

本文書は3通作成し、1通は厚生労働省エイズ治療薬研究班事務局へ書留郵便で提出し、他は患者、主治医がそれぞれ保管してください。(同一薬剤の継続時は初回のみ必要です。)

(4) 患者同意書

年 月 日

厚生労働省エイズ治療薬研究班 班長 福武 勝幸 殿

フリガナ 申請者(主治医)氏名		病院名・〒住所	
診療科名			
職 責			
患者氏名(イニシャル) 姓 [] . 名 [] .		男 ・ 女	
カルテ番号 []	生年月日	年 月 日	

上記の患者さんに対して、以下の内容について十分に説明したうえ同意を得ました。

同意書

私は私の病気()の治療のために、厚生労働省エイズ治療薬研究班から治療薬()の提供を受けることに関して、上記の担当医師から下記の内容について説明を受け、また質問する機会も得て理解いたしましたので、この治療を受けることに同意いたします。

説明内容

- 1.この治療の目的と意義
- 2.予期される効果と副作用
- 3.他の治療法の有無とその内容
- 4.同意しない場合でも今後の治療に不利益を受けないこと。
- 5.同意した場合でも随時これを撤回でき今後の治療に不利益を受けないこと。
- 6.わからない点は、いつでも質問し説明を受けられること。
- 7.プライバシーは厳重に守られること。

同意取得日	年 月 日		
フリガナ 患者氏名 (自署)	印	フリガナ 代諾者氏名 (自署)	印
生年月日	年 月 日		続柄
住所		代諾者住所	

本文書は薬剤を受け取り次第、念書とともに厚生労働省エイズ治療薬研究班事務局へ郵便で提出してください。

(5) 薬剤受領書

年 月 日

厚生労働省エイズ治療薬研究班 班長 福武 勝幸 殿

薬 剤 名	数 量

上記の薬剤を確かに受領いたしました。

フリガナ 受領者（主治医） 氏名	印
診療科名	
職 責	
病院名・〒住所	

班長連絡先 東京医科大学病院 臨床検査医学科 主任教授 福武 勝幸
〒160-0023 東京都新宿区西新宿 6-7-1
TEL03-3342-6111 EXT5086 FAX 03-3340-5448

事務局連絡先 パレクセル・インターナショナル株式会社
エイズ治療薬研究班事務局担当者
〒104-0033 東京都中央区新川 1-17-21 茅場町ファーストビル 6F
TEL : 03-3537-5902 FAX : 03-3552-0452

念 書

平成 年 月 日

厚生労働大臣 殿

輸入業者（受取人）氏名（法人にあっては名称及び代表者の氏名）

_____ 印

同住所（法人にあっては主たる事務所の所在地）

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厚生労働省エイズ治療薬研究班

主任研究者(班長) 福武 勝幸

この念書は医師個人輸入の手続きにおいて厚生労働省へ必ず提出しなければならないものです。研究班の存続のために最も重要な書類ですので、遅滞なく班長へご返送いただきますようお願いいたします。

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念書返送先

班長連絡先 東京医科大学病院 臨床検査医学科 主任教授 福武 勝幸
〒160-0023 東京都新宿区西新宿 6-7-1
TEL03-3342-6111 EXT5086 FAX 03-3340-5448

薬剤受領書返送先

事務局連絡先 パレクセル・インターナショナル株式会社
エイズ治療薬研究班事務局担当者
〒104-0033 東京都中央区新川 1-17-21
茅場町ファーストビル 6F
TEL : 03-3537-5902 FAX : 03-3552-0452

2007.10.09 厚生労働省エイズ治療薬研究班

TAXOL[®] (paclitaxel) INJECTION

(Patient Information Included)

Rx only

WARNING

TAXOL[®] (paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H₂ antagonists. (See **DOSAGE AND ADMINISTRATION**.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

TAXOL therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm³ and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL.

