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Phase Ⅲ two by two factorial comparison of Doxorubicin and Cyclophosphamide followed by a taxane vs. a taxane alone, and Paclitaxel vs. Docetaxel in operable node positive breast cancer - results of the first interim analysis of N-SAS BC02 trial, Japan.

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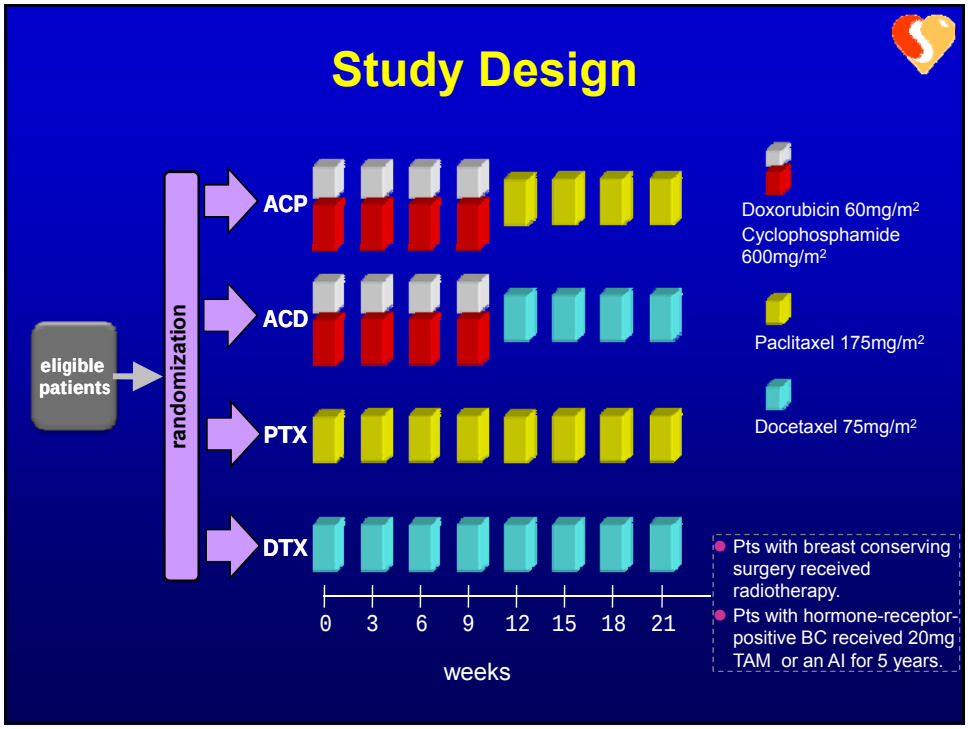
Comprehensive Support Project

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 three weeks in terms of survival
- ◆To compare disease-free survival and overall survival between Docetaxel (75 mg/m^2) (DTX) and Paclitaxel (175 mg/m^2) (PTX) given every three weeks
- ◆To compare health-related quality of life (HRQOL), adverse events, and medical cost performance between 8 cycles of a taxane and 4 cycles of AC followed by 4 cycles of a taxane
- ◆To compare HRQOL, adverse events and cost/performance between DTX and PTX
- ◆To explore the association of HER2 expression with a benefit from the addition of AC



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. Prior treatment:
    1. ≤ 84 days from breast surgery and/or axillary dissection
    2. Postoperative radiotherapy given after the assigned regimen of chemotherapy
    3. No prior chemotherapy or hormonal therapy
6. Adequate organ function:
    1. WBC ≥ 4,000/mm^3 or neutrophil ≥ 2,000/mm^3, platelet ≥ 100,000/mm^3
    2. Total bilirubin ≤ 1.5mg/dL, ALT ≤ 2.5 × the upper limits of normal Creatinine ≤ 1.5mg/dL
7. Written informed consent

