patients in 6 domains of symptoms and/or conditions that are commonly related to AIDS-related Kaposi's sarcoma.

Cutaneous Tumor Response (Amended ACTG Criteria): The objective response rate was 59% (95% CI, 46–72%) (35 of 59 patients) in patients with prior systemic therapy. Cutaneous responses were primarily defined as flattening of more than 50% of previously raised lesions.

TABLE 8
OVERALL BEST RESPONSE (AMENDED ACTG CRITERIA)
Percent of Patients

	Prior Systemic Therapy (n=59)
Complete response	3
Partial response	56
Stable disease	29
Progression	8
Early death/toxicity	3

The median time to response was 8.1 weeks and the median duration of response measured from the first day of treatment was 10.4 months (95% CI, 7.0–11.0 months) for the patients who had previously received systemic therapy. The median time to progression was 6.2 months (95% CI, 4.6–8.7 months).

Additional Clinical Benefit: Most data on patient benefit were assessed retrospectively (plans for such analyses were not included in the study protocols). Nonetheless, clinical descriptions and photographs indicated clear benefit in some patients, including instances of improved pulmonary function in patients with pulmonary involvement, improved ambulation, resolution of ulcers, and decreased analgesic requirements in patients with Kaposi's sarcoma (KS) involving the feet and resolution of facial lesions and edema in patients with KS involving the face, extremities, and genitalia.

Safety: The adverse event profile of TAXOL administered to patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma was generally similar to that seen in the pooled analysis of data from 812 patients with solid tumors. These adverse events and adverse events from the Phase 2 second-line Kaposi's sarcoma studies are described in the **ADVERSE REACTIONS** section in tabular (**TABLES 10** and **16**) and narrative form. In this immunosuppressed patient population, however, a lower dose intensity of TAXOL and supportive therapy including hematopoietic growth factors in patients with severe neutropenia are recommended. Patients with AIDS-related Kaposi's sarcoma may have more severe hematologic toxicities than patients with solid tumors.

INDICATIONS AND USAGE

TAXOL is indicated as first-line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As first-line therapy, TAXOL is indicated in combination with cisplatin.

TAXOL is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy. In the clinical trial, there was an overall favorable effect on disease-free and overall survival in the total population of patients with receptor-positive and receptor-negative tumors, but the benefit has been specifically demonstrated by available data (median follow-up 30 months) only in the patients with estrogen and progesterone receptor-negative tumors. (See **CLINICAL STUDIES: Breast Carcinoma**.)

TAXOL is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

TAXOL, in combination with cisplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.

TAXOL is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.

CONTRAINDICATIONS

TAXOL is contraindicated in patients who have a history of hypersensitivity reactions to TAXOL or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil).

TAXOL should not be used in patients with solid tumors who have baseline neutrophil counts of <1500 cells/mm^3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm^3.

WARNINGS

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.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. TAXOL should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm^3 (<1000 cells/mm^3 for patients with KS). Frequent monitoring of blood counts should be instituted during TAXOL treatment. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophils recover to a level >1500 cells/mm^3 (>1000 cells/mm^3 for patients with KS) and platelets recover to a level >100,000 cells/mm^3.

Severe conduction abnormalities have been documented in <1% of patients during TAXOL therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during TAXOL infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with TAXOL.

Pregnancy

TAXOL can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3.0 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions, and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1.0 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m^2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If TAXOL is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which

may be leached from PVC infusion bags or sets, diluted TAXOL solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

TAXOL should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Drug Interactions: In a Phase 1 trial using escalating doses of TAXOL (110–200 mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusions, myelosuppression was more profound when TAXOL was given after cisplatin than with the alternate sequence (ie, TAXOL before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when TAXOL was administered following cisplatin.

The metabolism of TAXOL is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when TAXOL is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. (See **CLINICAL PHARMACOLOGY**.)

Caution should also be exercised when TAXOL is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8. (See **CLINICAL PHARMACOLOGY**.)

Potential interactions between TAXOL, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

IVEX-2® is the registered trademark of the Millipore Corporation.