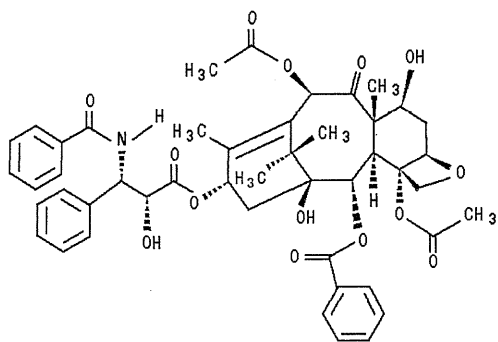
DESCRIPTION

TAXOL (paclitaxel) Injection is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor[®] EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

*Cremophor[®] EL is the registered trademark of BASF Aktiengesellschaft.
Cremophor[®] EL is further purified by a Bristol-Myers Squibb Company proprietary process before use.

Paclitaxel is a natural product with antitumor activity. TAXOL (paclitaxel) is obtained via a semi-synthetic process from *Taxus baccata*. The chemical name for paclitaxel is 5 β ,20-Epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216–217° C.

CLINICAL PHARMACOLOGY

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Following intravenous administration of TAXOL, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

Pharmacokinetic parameters of paclitaxel following 3- and 24-hour infusions of TAXOL at dose levels of 135 and 175 mg/m² were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table.

TABLE 1
SUMMARY OF PHARMACOKINETIC PARAMETERS—MEAN VALUES

Dose (mg/m ²)	Infusion Duration (h)	N (patients)	C _{max} (ng/mL)	AUC _(0-∞) (ng•h/mL)	T-HALF (h)	CL _T (L/h/m ²)
135	24	2	195	6300	52.7	21.7
175	24	4	365	7993	15.7	23.8
135	3	7	2170	7952	13.1	17.7
175	3	5	3650	15007	20.2	12.2

C_{max}=Maximum plasma concentration

AUC_(0-∞)=Area under the plasma concentration-time curve from time 0 to infinity

CL_T=Total body clearance

It appeared that with the 24-hour infusion of TAXOL, a 30% increase in dose (135 mg/m² vs 175 mg/m²) increased the C_{max} by 87%, whereas the AUC_(0-∞) remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C_{max} and AUC_(0-∞) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24-hour infusion of TAXOL, ranged from 227 to 688 L/m², indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15 to 135 mg/m² given by 1-hour infusions (n=15), 30 to 275 mg/m² given by 6-hour infusions (n=36), and 200 to 275 mg/m² given by 24-hour infusions (n=54) in Phase 1 and 2 studies. Values for CL_T and volume of distribution were consistent with the findings in the Phase 3 study. The pharmacokinetics of TAXOL in patients with AIDS-related Kaposi's sarcoma have not been studied.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89 to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15 to 275 mg/m² doses of TAXOL as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In 5 patients administered a 225 or 250 mg/m² dose of radiolabeled TAXOL as a 3-hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6α-hydroxypaclitaxel, accounted for

the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6 α -hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to 2 minor metabolites, 3'-*p*-hydroxypaclitaxel and 6 α , 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6 α -hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17 α -ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6 α -hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. (See **PRECAUTIONS: Drug Interactions.**)

The disposition and toxicity of paclitaxel 3-hour infusion were evaluated in 35 patients with varying degrees of hepatic function. Relative to patients with normal bilirubin, plasma paclitaxel exposure in patients with abnormal serum bilirubin ≤ 2 times upper limit of normal (ULN) administered 175 mg/m² was increased, but with no apparent increase in the frequency or severity of toxicity. In 5 patients with serum total bilirubin > 2 times ULN, there was a statistically nonsignificant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m²), but no observed increase in plasma exposure. (See **PRECAUTIONS: Hepatic** and **DOSAGE AND ADMINISTRATION.**) The effect of renal dysfunction on the disposition of paclitaxel has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES

Ovarian Carcinoma

First-Line Data: The safety and efficacy of TAXOL followed by cisplatin in patients with advanced ovarian cancer and no prior chemotherapy were evaluated in 2, Phase 3 multicenter, randomized, controlled trials. In an Intergroup study led by the European Organization for Research and Treatment of Cancer involving the Scandinavian Group NOCOVA, the National Cancer Institute of Canada, and the Scottish Group, 680 patients with Stage II_{B-C}, III, or IV disease (optimally or non-optimally debulked) received either TAXOL 175 mg/m² infused over 3 hours followed by cisplatin 75 mg/m² (Tc) or

cyclophosphamide 750 mg/m² followed by cisplatin 75 mg/m² (Cc) for a median of 6 courses. Although the protocol allowed further therapy, only 15% received both drugs for 9 or more courses. In a study conducted by the Gynecological Oncology Group (GOG), 410 patients with Stage III or IV disease (>1 cm residual disease after staging laparotomy or distant metastases) received either TAXOL 135 mg/m² infused over 24 hours followed by cisplatin 75 mg/m² or cyclophosphamide 750 mg/m² followed by cisplatin 75 mg/m² for 6 courses.

In both studies, patients treated with TAXOL (paclitaxel) in combination with cisplatin had significantly higher response rate, longer time to progression, and longer survival time compared with standard therapy. These differences were also significant for the subset of patients in the Intergroup study with non-optimally debulked disease, although the study was not fully powered for subset analyses (TABLES 2A and 2B). Kaplan-Meier survival curves for each study are shown in FIGURES 1 and 2.

TABLE 2A
EFFICACY IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA STUDIES

	Intergroup (non-optimally debulked subset)		GOG-111	
	T175/3 ^a c75 (n=218)	C750 ^a c75 (n=227)	T135/24 ^a c75 (n=196)	C750 ^a c75 (n=214)
• Clinical Response ^b	(n=153)	(n=153)	(n=113)	(n=127)
—rate (percent)	58	43	62	48
—p-value ^c		0.016		0.04
• Time to Progression				
—median (months)	13.2	9.9	16.6	13.0
—p-value ^c		0.0060		0.0008
—hazard ratio (HR) ^c		0.76		0.70
—95% CI ^c		0.62–0.92		0.56–0.86
• Survival				
—median (months)	29.5	21.9	35.5	24.2
—p-value ^c		0.0057		0.0002
—hazard ratio ^c		0.73		0.64
—95% CI ^c		0.58–0.91		0.50–0.81

^a TAXOL dose in mg/m²/infusion duration in hours; cyclophosphamide and cisplatin doses in mg/m².

^b Among patients with measurable disease only.

^c Unstratified for the Intergroup Study, Stratified for Study GOG-111.

TABLE 2B
EFFICACY IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA INTERGROUP STUDY

	T175/3 ^a c75 (n=342)		C750 ^a c75 (n=338)
• Clinical Response ^b	(n=162)		(n=161)
—rate (percent)	59		45
—p-value ^c		0.014	
• Time to Progression			
—median (months)	15.3		11.5
—p-value ^c		0.0005	
—hazard ratio ^c		0.74	
—95% CI ^c		0.63–0.88	
• Survival			
—median (months)	35.6		25.9
—p-value ^c		0.0016	
—hazard ratio ^c		0.73	
—95% CI ^c		0.60–0.89	

^a TAXOL dose in mg/m²/infusion duration in hours; cyclophosphamide and cisplatin doses in mg/m².

^b Among patients with measurable disease only.

^c Unstratified.

FIGURE 1
SURVIVAL: Cc VERSUS Tc (INTERGROUP)

