the subset of HER2-positive patients, **AC (×4) → a taxane (×4)** produced superior DFS than did **a taxane (×8)**. This result was not obtained in patients with HER2-negative or unknown tumors.
- For ER, there was no interaction with the addition of AC.
- Regarding the incidences of adverse events;
  - Nausea and vomiting were higher with **AC (×4) → taxane(×4)** than with **taxane (×8)**.
  - Edema and febrile neutropenia were higher with **Docetaxel (75 mg/m²)** than with **Paclitaxel (175 mg/m²)** .
  - Sensory neuropathy was higher with **Paclitaxel (175 mg/m²)** than **Docetaxel (75 mg/m²)**.

Conclusions

- AC can be omitted in certain subsets of patients with postoperative breast cancer.
- When given every 3 weeks, **Docetaxel (75 mg/m²)** improves DFS in women with node-positive breast cancer as compared with **Paclitaxel (175 mg/m²)** .
- The expression of HER2 may be associated with a benefit from the addition of AC.