USE OF DOCETAXEL/DOXORUBICIN/CYCLOPHOSPHAMIDE IN ADJUVANT THERAPY OF BREAST AND OVARIAN CANCER

DESCRIPTION OF THE INVENTION

Field of the Invention

This invention relates to a novel therapeutic combination of taxotere with other antineoplastic agents which are useful in the adjuvant therapy of metastatic breast and ovarian cancer.

Background of the Invention

The present invention relates more specifically to the use of docetaxel in combination with doxorubicin and cyclophosphamide as adjuvant therapy in the treatment of cancer after surgery or other first line therapy.

Selected term definitions used herein and in Tables 1-36 are as follows:

"Adjuvant therapy" refers to chemotherapy started within but no greater than 60 days from surgery.

"AT" refers to Adriamycin/Taxotere;

"docetaxel" refers to the active ingredient of TAXOTERE® or TAXOTERE® itself;

"doxorubicin" refers to the active ingredient of ADRIAMYCIN® or ADRIAMYCIN® itself.

"ER" refers to estrogen receptor;

"FAC" refers to the combination of 5-fluorouracil, doxorubicin and cyclophosphamide;

"HER2" refers to is a transmembrane receptor tyrosine kinase with partial homology with the epidermal growth factor 2 receptor, both of which receptors belong to the type 1 tyrosine kinase receptor superfamily;

"KPS" refers to Karnovsky Performance Status which is an index of a patient's physical condition;

"MF" refers to Methotrexate/5-Fluorouracil;

"MV" refers to Mitomycin/Vinblastin combination;

"PR" refers to progesterone receptor;

"TAC" refers to the combination of TAXOTERE© (docetaxel), ADRIAMYCIN (doxorubicin) and cyclophosphamide;

and

"drug" or "drugs" refers to the above-mentioned active ingredients or medicaments or pharmaceutical preparations containing them.

Previous researchers have noted that docetaxel (TAXOTERE®) and its derivatives (such as TAXOL®, paclitaxel) are useful in the treatment of malignant neoplasms, such as solid tumors and other malignancies. European Patent EP 0 253 738 and International Patent Application WO 92/09589 describe a method of preparation of docetaxel. Generally, the doses, which vary depending on the patient, comprise between 60 and 400 mg/m^2 of docetaxel. Commonly, docetaxel is administered via intravenous route at doses of 60 to 100 mg/m^2 over 1 hour every 3 weeks (*Textbook of Medical Oncology*, Franco Cavelli et al., Martin Dunitz Ltd., p. 4623 (1997)).

Many clinical studies have confirmed the efficacy of docetaxel in treating many types of cancer, particularly breast, non-small cell lung, and ovarian cancer. Docetaxel's effects are shown in both first and second line therapies. The mechanism of docetaxel's action is thought to be via enhancement of microtubule assembly and inhibition of the depolymerization of tubulin at the cellular level.

However, all treatments based on taxoid derivatives, including docetaxel, can show serious and troubling toxicities, such as myelosuppression, neutropenia, hypersensitivity, peripheral neuropathy, and fluid retention, among others (Fumoleau et al., *Bull. Cancer*, (82)8: 629-636 (1995)). When such toxicities appear, dosages of the drugs must be limited with a resulting limitation on the efficacy of the treatment.

Consequently, there is an unmet need in the art for pharmaceutical preparations and methods of treating cancer which enhance the activity of docetaxel without increasing the amount of the dosages administered and without increasing adverse side effects.

There is also an unmet need in the art for treatment of cancer which has spread beyond the initial tumor site. In metastatic breast and ovarian cancer

especially, there is a need for effective post-surgery adjuvant therapy, which will result in disease free survival or at least, an extension of the duration of progression free survival.

In recent studies, docetaxel containing regimens have shown superior activity over standard regimens in metastatic breast cancer. Anthracycline-based regimens, using e.g. doxorubicin, are standard adjuvant therapy in node positive breast cancer patients. Therefore, considering the efficacy of both docetaxel and doxorubicin in treating advanced breast cancer and their potential noncross-resistance, it was decided to combine them with cyclophosphamide as a possible design for a more effective adjuvant therapy for metastatic breast cancer. The combination of the docetaxel, doxorubicin, and cyclophosphamide (TAC) was tested in a phase III trial in 20 countries by more than 112 investigators. The results which are elaborated below show that the combination used as adjuvant therapy enhances the effect of docetaxel without increasing its dosage and results in increased survival for metastatic breast cancer patients.

SUMMARY OF THE INVENTION

In an aspect of the present invention , there is provided a use of docctaxel in the manufacture of a medicament for treating metastatic breast ovarian cancer by adjuvant therapy in combination with doxorubicine and cyclophosphamide only and which provides an increased survival rate.

Disclosed herein are methods for treating metastatic cancer, especially metastatic breast cancer and ovarian cancer, comprising administering docetaxel, doxorubicin and cyclophosphamide (TAC) in amounts effective to reduce or eliminate the presence of cancer. The efficacy of this combination has been demonstrated over a period of thirty-three months in more than seven hundred human patients who demonstrated positive nodal involvement and were treated post-surgery with TAC.

Disclosed herein are new pharmaceutical kits and medicaments comprising docetaxel in combination with doxorubicin and cyclophosphamide for treating cancers.

Further disclosed herein are schedules of administration of TAC for the adjuvant treatment of cancer wherein the individual drugs in the TAC combination are infused separately on the same day, once every three weeks. This cycle is repeated six times.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The inventors of the present invention have demonstrated via clinical trials, that TAC dosages in particular manifest an unexpected and strong therapeutic effect on the treatment of neoplastic diseases, particularly breast cancers, and more particularly, in metastatic breast cancers in which ER/PR and HER2 are overexpressed. Generally, according to the invention, docetaxel is administered in a dosage of 75 mg/m^2, doxorubicin in a dosage of 50 mg/m^2 and cyclophosphamide in a dosage of 500 mg/m^2, once every three weeks. This cycle is generally repeated six times.

Docetaxel alone, in several in-house proprietary studies, gave overall response rates of 40 to 43% (in second line therapy at a dose of 100 mg/m^2), 48% (in first line therapy at a dose of 75 mg/m^2) and 61% (in first line therapy at a dose of 100 mg/m^2).

In comparison, in the example below, 75 mg/m^2 of docetaxel administered in combination with 50 mg/m^2 doxorubicin and 500 mg/m^2 cyclophosphamide resulted in an 82% response rate.

According to the invention, the new use of docetaxel as a component of TAC is very advantageous for treating cancers of the breast, ovary, and lung; still more preferably, the new use of docetaxel is particularly suitable for treating metastatic breast cancer.