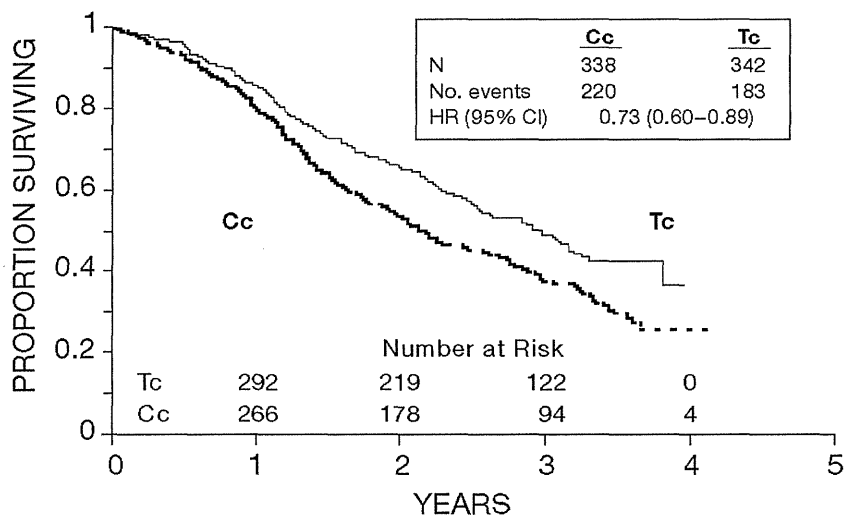
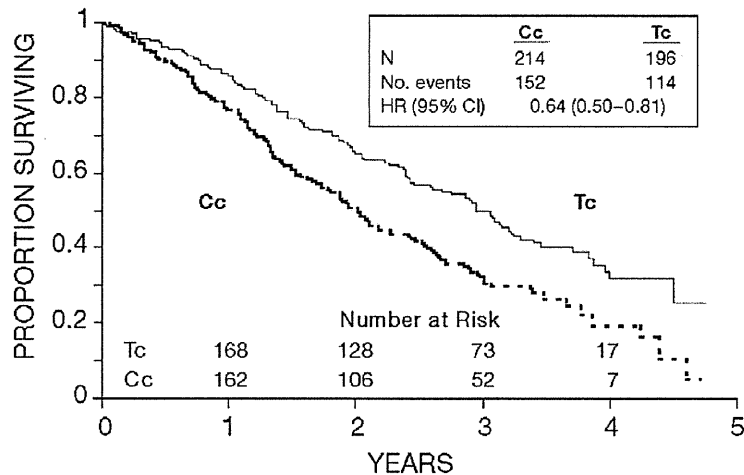


FIGURE 2
SURVIVAL: Cc VERSUS Tc (GOG-111)



The adverse event profile for patients receiving TAXOL in combination with cisplatin in these studies was qualitatively consistent with that seen for the pooled analysis of data from 812 patients treated with single-agent TAXOL in 10 clinical studies. These adverse events and adverse events from the Phase 3 first-line ovarian carcinoma studies are described in the **ADVERSE REACTIONS** section in tabular (**TABLES 10 and 11**) and narrative form.

Second-Line Data: Data from 5, Phase 1 and 2 clinical studies (189 patients), a multicenter randomized Phase 3 study (407 patients), as well as an interim analysis of data from more than 300 patients enrolled in a treatment referral center program were used in support of the use of TAXOL in patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary. Two of the Phase 2 studies (92 patients) utilized an initial dose of 135 to 170 mg/m² in most patients (>90%) administered over 24 hours by continuous infusion. Response rates in these 2 studies were 22% (95% CI, 11-37%) and 30% (95% CI, 18-46%) with a total of 6 complete and 18 partial responses in 92 patients. The median duration of overall response in these 2 studies measured from the first day of treatment was 7.2 months (range, 3.5-15.8 months) and 7.5 months (range, 5.3-17.4 months), respectively. The median survival was 8.1 months (range, 0.2-36.7 months) and 15.9 months (range, 1.8-34.5+ months).

The Phase 3 study had a bifactorial design and compared the efficacy and safety of TAXOL (paclitaxel), administered at 2 different doses (135 or 175 mg/m²) and schedules (3- or 24-hour infusion). The overall response rate for the 407 patients was 16.2%

(95% CI, 12.8–20.2%), with 6 complete and 60 partial responses. Duration of response, measured from the first day of treatment was 8.3 months (range, 3.2–21.6 months). Median time to progression was 3.7 months (range, 0.1+ to 25.1+ months). Median survival was 11.5 months (range, 0.2 to 26.3+ months).