Hematology: TAXOL therapy should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of TAXOL therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

For patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, TAXOL, at the recommended dose for this disease, can be initiated and repeated if the neutrophil count is at least 1000 cells/mm^3.

Hypersensitivity Reactions: Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL (eg, cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with TAXOL. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with TAXOL should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and H_2 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of TAXOL and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with TAXOL.

Cardiovascular: Hypotension, bradycardia, and hypertension have been observed during administration of TAXOL, but generally do not require treatment. Occasionally TAXOL infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of TAXOL infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. (See **WARNINGS**.) When TAXOL is used in combination with doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended. (See **ADVERSE REACTIONS**.)

Nervous System: Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of TAXOL.

TAXOL contains dehydrated alcohol USP, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol. (See **PRECAUTIONS: Pediatric Use**.)

Hepatic: There is limited evidence that the myelotoxicity of TAXOL may be exacerbated in patients with serum total bilirubin >2 times ULN (see **CLINICAL PHARMACOLOGY**). Extreme caution should be exercised when administering TAXOL to such patients, with dose reduction as recommended in **DOSAGE AND ADMINISTRATION, TABLE 17**.

Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of TAXOL at a different site, ie, "recall," has been reported.

More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been reported. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of TAXOL (paclitaxel) has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m^2 basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity. (See **WARNINGS**.)

Pregnancy: Pregnancy Category D. (See **WARNINGS**.)

Nursing Mothers: It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon 14-labeled TAXOL to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving TAXOL therapy.

Pediatric Use: The safety and effectiveness of TAXOL (paclitaxel) in pediatric patients have not been established.

There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which TAXOL was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. The toxicity is most likely attributable to the high dose of the ethanol component of the TAXOL vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of TAXOL for use in this population.

Geriatric Use: Of 2228 patients who received TAXOL in 8 clinical studies evaluating its safety and effectiveness in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive TAXOL in the adjuvant breast cancer study, 649 patients (17%) were 65 years or older and 49 patients (1%) were 75 years or older. In most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In 2 clinical studies in NSCLC, the elderly patients treated with TAXOL had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied. In a study of first-line treatment of ovarian cancer, elderly patients had a lower median survival than younger patients, but no other efficacy parameters favored the younger group. **TABLE 9** presents the incidences of Grade IV neutropenia and severe neuropathy in clinical studies according to age.

TABLE 9
SELECTED ADVERSE EVENTS IN GERIATRIC PATIENTS RECEIVING TAXOL IN CLINICAL STUDIES

	Patients (n/total [%])			
	Neutropenia (Grade IV)		Peripheral Neuropathy (Grades III/IV)	
INDICATION	Age (y)		Age (y)	
(Study/Regimen)	≥65	<65	≥65	<65
• ***OVARIAN Cancer***				
(Intergroup First-Line/T175/3 c75[a])	34/83 (41)	78/252 (31)	24/84 (29)*[b]	46/255 (18)[b]
(GOG-111 First-Line/T135/24 c75[a])	48/61 (79)	106/129 (82)	3/62 (5)	2/134 (1)
(Phase 3 Second-Line/T175/3[c])	5/19 (26)	21/76 (28)	1/19 (5)	0/76 (0)
(Phase 3 Second-Line/T175/24[c])	21/25 (84)	57/79 (72)	0/25 (0)	2/80 (3)
(Phase 3 Second-Line/T135/3[c])	4/16 (25)	10/81 (12)	0/17 (0)	0/81 (0)
(Phase 3 Second-Line/T135/24[c])	17/22 (77)	53/83 (64)	0/22 (0)	0/83 (0)
(Phase 3 Second-Line Pooled)	47/82 (57)*	141/319 (44)	1/83 (1)	2/320 (1)
• ***Adjuvant BREAST Cancer***				
(Intergroup/AC followed by T[d])	56/102 (55)	734/1468 (50)	5/102 (5)[e]	46/1468 (3)[e]
• ***BREAST Cancer After Failure of Initial Therapy***				
(Phase 3/T175/3[c])	7/24 (29)	56/200 (28)	3/25 (12)	12/204 (6)
(Phase 3/T135/3[c])	7/20 (35)	37/207 (18)	0/20 (0)	6/209 (3)
• ***Non-Small Cell LUNG Cancer***				
(ECOG/T135/24 c75[a])	58/71 (82)	86/124 (69)	9/71 (13)[f]	16/124 (13)[f]
(Phase 3/T175/3 c80[a])	37/89 (42)*	56/267 (21)	11/91 (12)*	11/271 (4)

* $p<0.05$

[a] TAXOL dose in mg/m^2/infusion duration in hours; cisplatin doses in mg/m^2.