The safety and the efficacy of the combination of docetaxel, doxorubicin and cyclophosphamide was tested in patients according to the following protocol:

Patients were eligible for the study if they had histologically proven breast cancer, definitive surgery with axillary lymph node dissection (greater than or equal to 6 lymph nodes), a period of 60 days or less between surgery and randomization, stage 1 to 3 cancer, at least one node that was positive for cancer, were 70 years old or less, had a KPS index greater than or to 80% and had normal bone marrow, liver, renal and cardiac function. *See* Table 4.

One thousand, four hundred and ninety-one patients were accepted into the study. Seven hundred and forty-five received TAC as adjuvant therapy and seven hundred and forty-six received FAC. The TAC patients had a median age of 49

years, 51 % were premenopausal, and 60% percent had had a mastectomy. Sixty-eight % had had radiotherapy and 68% had taken tamoxifen. The patient characteristics for the FAC group were similar (*See* Table 6).

Of the seven hundred and forty-five TAC patients, 62% had 1-3 cancer-positive nodes, 30% had 4 to 10 positive nodes and 8% had more than 10 positive nodes. In 40% of the patients, the size of the tumor was 2 cm or less, in 53%, the size of the tumor was more than 2 cm but equal to or less than 5 cm., and in 7 % of the patients, the tumor was larger than 5 cm. Sixty-nine per cent of the patients had overexpressing ER or PR tumors and 19% had overexpressing HER2 + (FISH) tumors. Again, the tumor characteristics of the FAC group were comparable. *See* Table 7.

The primary endpoint of this Phase III study was to facilitate disease free survival while secondary endpoints were overall survival, toxicity, quality of life and monitoring pathological and molecular markers.

Post-TAC and post-FAC treatment included 1) radiation therapy for all patients with breast conserving surgery and 2) tamoxifen (20 mg/day for 5 years) for those patients with ER or PR positive tumors. *See* Table 3.

The Example below illustrates the new use of docetaxel according to the invention without limiting it.

EXAMPLE:

Dexamethasone, 8 mg BID was given as a premedication for 3 days. The combination adjuvant therapy was then administered on Day 4. One group of patients received docetaxel, doxorubicin and cyclophosphamide (TAC) administered intravenously in that order. Another group of patients received 5-FU, doxorubicin, and cyclophosphamide (FAQ administered intravenously in that order. Prophylactic Cipro was then given to both groups on days 5-14 in a dose of 500 mg BID. This course of drugs was repeated every three weeks for six cycles. *See* Table 2.

Six hundred and seventy-nine patients (91%) completed six cycles of TAC adjuvant therapy followed by the postchemical therapy regimens described above.

The median total dose per patient over the six cycles was 446 mg/m^2 of docetaxel, 297 mg/m^2 of doxorubicin, and 2978 mg/m^2 of cyclophosphamide. *See* Table 8.

Seven hundred and eleven patients (96%) completed six cycles of FAC adjuvant therapy followed by the postchemical therapy regimens described above. The median total dose per patient over the six cycles was 2985 mg/m^2 of 5-FU, 298 mg/m^2 of doxorubicin, and 2985 mg/m^2 of cyclophosphamide. Id.

Thirty-three months after adjuvant therapy, 82% of the TAC group vs. 74% of the FAC group were alive and disease free (Table 10). At the same time, the overall survival of the TAC group was 92% vs. 87% for the FAC group (Table 13).

Results by Nodal Status

If disease free survival of the TAC and FAC groups is compared by nodal status, 90% of patients with 1-3 positive nodes who received TAC were alive and disease free at 33 months after therapy vs. 79% of the FAC group. There was no statistical difference between the two adjuvant therapies in patients with 4 nodes, although 69% of patents receiving TAC therapy were alive and disease free at 36 months compared to 67% who received FAC. *See* Table 15.

The overall survival rate for patients with 1-3 positive nodes was 96% for TAC and 89% for FAC. Again, there was no statistical difference between the two therapies in patients with 4 or more positive nodes, although again more TAC patients (86%) survived than FAC patients (84%). *See* Tables 16 and 32.

Results by Hormonal Status

In patients with negative ER/PR tumors, the disease free survival rate was about 70% in those who had received TAC adjuvant therapy and about 62% in those receiving FAC. In patients with positive ER/PR nodes, the disease free survival rate among those who received TAC was about 88% vs. 82% in those who received FAC. *See* Tables 17 and 33.

If one calculates overall survival by hormonal status, about 83% of TAC recipients with negative ER/PR tumors survived vs. about 72% of FAC recipients. Among patients with positive tumors, about 90% of TAC recipients survived vs. about 88% of FAC recipients. *See* Tables 18 and 35.

Results by HER2 Status

In patients with negative HER2 tumors, the disease free survival rate at 33 months was about 86% in those who had received TAC adjuvant therapy and about 80% in those receiving FAC. In patients with positive HER2 tumors, the disease free survival rate among those who received TAC was about 75% vs. 60% in those who received FAC. *See* Table 19.

Based on this data, the combination of docetaxel, doxorubicin and cyclophosphamide as adjuvant therapy is well-tolerated and results in a significant advantage over 5FU, doxorubicin and cyclophosphamide as adjuvant therapy. If one measures disease free survival, at 33 months, TAC provided over FAC a 32% reduction in deaths overall, a 50% reduction in deaths where the patients had 1-3 positive nodes, a 38% reduction in deaths where the hormonal status of the tumor was negative and a 32% reduction where the hormonal status was positive. *See* Table 22.

If one measures overall survival, there was a 24% reduction in deaths of those receiving TAC adjuvant therapy and a 54% reduction in those patients with 1 to 3 positive nodes. Id.

The difference between TAC and FAC is the presence of docetaxel rather than 5-FU. These statistics prove conclusively that the observed benefit of docetaxel in combination with doxorubicin and cyclophophamide is large enough to be of clinical value in the adjuvant treatment of node positive breast cancer patients.

The described embodiments are to be considered in all respects as illustrative only and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

CLAIMS

1. Use of docetaxel in the manufacture of a medicament for the treatment of node positive, M_o breast cancer by adjuvant therapy in combination with doxorubicin and cyclophosphamide only and which provides an increased survival rate.

2. Use according to claim 1 wherein the docetaxel, doxorubicin and cyclophosphamide are suitable for administration separately.

3. Use according to one of claims 1 or 2 wherein breast cancer ER, PR and/or HER2 is overexpressed.

4. Use according to any of claims 1 to 3 wherein the medicament is administered once every 3 weeks in six cycles at a dose per cycle of

75 mg/m^2 of docetaxel,
50 mg/m^2 of doxorubicin, and
500 mg/m^2 of cyclophosphamide.