Patient Disposition

Patients randomly assigned (n=1060)			
ACP 263	ACD 265	PTX 267	DTX 265

Patients eligible for this trial (n=1060)			
ACP 263	ACD 265	PTX 267	DTX 265

Patients analyzed for safety and efficacy (n=1044)			
ACP 260	ACD 262	PTX 263	DTX 259

Patients completed protocol therapy (n=902)			
ACP 227	ACD 226	PTX 228	DTX 221

Patients enrollment:
December 2001 – April 2006
Number of participating institution: 84
Date of the first interim analysis: June 15 2007

Did not receive protocol therapy (n= 16)			
ACP 3	ACD 3	PTX 4	DTX 6

Did not complete protocol therapy (n= 142)			
ACP 33	ACD 36	PTX 35	DTX 38

Demographics and Baseline Characteristics - 1

	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

Demographics and Baseline Characteristics - 2

	ACP (n=260)	ACD (n=262)	PTX (n=263)	DTX (n=259)
Estrogen Receptor				
positive	147	144	147	144
negative	110	116	111	112
not tested	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

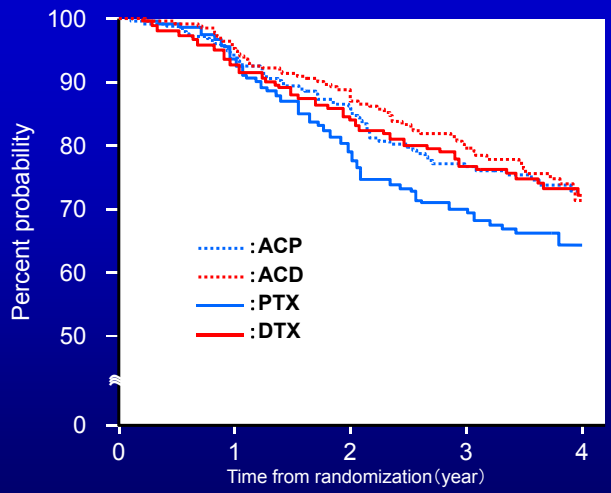
Grade 3 - 4 Adverse Events -1 (%)

	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

Grade 3 - 4 Adverse Events - 2 (%)

	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



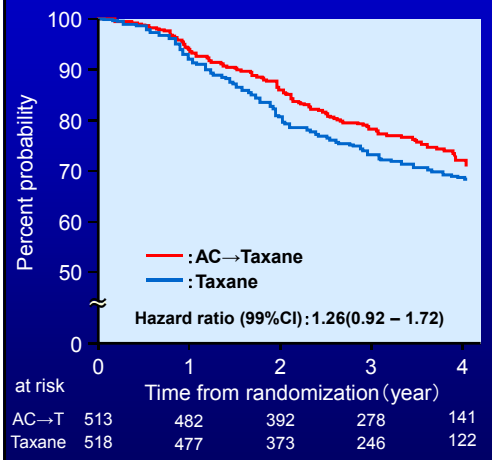
ACP	258	239	196	136	66
ACD	255	243	196	142	75
PTX	261	240	180	117	56
DTX	257	237	193	129	66

