ＦＡＸ ０３-３３４０-５４４８ 厚生労働省エイズ治療薬研究班 班長 へFAXでお送り下さい。
原本は施設長承諾書とともに事務局へ郵送してください。

（2）班員登録書

年　月　日

厚生労働省エイズ治療薬研究班　班長　福武　勝幸　殿

私は厚生労働省エイズ治療薬研究班に研究協力者（班員）として参加することを承諾します。

フリガナ 氏　名	印
所属病院名 住　所	
診療科名	
職　責	
緊急連絡先 自宅住所　電話　FAX E-mail 等	

厚生労働省エイズ治療薬研究班の薬剤による治療研究を実施する医師は、当研究班の規定により研究協力者（班員）となっていただかなければなりません。厚生労働省エイズ治療薬研究班はヒューマンサイエンス振興財団のエイズ医薬品等開発推進事業からの研究費により運営されています。

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
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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

（3）施設長承諾書の原本は（2）班員登録書とともに、厚生労働省エイズ治療薬研究班事務局へ郵便にて提出してください。

（3）施設長承諾書

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 氏　名	
診療科名	
職　責	

上記の者が厚生労働省エイズ治療薬研究班に研究協力者（班員）として参加することを承諾します。

施　設　長　氏　名	印
職　　責	
施　設　名 住所	

厚生労働省エイズ治療薬研究班の薬剤による治療研究を実施する医師は、当研究班の規定により研究協力者（班員）となっていただかなければなりません。厚生労働省エイズ治療薬研究班はヒューマンサイエンス振興財団のエイズ医薬品等開発推進事業からの研究費により運営されています。

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TEL：03-3537-5902　FAX：03-3552-0452

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	続柄
生年月日	年　月　日			
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
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TEL：03-3537-5902　FAX：03-3552-0452

（6）臨床研究使用成績調査票（1）

臨床経過と検査値の推移を各ポイント記載する毎に本表のコピーも事務局へお送り下さい

主治医氏名	印	病院名・〒住所	
診療科名			
職　責			
電話番号	（　　）	ＦＡＸ番号	（　　）
E - Mail			

患者氏名（イニシャル）　姓［　　］．名［　　］．		男・女	身長　　　cm
カルテ番号［　　　　　　　　］	生年月日	年　　月　　日	
合併症 1．無し 2．慢性肝炎 3．肝硬変 4．腎障害 5．糖尿病 6．高脂血症 7．血友病 8．その他（　　　　　　　　　　　）			

今回使用した研究班の薬（研究班の薬剤を全てを記載して下さい。）

薬剤名	含有量・剤形	１日量と投与回数	投与期間（年/月/日）
		/日　回/日	/ /　-　/ /
		/日　回/日	/ /　-　/ /
		/日　回/日	/ /　-　/ /
		/日　回/日	/ /　-　/ /
		/日　回/日	/ /　-　/ /
		/日　回/日	/ /　-　/ /

研究班の薬剤を投与中に使用した併用薬を全て記載してください。

薬剤名	剤形	１日量と投与回数	投与期間（年/月/日）
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(7) 臨床研究使用成績調査票 (2)