5. Use according to any of claims 1 to 3 wherein a dose of docetaxel is 75 mg/m^2 per cycle.

6. Use according to any of claims 1 to 3 wherein a dose of doxorubicin is 50 mg/m^2 per cycle.

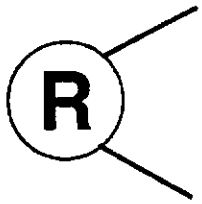
7. Use according to any of claims 1 to 3 wherein a dose of cyclophosphamide is 500 mg/m^2 per cycle.

Study Rationale

- ☐ Anthracycline-based regimens are standard adjuvant treatments in node positive breast cancer patients
- ☐ Docetaxel containing regimens have shown superior activity over standard regimens in MBC
  - ☐ Anthracycline failure
    - ☐ Docetaxel versus MV, Nabholtz et al, JCO'99
    - ☐ Docetaxel versus MF, Sjostrom et al, EJC '99
  - ☐ CMF failure
    - ☐ Docetaxel versus Doxorubicin, Chan et al, JCO '99
  - ☐ First-line
    - ☐ AT versus AC, Nabholtz et al, ASCO 2000
    - ☐ TAC versus FAC, Nabholtz et al, ASCO 2001
      Mackey et al, ASCO 2002

Table 1

DESIGN



F	5-FU	500 mg/m2
A	Doxorubicin	50 mg/m2
C	Cyclophosphamide	500 mg/m2

Every 3 weeks x 6 cycles

T	Taxotere	75 mg/m2
A	Doxorubicin	50 mg/m2
C	Cyclophosphamide	500 mg/m2

Stratification :
- Nodes
  1-3
  4+
- Center

Dexamethasone premedication, 8 mg BID, 3 days
Prophylactic Cipro 500 mg bid, day 5-14

Table 2

Post Chemotherapy Treatment

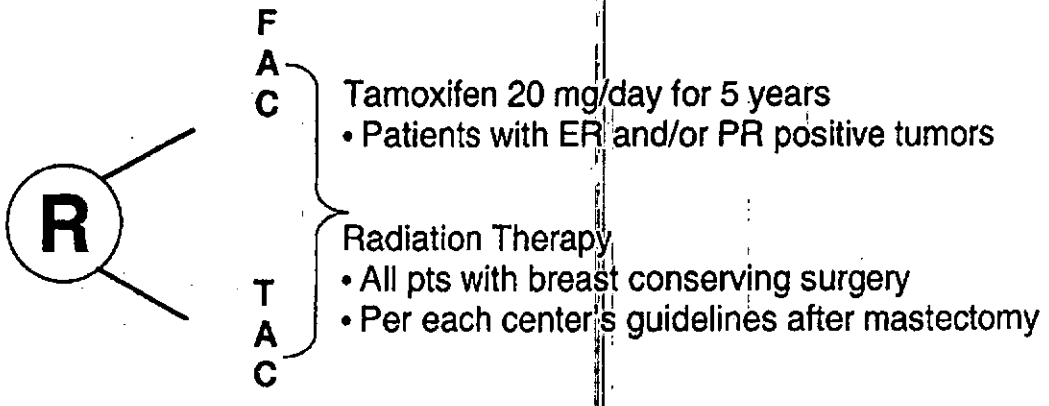


Table 3

Major Eligibility Criteria

- Histologically proven breast cancer
- Definitive surgery with axillary LN dissection (≥ 6 LNs)
- 60 days between surgery and randomisation
- Stage T 1-3, N1, M0
- Age ≤ 70 years, KPS ≥ 80 %
- Normal bone marrow, liver, renal and cardiac function
- Informed consent

Table 4

Endpoints

Primary

- Disease-free survival

Secondary

- Overall survival
- Toxicity
- Quality of Life, Socioeconomic analyses
- Pathologic & Molecular markers

Source verification : 100 % data for all patients

Table 5

Patient Characteristics

Randomized (n=1,491)	TAC n=745	FAC n=746
Median Age	49	49
Median KPS	100 %	100 %
Premenopausal	51 %	50 %
Mastectomy	60 %	59 %
Radiotherapy	68 %	71 %
Tamoxifen	68 %	69 %

Table 6

Tumor Characteristics

	TAC n=745	FAC n=746
Nodal Status	%	%
1-3	62	62
4-10	30	31
> 10	8	7
Tumor Size (cm)		
≤ 2	40	43
> 2 and ≤ 5	53	51
> 5	7	6
ER and/or PR +	69	69
HER2 + (FISH)	19	20

Table 7

Exposure to Treatment

	TAC n=745	FAC n=746
Completed 6 cycles	679 (91 %)	711 (96 %)
Relative dose intensity		
median	0.98	0.97
> 0.90	89 %	84 %
Median total dose mg/m2		
Docetaxel	446	-
Doxorubicin	297	298
Cyclophosphamide	2978	2985
5FU	-	2985

Table 8

Protocol Defined Statistical Analyses
Disease Free Survival and Overall Survival

- First planned analysis : 3 years
- Cohort : Intent to treat
  - Main Analysis
    - Log rank test stratified by nodal status
    - p-value not adjusted for Interim analysis
  - Confirmatory analyses
    - Unadjusted
    - Multivariate (Cox model)

Table 9

Disease Free Survival (ITT)
Median follow-up : 33 months

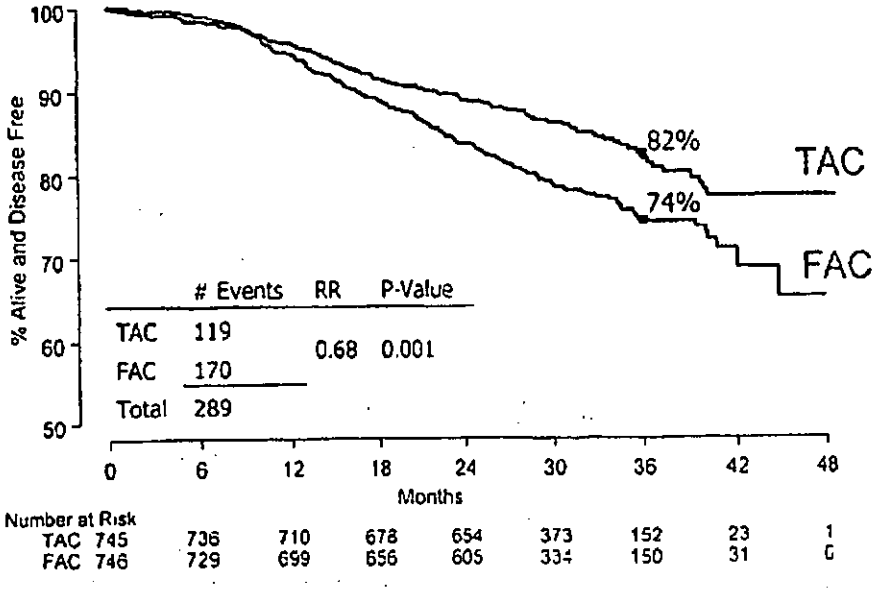


Table 10

Confirmatory Analyses : DFS

Analysis	Cohort	RR	p
Stratify on Nodes	ITT	0.68 (0.54-0.86)	0.001
Unadjusted	ITT	0.67 (0.53-0.85)	0.0008
Cox Model *	ITT	0.64 (0.50-0.81)	0.0002