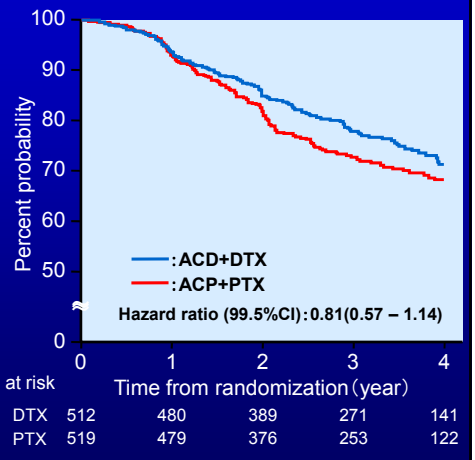
Patients at risk

Disease-free Survival - 2

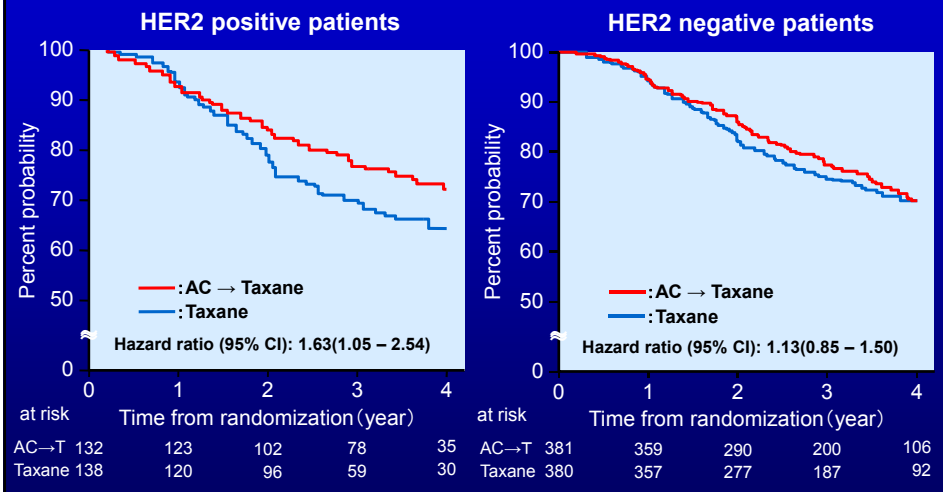
Summary of events (disease-free survival)				
	ACP	ACD	PTX	DTX
No. of pts	258	255	261	257
Hypothesis 1: A taxane alone is not inferior to AC + a taxane				
Hazard ratio (AC + a taxane as tandard)	1.26			
99% CI	0.92 - 1.72			
90% CI	1.03 - 1.53			
p value	0.67			
Hypothesis 2: Whether PTX or DTX is more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

Disease-free Survival - 3





Disease-free Survival - 4



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.

- To verify these hypotheses, we analyzed disease-free survival as the primary endpoint and overall survival and relapse-free survival as secondary endpoints. To adjust for multiplicity, a two-sided significance level of 0.5% was used to verify superiority, and a one-sided significance level of 0.5% (1% for a two-sided test) was used to verify inferiority.
- For the estimation of hazard ratios, these values correspond to calculating a two-sided confidence interval of 99.5% and a two-sided confidence interval of 99%, respectively. For hypothesis 1, if the upper limit of the confidence interval for the hazard ratio with a taxane alone relative to that with AC + a taxane is 1.321 or less, a taxane alone is proven to be equivalent to AC + a taxane. For hypothesis 2, if the confidence interval of the hazard ratio for either taxane is not 1, one of the two taxanes is shown to be superior to the other.

Summary

- 8 cycles of a taxane is not inferior to 4 cycles of AC followed by 4 cycles of a taxane in all analyzed patients in terms of disease-free survival.
- Docetaxel (75 mg/m^2) is superior to Paclitaxel (175 mg/m^2) when given every three weeks in terms of disease-free survival.
- Regarding adverse events;
  - Incidence of nausea and vomiting was higher with 4 cycles of AC followed by 4 cycles of a taxane as compared to 8 cycles of a taxane.
  - Incidence of edema and febrile neutropenia was higher with Docetaxel (75 mg/m^2) as compared to Paclitaxel (175 mg/m^2) .
  - Incidence of sensory neuropathy was higher with Paclitaxel (175 mg/m^2) as compared to Docetaxel (75 mg/m^2) .
- In the subset of HER2 positive patients, 4 cycles of AC followed by 4 cycles of a taxane produced superior DFS as compared with 8 cycles of a taxane. This is not observed in patients with HER2 negative patients.

Conclusion

- **Anthracycline containing regimen can be omitted in certain subsets of postoperative breast cancer patients.**
- **When given every 3 weeks, Docetaxel (75 mg/m^2) improves disease-free survival in woman with node positive breast cancer as compared with Paclitaxel (175 mg/m^2) .**
- **The expression of HER2 may be associated with a benefit from the addition of Anthracycline containing regimens.**