Response rates, median survival, and median time to progression for the 4 arms are given in the following table.

TABLE 3
EFFICACY IN THE PHASE 3 SECOND-LINE OVARIAN CARCINOMA STUDY

	175/3 (n=96)	175/24 (n=106)	135/3 (n=99)	135/24 (n=106)
• Response				
—rate (percent)	14.6	21.7	15.2	13.2
—95% Confidence Interval	(8.5–23.6)	(14.5–31.0)	(9.0–24.1)	(7.7–21.5)
• Time to Progression				
—median (months)	4.4	4.2	3.4	2.8
—95% Confidence Interval	(3.0–5.6)	(3.5–5.1)	(2.8–4.2)	(1.9–4.0)
• Survival				
—median (months)	11.5	11.8	13.1	10.7
—95% Confidence Interval	(8.4–14.4)	(8.9–14.6)	(9.1–14.6)	(8.1–13.6)

Analyses were performed as planned by the bifactorial study design described in the protocol, by comparing the 2 doses (135 or 175 mg/m²) irrespective of the schedule (3 or 24 hours) and the 2 schedules irrespective of dose. Patients receiving the 175 mg/m² dose had a response rate similar to that for those receiving the 135 mg/m² dose: 18% versus 14% (p=0.28). No difference in response rate was detected when comparing the 3-hour with the 24-hour infusion: 15% versus 17% (p=0.50). Patients receiving the 175 mg/m² dose of TAXOL had a longer time to progression than those receiving the 135 mg/m² dose: median 4.2 versus 3.1 months (p=0.03). The median time to progression for patients receiving the 3-hour versus the 24-hour infusion was 4.0 months versus 3.7 months, respectively. Median survival was 11.6 months in patients receiving the 175 mg/m² dose of TAXOL and 11.0 months in patients receiving the 135 mg/m² dose (p=0.92). Median survival was 11.7 months for patients receiving the 3-hour infusion of TAXOL and 11.2 months for patients receiving the 24-hour infusion (p=0.91). These statistical analyses should be viewed with caution because of the multiple comparisons made.

TAXOL remained active in patients who had developed resistance to platinum-containing therapy (defined as tumor progression while on, or tumor relapse within 6 months from

completion of, a platinum-containing regimen) with response rates of 14% in the Phase 3 study and 31% in the Phase 1 and 2 clinical studies.

The adverse event profile in this Phase 3 study was consistent with that seen for the pooled analysis of data from 812 patients treated in 10 clinical studies. These adverse events and adverse events from the Phase 3 second-line ovarian carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (**TABLES 10 and 12**) and narrative form.

The results of this randomized study support the use of TAXOL at doses of 135 to 175 mg/m², administered by a 3-hour intravenous infusion. The same doses administered by 24-hour infusion were more toxic. However, the study had insufficient power to determine whether a particular dose and schedule produced superior efficacy.

Breast Carcinoma

Adjuvant Therapy

A Phase 3 Intergroup study (Cancer and Leukemia Group B [CALGB], Eastern Cooperative Oncology Group [ECOG], North Central Cancer Treatment Group [NCCTG], and Southwest Oncology Group [SWOG]) randomized 3170 patients with node-positive breast carcinoma to adjuvant therapy with TAXOL or to no further chemotherapy following 4 courses of doxorubicin and cyclophosphamide (AC). This multicenter trial was conducted in women with histologically positive lymph nodes following either a mastectomy or segmental mastectomy and nodal dissections. The 3 x 2 factorial study was designed to assess the efficacy and safety of 3 different dose levels of doxorubicin (A) and to evaluate the effect of the addition of TAXOL administered following the completion of AC therapy. After stratification for the number of positive lymph nodes (1–3, 4–9, or 10+), patients were randomized to receive cyclophosphamide at a dose of 600 mg/m² and doxorubicin at doses of either 60 mg/m² (on day 1), 75 mg/m² (in 2 divided doses on days 1 and 2), or 90 mg/m² (in 2 divided doses on days 1 and 2 with prophylactic G-CSF support and ciprofloxacin) every 3 weeks for 4 courses and either TAXOL 175 mg/m² as a 3-hour infusion every 3 weeks for 4 additional courses or no additional chemotherapy. Patients whose tumors were positive were to receive subsequent tamoxifen treatment (20 mg daily for 5 years); patients who received segmental mastectomies prior to study were to receive breast irradiation after recovery from treatment-related toxicities.