- **Controls for nodes, age, tumor size, histology, ER/PR, HER2**

Table 11

Sites of First Events

	TAC (N)	FAC (N)
Distant	**80**	**119**
Local/Regional	**23**	**31**
Contralateral	**3**	**6**
Other 2nd Primary	**6**	**10**
Death NED	**7**	**4**
	119	**170**

Table 12

Overall Survival (ITT)

Median follow-up : 33 months

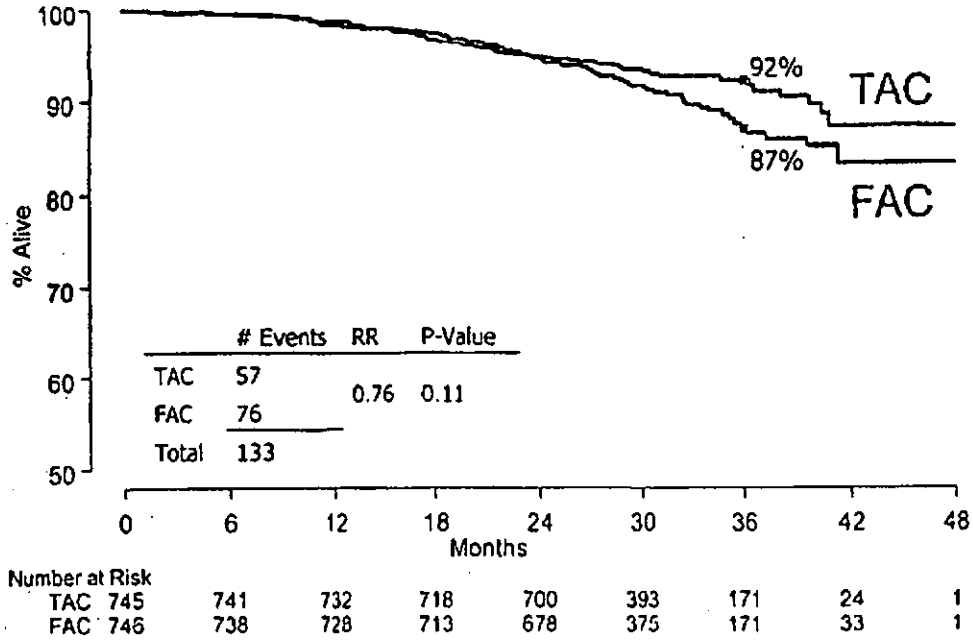


Table 13

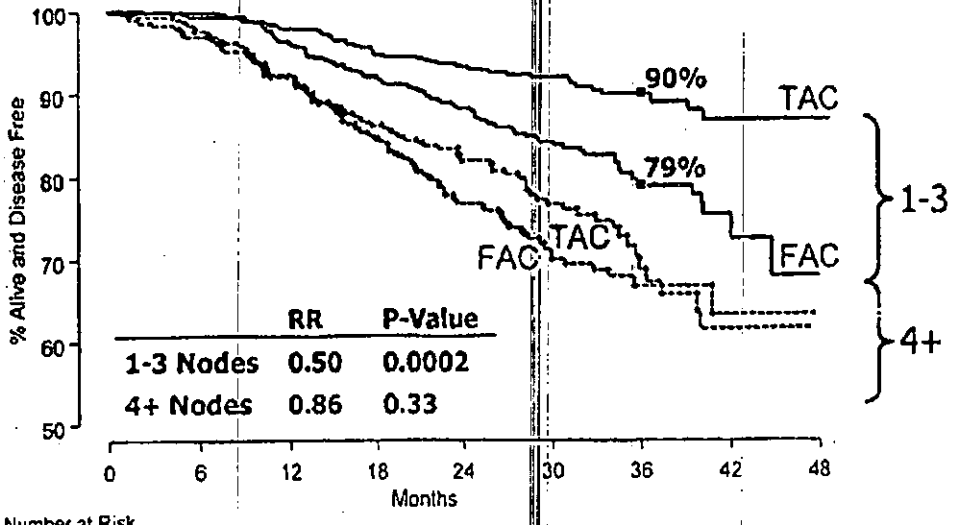
Confirmatory Analyses of Overall Survival

Analysis	Cohort	RR	p
Stratify on Nodes	ITT	**0.76** (0.54-1.07)	0.11
Unadjusted	ITT	**0.75** (0.53-1.06)	0.10
Cox Model *	ITT	**0.71** (0.50-1.00)	0.049

- Controls for nodes, age, tumor size, histology, ER/PR, HER2

Table14

Disease Free Survival by Nodal Status

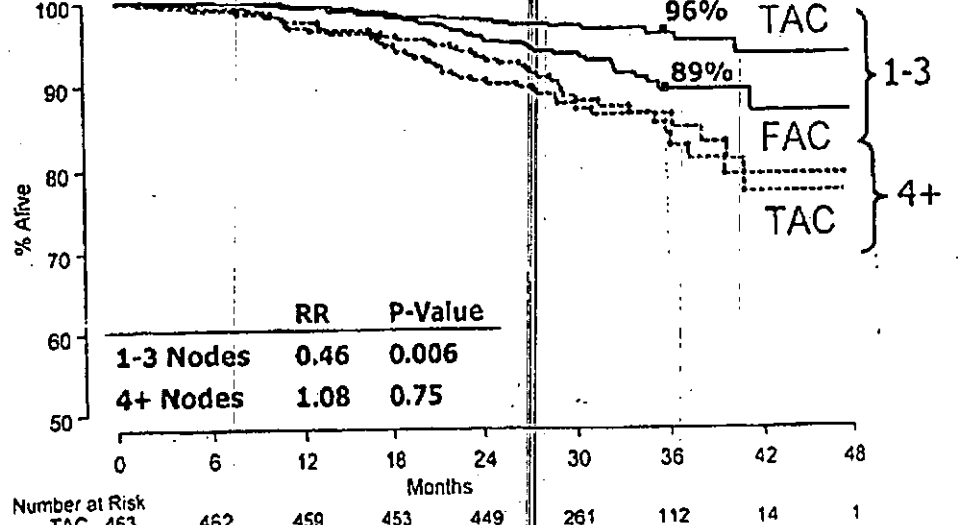


Number at Risk

1-3	TAC	463	462	452	437	427	250	103	14	1
	FAC	459	454	438	417	393	224	98	26	0
4+	TAC	282	274	258	241	227	123	49	9	0
	FAC	287	275	261	239	212	110	52	5	0