[b] Peripheral neuropathy was included within the neurotoxicity category in the Intergroup First-Line Ovarian Cancer study (see **TABLE 11**).

[c] TAXOL dose in mg/m^2/infusion duration in hours.

[d] TAXOL (T) following 4 courses of doxorubicin and cyclophosphamide (AC) at a dose of 175 mg/m^2/3 hours every 3 weeks for 4 courses.

[e] Peripheral neuropathy reported as neurosensory toxicity in the Intergroup Adjuvant Breast Cancer study (see **TABLE 13**).

[f] Peripheral neuropathy reported as neurosensory toxicity in the ECOG NSCLC study (see **TABLE 15**).

Information for Patients: (See **Patient Information Leaflet**.)

ADVERSE REACTIONS

Pooled Analysis of Adverse Event Experiences from Single-Agent Studies

Data in the following table are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single-

agent TAXOL. Two hundred and seventy-five patients were treated in 8, Phase 2 studies with TAXOL doses ranging from 135 to 300 mg/m^2 administered over 24 hours (in 4 of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared 2 doses (135 or 175 mg/m^2) and 2 schedules (3 or 24 hours) of TAXOL. Two hundred and thirty-six patients with breast carcinoma received TAXOL (135 or 175 mg/m^2) administered over 3 hours in a controlled study.

TABLE 10

SUMMARY[a] OF ADVERSE EVENTS IN PATIENTS WITH SOLID TUMORS RECEIVING SINGLE-AGENT TAXOL

		Percent of Patients (n=812)
• ***Bone Marrow***		
—Neutropenia	<2000/mm^3	90
	<500/mm^3	52
—Leukopenia	<4000/mm^3	90
	<1000/mm^3	17
—Thrombocytopenia	<100,000/mm^3	20
	<50,000/mm^3	7
—Anemia	<11 g/dL	78
	<8 g/dL	16
—Infections		30
—Bleeding		14
—Red Cell Transfusions		25
—Platelet Transfusions		2
• ***Hypersensitivity Reaction***[b]		
—All		41
—Severe[†]		2
• ***Cardiovascular***		
—Vital Sign Changes[c]		
—Bradycardia (n=537)		3
—Hypotension (n=532)		12
—Significant Cardiovascular Events		1
• ***Abnormal ECG***		
—All Pts		23
—Pts with normal baseline (n=559)		14
• ***Peripheral Neuropathy***		
—Any symptoms		60
—Severe symptoms[†]		3
• ***Myalgia/Arthralgia***		
—Any symptoms		60
—Severe symptoms[†]		8
• ***Gastrointestinal***		
—Nausea and vomiting		52
—Diarrhea		38
—Mucositis		31
• ***Alopecia***		87
• ***Hepatic*** (Pts with normal baseline and on study data)		
—Bilirubin elevations (n=765)		7
—Alkaline phosphatase elevations (n=575)		22
—AST (SGOT) elevations (n=591)		19
• ***Injection Site Reaction***		13

[a] Based on worst course analysis.

[b] All patients received premedication.

[c] During the first 3 hours of infusion.

[†] Severe events are defined as at least Grade III toxicity.

None of the observed toxicities were clearly influenced by age.

Disease-Specific Adverse Event Experiences

First-Line Ovary in Combination: For the 1084 patients who were evaluable for safety in the Phase 3 first-line ovary combination therapy studies, **TABLE 11** shows the incidence of important adverse events. For both studies, the analysis of safety was based on all courses of therapy (6 courses for the GOG-111 study and up to 9 courses for the Intergroup study).