At the time of the current analysis, median follow-up was 30.1 months. Of the 2066 patients who were hormone receptor positive, 93% received tamoxifen. The primary analyses of disease-free survival and overall survival used multivariate Cox models, which included TAXOL administration, doxorubicin dose, number of positive lymph nodes, tumor size, menopausal status, and estrogen receptor status as factors. Based on the model for disease-free survival, patients receiving AC followed by TAXOL had a 22% reduction in the risk of disease recurrence compared to patients randomized to AC alone (Hazard Ratio [HR]=0.78, 95% CI, 0.67–0.91, p=0.0022). They also had a 26% reduction in the risk of death (HR=0.74, 95% CI, 0.60–0.92, p=0.0065). For disease-free survival and overall survival, p-values were not adjusted for interim analyses. Kaplan-Meier curves are shown in **FIGURES 3** and **4**. Increasing the dose of doxorubicin higher than 60 mg/m² had no effect on either disease-free survival or overall survival.

FIGURE 3
DISEASE-FREE SURVIVAL: AC VERSUS AC+T

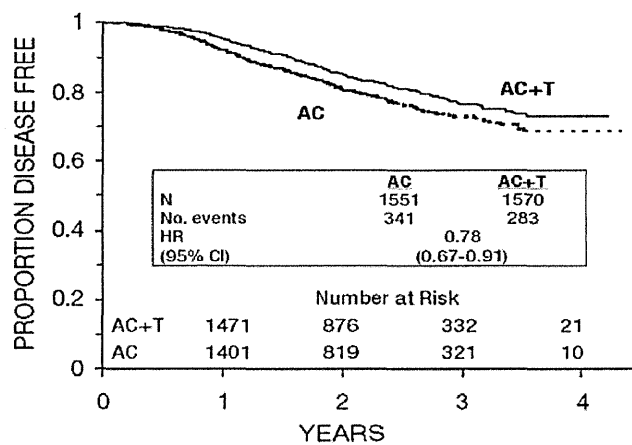
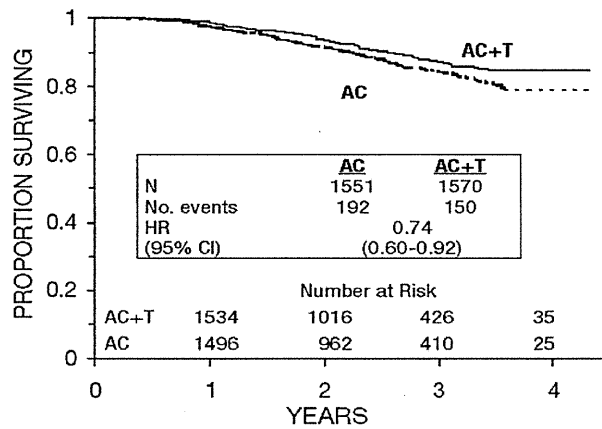


FIGURE 4
SURVIVAL: AC VERSUS AC+T



Subset analyses. Subsets defined by variables of known prognostic importance in adjuvant breast carcinoma were examined, including number of positive lymph nodes, tumor size, hormone receptor status, and menopausal status. Such analyses must be interpreted with care, as the most secure finding is the overall study result. In general, a reduction in hazard similar to the overall reduction was seen with TAXOL (paclitaxel) for both disease-free and overall survival in all of the larger subsets with one exception; patients with receptor-positive tumors had a smaller reduction in hazard (HR=0.92) for disease-free survival with TAXOL than other groups. Results of subset analyses are shown in **TABLE 4**.