Table 15

Overall Survival by Nodal Status



Number at Risk

1-3	TAC	463	462	459	453	449	261	112	14	1
	FAC	459	457	453	444	422	243	107	26	1
4+	TAC	282	279	273	265	251	132	59	10	0
	FAC	287	281	275	269	256	132	64	5	0

Table 16

Disease Free Survival by Hormonal Status

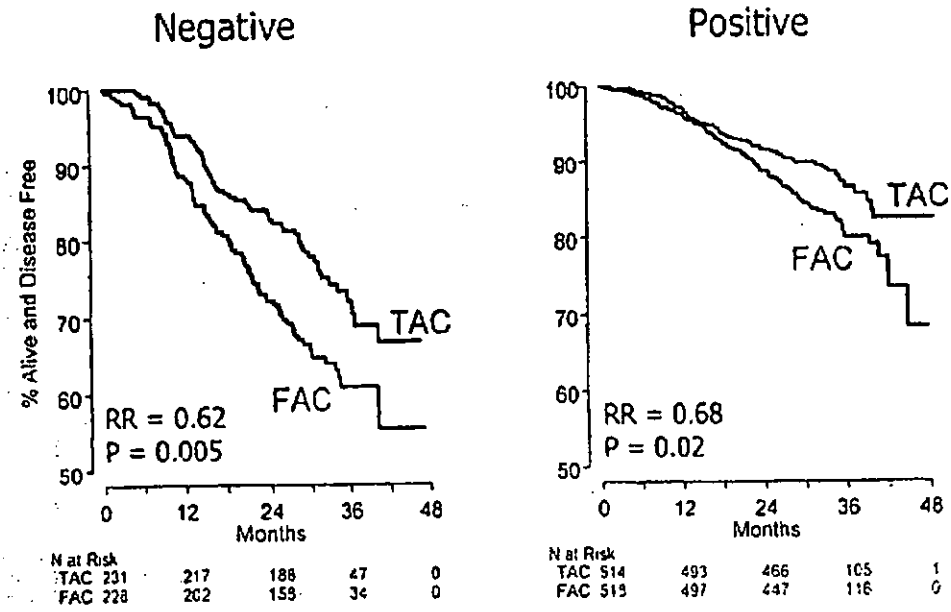


Table 17

Overall Survival by Hormonal Status

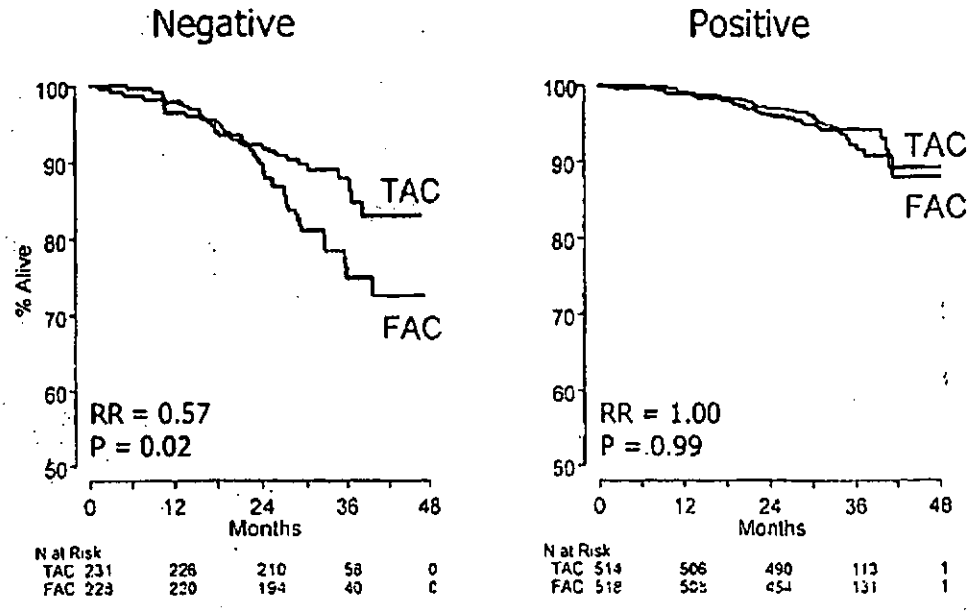


Table 18

Disease Free Survival by HER2 status

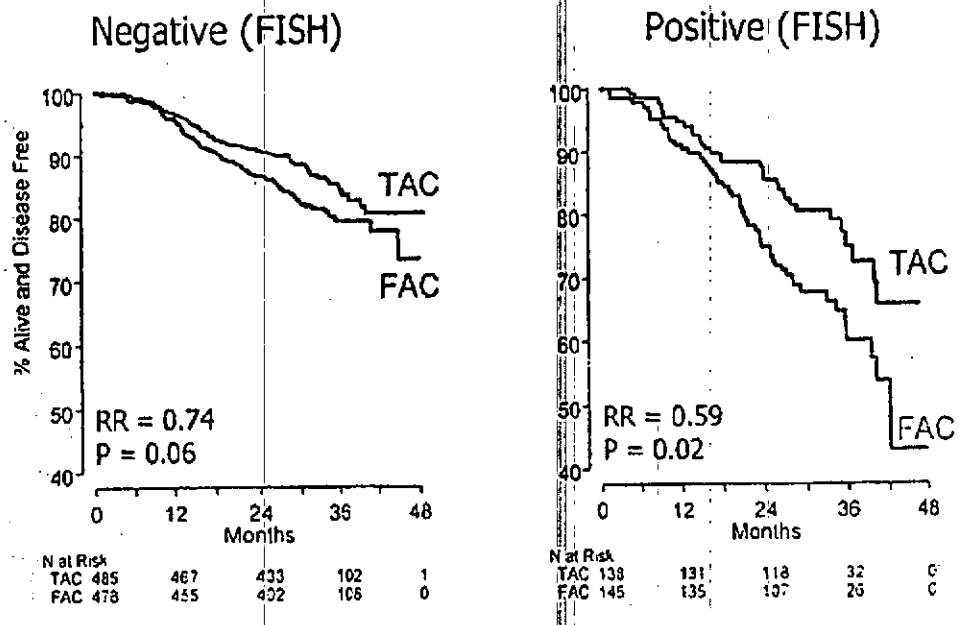


Table 19

Hematological Toxicity

Treated (n=1480)	TAC (n=744)	FAC (n=736)
	%	%
ANC < 1000∞	65.1*	49.0
Febrile Neutropenia§	23.9*	2.4
Infection (Gr 3/4)	3.1	1.5
Septic Death	0	0
Anemia (Gr 3/4)	4.8*	2.2
Thrombocytopenia (Gr 3/4)	2.4	1.8

∞ Protocol required blood counts every 3 weeks
§ Gr 4 neutropenia at time of grade ≥ 2 fever and i.v. antibiotics
$p \leq 0.05$