臨床経過と臨床検査値の推移　　ポイント毎に記入し、記入毎に事務局へお送り下さい。

主治医氏名	印	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

検査ポイント	投与前	開始後　ヶ月	開始後　ヶ月	開始後　ヶ月
検査日	年 月 日	年 月 日	年 月 日	年 月 日
外来・入院	外来・入院	外来・入院	外来・入院	外来・入院
体重	Kg	Kg	Kg	Kg
体温	℃	℃	℃	℃
血圧	/ mmHg	/ mmHg	/ mmHg	/ mmHg
症状の程度	3+・2+・1+・-	3+・2+・1+・-	3+・2+・1+・-	3+・2+・1+・-
CD4細胞数	/μl	/μl	/μl	/μl
HIV-RNA量	×10　/ml	×10　/ml	×10　/ml	×10　/ml
白血球数 WBC	/μl	/μl	/μl	/μl
赤血球数 RBC	/μl	/μl	/μl	/μl
Hb	g/dl	g/dl	g/dl	g/dl
Htc	%	%	%	%
血小板数	/μl	/μl	/μl	/μl
好中球%	%	%	%	%
好酸球%	%	%	%	%
好塩基球%	%	%	%	%
リンパ球%	%	%	%	%
単球%	%	%	%	%
TP	g/dl	g/dl	g/dl	g/dl
T-Bil	mg/dl	mg/dl	mg/dl	mg/dl
GOT	IU/L	IU/L	IU/L	IU/L
GPT	IU/L	IU/L	IU/L	IU/L
γGTP	IU/L	IU/L	IU/L	IU/L
BUN	mg/dl	mg/dl	mg/dl	mg/dl
クレアチニン	mg/dl	mg/dl	mg/dl	mg/dl
尿酸	mg/dl	mg/dl	mg/dl	mg/dl
総コレステロール	mg/dl	mg/dl	mg/dl	mg/dl
中性脂肪	mg/dl	mg/dl	mg/dl	mg/dl
グルコース	mg/dl	mg/dl	mg/dl	mg/dl
尿蛋白	－・+-・＋・＋＋	－・+-・＋・＋＋	－・+-・＋・＋＋	－・+-・＋・＋＋
尿糖	－・+-・＋・＋＋	－・+-・＋・＋＋	－・+-・＋・＋＋	－・+-・＋・＋＋
尿潜血反応	－・+-・＋・＋＋	－・+-・＋・＋＋	－・+-・＋・＋＋	－・+-・＋・＋＋
尿沈さ異常と内容	無・(　　)	無・(　　)	無・(　　)	無・(　　)

(8) 臨床研究使用成績調査票 (3)

その他の重要な臨床検査成績

XP，CT，MRI，シンチグラム等

検査毎に記入し、記入毎に事務局へお送り下さい。

主治医氏名	印	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

（9）有害事象発生報告書

年　月　日

有害事象が発生したら直ちに記入して、FAXで事務局03-3518-6014へお送り下さい。

主治医氏名	印	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

有害事象の内容		
発生日時	年　月　日　午前・午後　時	
経過と処置		
程度（主治医判断）	軽症　・　中等度　・　重篤	
薬剤との因果関係	1.関連有り　2．関連が否定出来ない　3．関連無し　4．不明	
関連有ると思われる薬剤	薬剤名	理由

転帰報告書

転帰を判定したら直ちに記入し事務局へお送り下さい。

判定日時	年　月　日　午前・午後　時
転　帰	回復　・　軽快　・　死亡　・　後遺症
死因・後遺症	
薬剤との因果関係	1．関連有り　2．関連が否定出来ない　3．関連無し　4．不明

[別紙第２号様式]

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）

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

今般、別紙輸入報告書により報告いたしました下記 医薬品は（　医師個人用　）として使用するもので、他に販売、授与するものではありません。
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品　　名	数　　量

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念書の取扱についてのお願い

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。

当研究班においては、厚生労働省の特別な配慮により薬剤を班長名であらかじめ輸入し通関しておりますが、本念書をご提出いただくことにより、各主治医か個人輸入したのと同等に扱うこととなり、薬事法に抵触することなく各医師へ薬剤をお届けする形で研究班が機能できる仕組みになっております。(この念書は当研究班専用のもので、一般の個人輸入の書式とは異なります。)

記載上の注意

日付欄には薬剤をお受け取りになった日付をご記入ください。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）の欄には、薬剤を研究班へ申請された医師の所属施設と氏名をご記入ください。また、同住所（法人にあっては主たる事務所の所在地）の欄には、医師の所属する施設の住所を御記載ください。お受け取りになった薬剤の品名と数量をご記載ください。

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
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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

TAXOL® (paclitaxel) INJECTION

Rx only

(Patient Information Included)

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 H_2 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/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. 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.

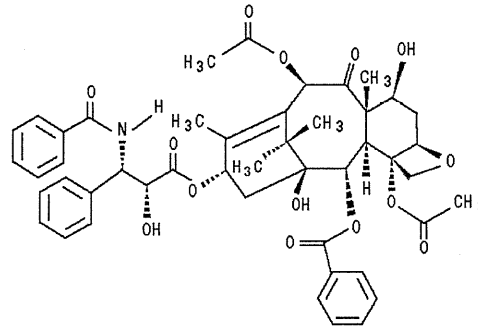
DESCRIPTION

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 5β,20-Epoxy-1,2α,4,7β,10β,13α-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/m^2 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)	$AUC_{(0-\infty)}$ (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
$AUC_{(0-\infty)}$=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/m^2 vs 175 mg/m^2) increased the C_{max} by 87%, whereas the $AUC_{(0-\infty)}$ remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C_{max} and $AUC_{(0-\infty)}$ 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/m^2, 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/m^2 given by 1-hour infusions (n=15), 30 to 275 mg/m^2 given by 6-hour infusions (n=36), and 200 to 275 mg/m^2 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/m^2 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/m^2 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 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to 2 minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-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, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-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/m^2 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/m^2), 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/m^2 infused over 3 hours followed by cisplatin 75 mg/m^2 (Tc) or

cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2 (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/m^2 infused over 24 hours followed by cisplatin 75 mg/m^2 or cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2 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/m^2/infusion duration in hours; cyclophosphamide and cisplatin doses in mg/m^2.
[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/m^2/infusion duration in hours; cyclophosphamide and cisplatin doses in mg/m^2.

[b] Among patients with measurable disease only.

[c] Unstratified.

FIGURE 1

SURVIVAL: Cc VERSUS Tc (INTERGROUP)

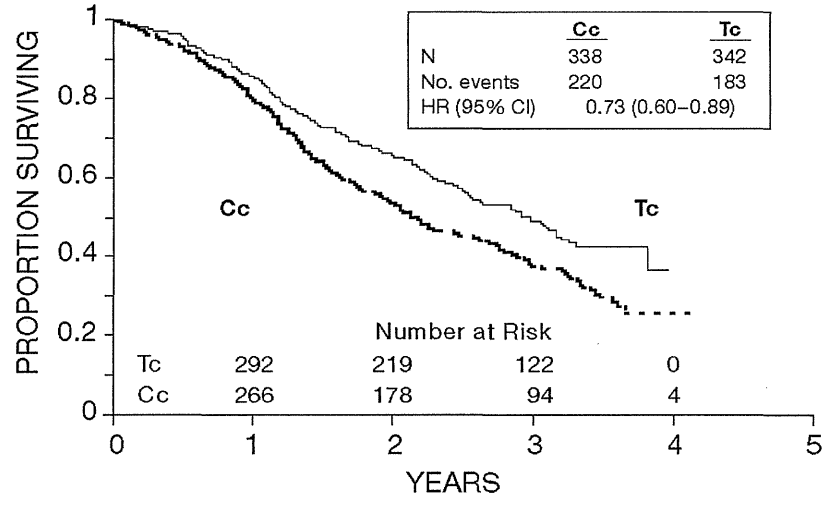
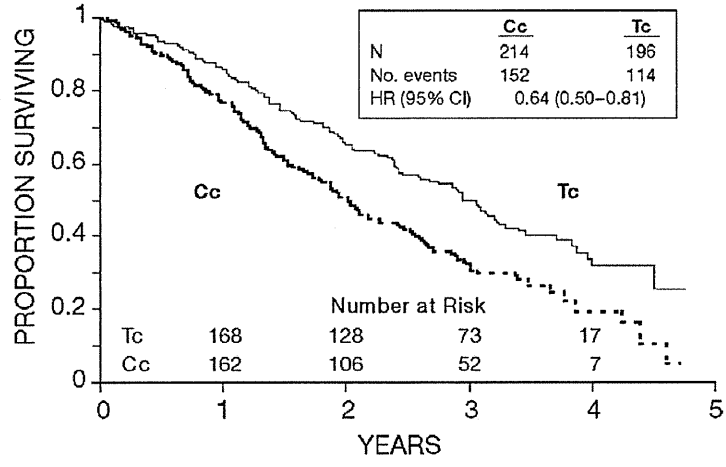


FIGURE 2
SURVIVAL: Cc VERSUS Tc (GOG-111)



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/m^2 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/m^2) 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/m^2) irrespective of the schedule (3 or 24 hours) and the 2 schedules irrespective of dose. Patients receiving the 175 mg/m^2 dose had a response rate similar to that for those receiving the 135 mg/m^2 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/m^2 dose of TAXOL had a longer time to progression than those receiving the 135 mg/m^2 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/m^2 dose of TAXOL and 11.0 months in patients receiving the 135 mg/m^2 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/m^2, 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/m^2 and doxorubicin at doses of either 60 mg/m^2 (on day 1), 75 mg/m^2 (in 2 divided doses on days 1 and 2), or 90 mg/m^2 (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/m^2 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.