Table 20

Non-Hematological Toxicity Grade 3/4 Incidence > 1 %

	TAC n=744	FAC n=736
	%	%
Nausea	5.1.	9.5*
Vomiting	4.3	7.3*
Diarrhea	3.4*	1.0
Stomatitis	7.1*	2.0
Asthenia	11.2*	5.3
CHF	1.6	0.7
Premenopausal pts	n=383	n=375
Amenorrhea	51.4*	32.8

*$p \leq 0.05$

Table 21

Conclusions

At 33 months median follow-up, TAC provides over FAC :

- **Primary endpoint : Disease-Free Survival**
  - **Overall :** **32 % reduction (p=0.001)**
  - **By nodal status :** **1-3 : 50 % reduction (p=0.0002)**
    4+ : No difference
  - **By hormonal status :** **HR- : 38 % reduction (p=0.005)**
    HR+ : 32 % reduction (p=0.02)
- **Secondary endpoint : Overall Survival**
  - **Overall :** **24 % reduction (p=0.11)**
  - **By nodal status** **1-3 : 54 % reduction (p=0.006)**
    4+ : No différence

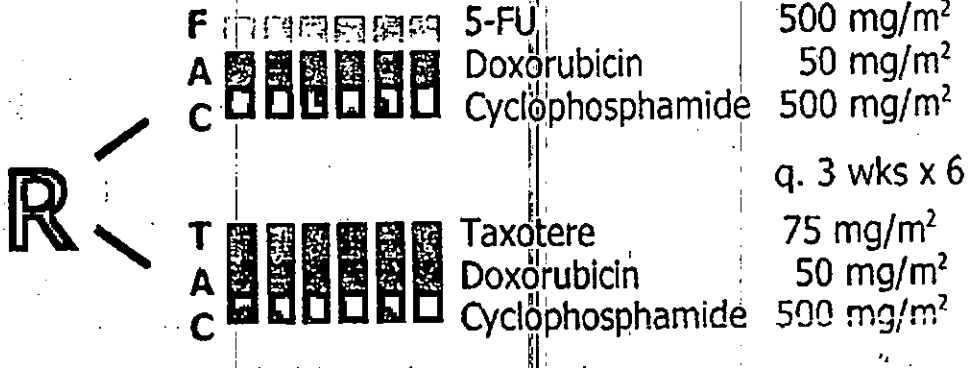
Table 22

Conclusions

- Febrile neutropenia was more frequent on TAC, without increased incidence of infection and no septic deaths
- Other toxicities were acceptable and manageable in both arms
- The observed benefit of TAC is large enough to be of clinical value in the adjuvant treatment of node positive breast cancer patients
- Additional follow-up is necessary to confirm the integration of TAC in this patient population

Table 23

Design



Standard dexamethasone premed
Prophylactic Cipro 500mg bid, day 5-14

Stratification
- Nodes: 1-3, 4+
- Center

Table 24

Protocol defined statistical analyses (II)

- Analysis by Nodal Status
  - Prospectively defined
  - Closed testing procedure to prevent multiplicity (Performed only if main analysis statistically significant)
  - 1-3 nodes (70 % of patients/events)
    -α 0.05, power 91 % to detect DFS improvement of 38 %
  - 4+ nodes (30 % of patients/events)
    -α 0.05, power 81 % to detect DFS improvement of 40 %

Table 25

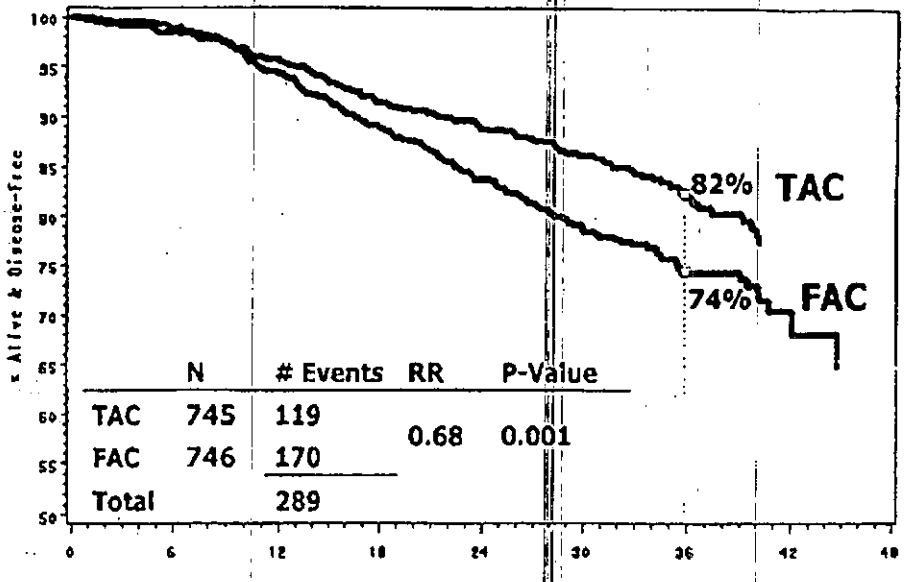
DFS and OS
Absolute difference at 3 Years

		TAC	FAC
Intent to Treat	**DFS** **Survival**	**82 %** **92 %**	**74 %** **87 %**
1-3 nodes	DFS Survival	90 % 96 %	79 % 89 %
≥ 4 nodes	DFS Survival	69 % 86 %	67 % 84 %

Table 26

Disease Free Survival (ITT)

Median follow-up : 33 months

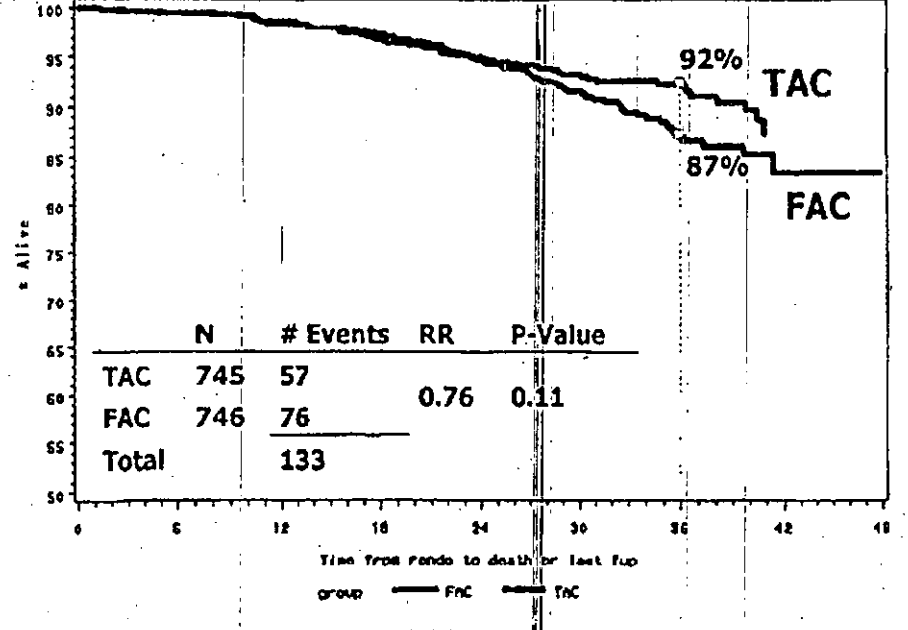


	N	# Events	RR	P-Value
TAC	745	119	0.68	0.001
FAC	746	170		
Total		289		

Table 27

Survival (ITT)

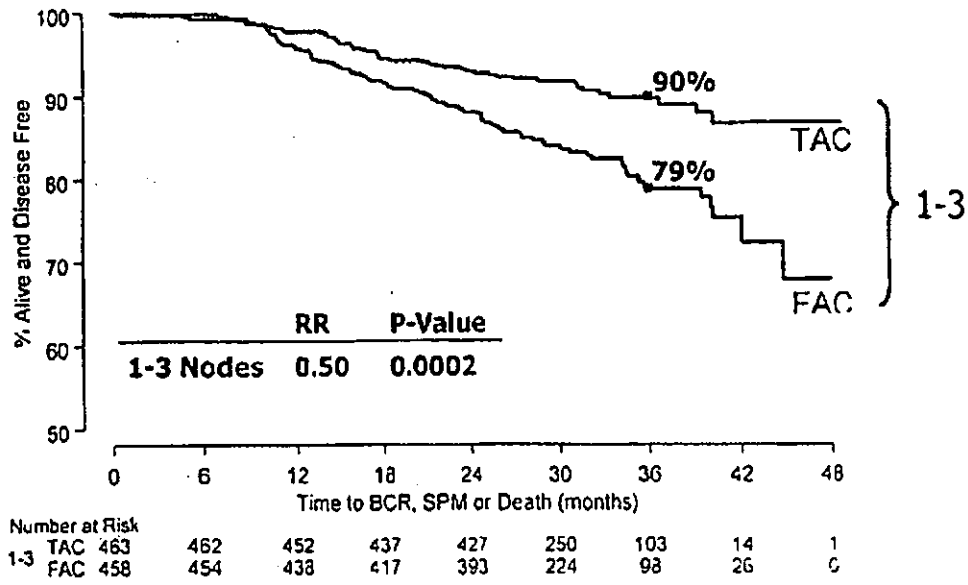
Median follow-up : 33 months



	N	# Events	RR	P-Value
TAC	745	57	0.76	0.11
FAC	746	76		
Total		133		

Table 28

Disease Free Survival by Nodal Status

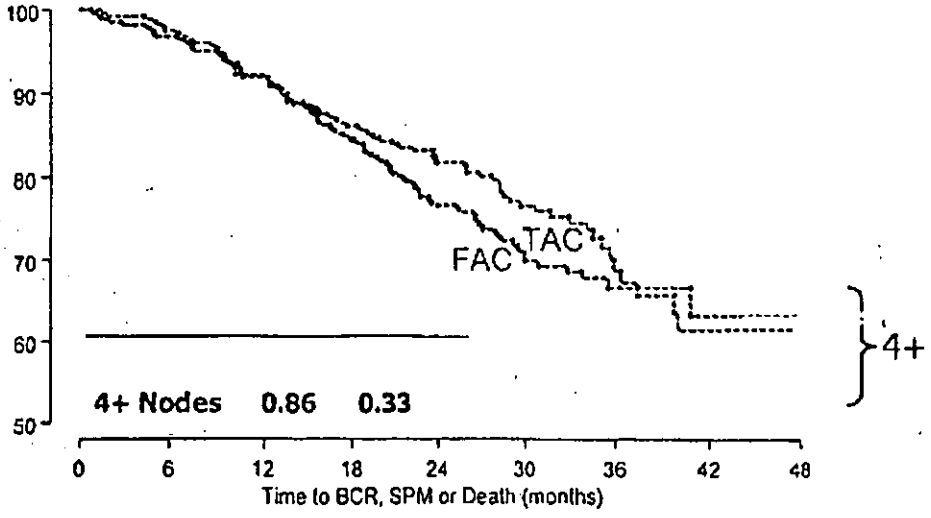


Number at Risk

1-3	TAC	463	462	452	437	427	250	103	14	1
	FAC	458	454	438	417	393	224	98	26	0

Table 29

DFS 4+ Nodes



4+	TAC	282	274	258	241	227	123	49	9	0
	FAC	285	275	261	239	212	110	52	5	0

Table 30

Disease Free Survival by Nodal Status

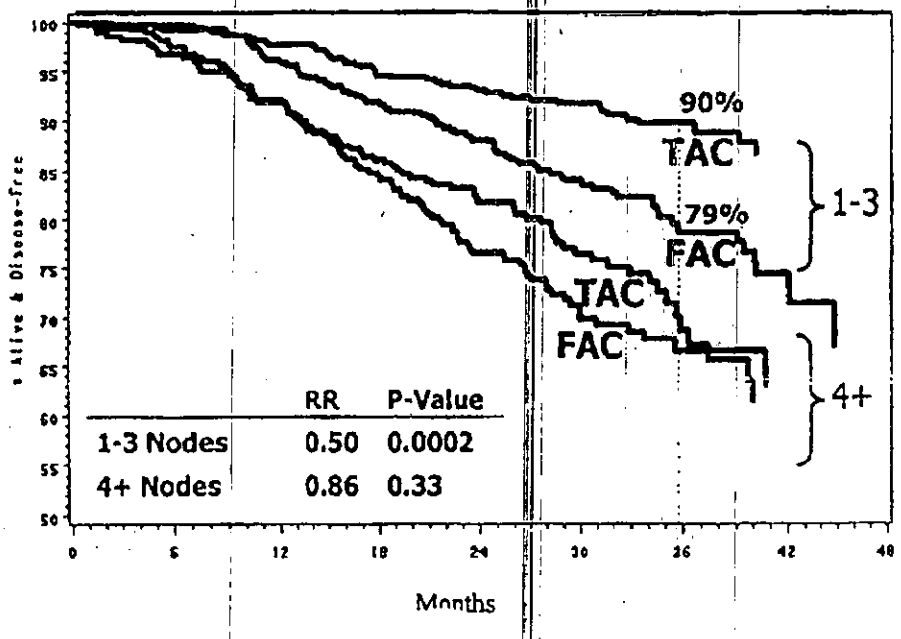


Table 31

Overall Survival by Nodal Status

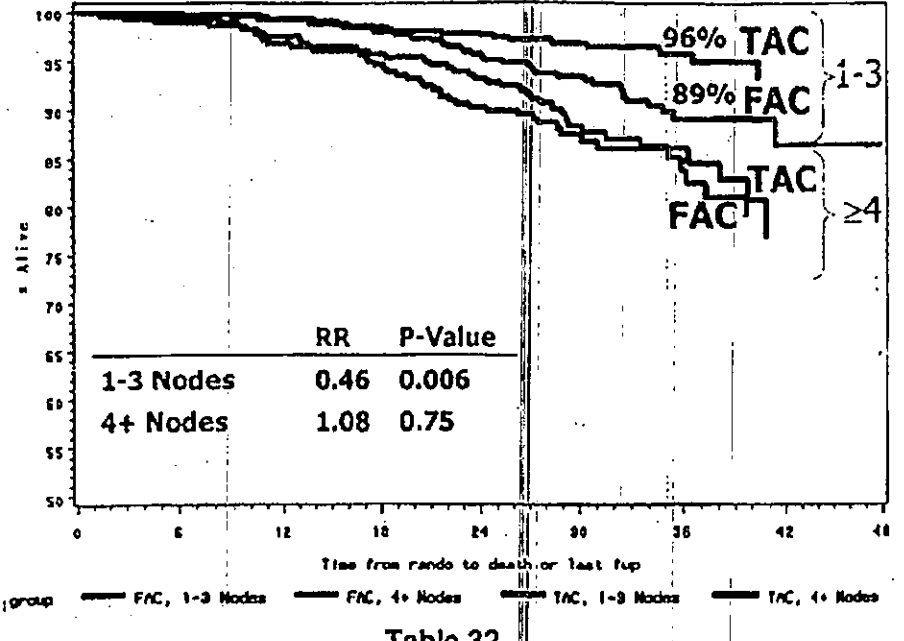


Table 32

Disease Free Survival by Hormonal Status

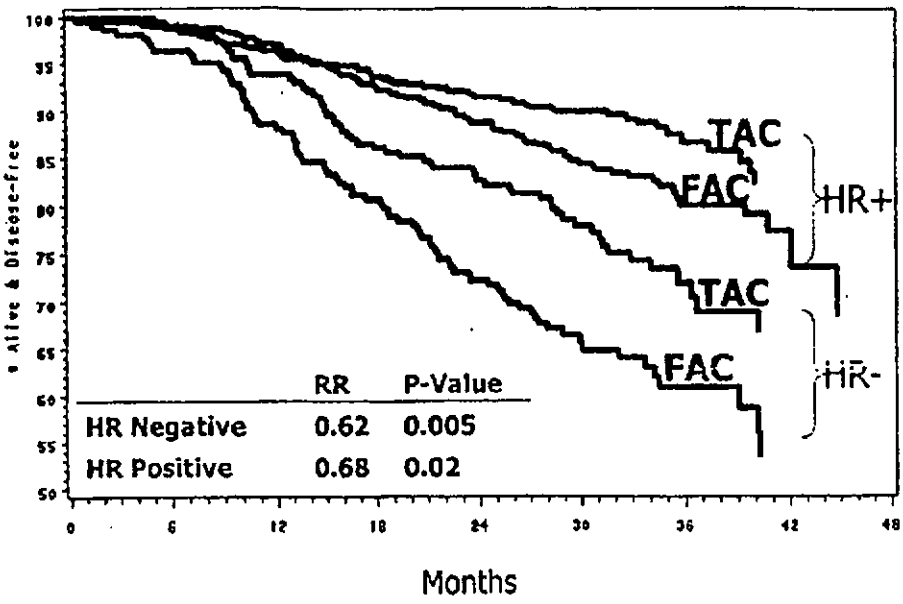


Table 33

Patient Characteristics

Randomized (n=1,491)	TAC n=745	FAC n=746
Median Age	49	49
Median KPS	100 %	100 %
Premenopausal	51 %	50 %
Mastectomy	60 %	59 %
Radiotherapy	68 %	71 %
Tamoxifen	68 %	69 %

Table 34

Overall Survival by Nodal Status

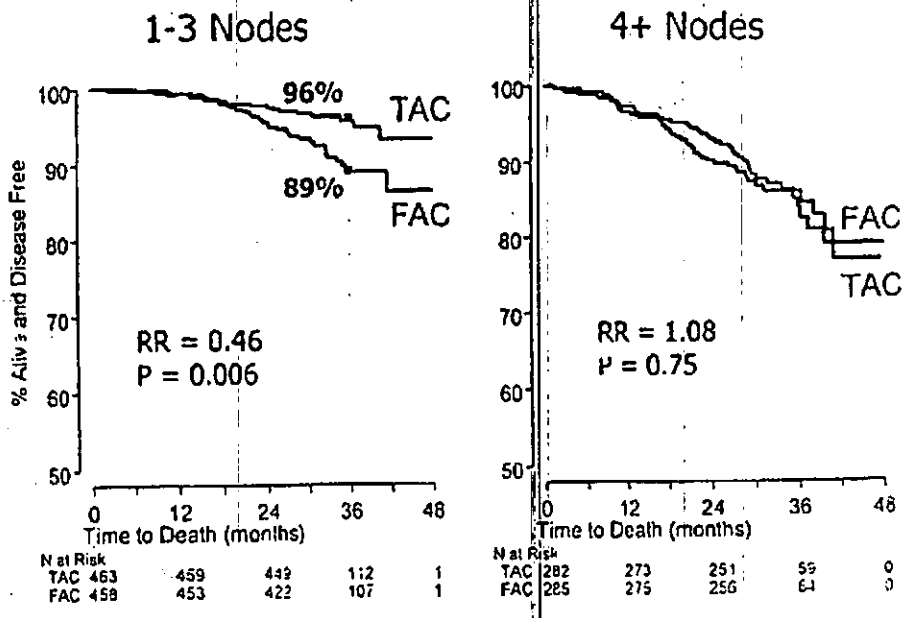


Table 35

Analyses by HER2 Status (FISH)

	DFS RR	p	OS RR	p
Negative	**0.74** (0.54-1.01)	0.06	**0.80** (0.50-1.26)	0.33
Positive	**0.59** (0.38-0.91)	0.02	**0.76** (0.39-1.45)	0.40

Table 36

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ACTION

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(54) Title: USE OF DOCETAXEL/DOXORUBICIN/CYCLOPHOSPHAMIDE IN ADJUVANT THERAPY OF BREAST AND OVARIAN CANCER

(57) Abstract: The present invention relates to a new method of adjuvant therapy in the treatment of metastatic breast or ovarian cancer, comprising administering six cycles of docetaxel, doxorubicin and cyclophosphamide to a patient in need thereof, wherein said dosages have a marked therapeutic effect when compared to other adjuvant therapies.