TABLE 11

FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA STUDIES

		Percent of Patients			
		Intergroup		**GOG-111**	
		T175/3[b] c75[c] (n=339)	C750[c] c75[c] (n=336)	T135/24[b] c75[c] (n=196)	C750[c] c75[c] (n=213)
• ***Bone Marrow***					
—Neutropenia	<2000/mm^3	91[d]	95[d]	96	92
	<500/mm^3	33[d]	43[d]	81[d]	58[d]
—Thrombocytopenia	<100,000/mm^3[e]	21[d]	33[d]	26	30
	<50,000/mm^3	3[d]	7[d]	10	9
—Anemia	<11 g/dL[f]	96	97	88	86
	<8 g/dL	3[d]	8[d]	13	9
—Infections		25	27	21	15
—Febrile Neutropenia		4	7	15[d]	4[d]
• ***Hypersensitivity Reaction***					
—All		11[d]	6[d]	8[d,g]	1[d,g]
—Severe[†]		1	1	3[d,g]	—[d,g]
• ***Neurotoxicity***[h]					
—Any symptoms		87[d]	52[d]	25	20
—Severe symptoms[†]		21[d]	2[d]	3[d]	—[d]
• ***Nausea and Vomiting***					
—Any symptoms		88	93	65	69
—Severe symptoms[†]		18	24	10	11
• ***Myalgia/Arthralgia***					
—Any symptoms		60[d]	27[d]	9[d]	2[d]
—Severe symptoms[†]		6[d]	1[d]	1	—
• ***Diarrhea***					
—Any symptoms		37[d]	29[d]	16[d]	8[d]
—Severe symptoms[†]		2	3	4	1
• ***Asthenia***					
—Any symptoms		NC	NC	17[d]	10[d]
—Severe symptoms[†]		NC	NC	1	1
• ***Alopecia***					
—Any symptoms		96[d]	89[d]	55[d]	37[d]
—Severe symptoms[†]		51[d]	21[d]	6	8

[a] Based on worst course analysis.

[b] TAXOL (T) dose in mg/m^2/infusion duration in hours.

[c] Cyclophosphamide (C) or cisplatin (c) dose in mg/m^2.

[d] $p<0.05$ by Fisher exact test.

[e] <130,000/mm^3 in the Intergroup study.

[f] <12 g/dL in the Intergroup study.

[g] All patients received premedication.

[h] In the GOG-111 study, neurotoxicity was collected as peripheral neuropathy and in the Intergroup study, neurotoxicity was collected as either neuromotor or neurosensory symptoms.

[†] Severe events are defined as at least Grade III toxicity.

NC Not Collected

Second-Line Ovary: For the 403 patients who received single-agent TAXOL in the Phase 3 second-line ovarian carcinoma study, the following table shows the incidence of important adverse events.

TABLE 12
FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 SECOND-LINE OVARIAN CARCINOMA STUDY

		Percent of Patients			
		175/3[b] (n=95)	175/24[b] (n=105)	135/3[b] (n=98)	135/24[b] (n=105)
• ***Bone Marrow***					
—Neutropenia	<2000/mm^3	78	98	78	98
	<500/mm^3	27	75	14	67
—Thrombocytopenia	<100,000/mm^3	4	18	8	6
	<50,000/mm^3	1	7	2	1
—Anemia	<11 g/dL	84	90	68	88
	<8 g/dL	11	12	6	10
—Infections		26	29	20	18
• ***Hypersensitivity Reaction***[c]					
—All		41	45	38	45
—Severe[†]		2	0	2	1
• ***Peripheral Neuropathy***					
—Any symptoms		63	60	55	42
—Severe symptoms[†]		1	2	0	0
• ***Mucositis***					
—Any symptoms		17	35	21	25
—Severe symptoms[†]		0	3	0	2

[a] Based on worst course analysis.
[b] TAXOL dose in mg/m^2/infusion duration in hours.
[c] All patients received premedication.
[†] Severe events are defined as at least Grade III toxicity.

Myelosuppression was dose and schedule related, with the schedule effect being more prominent. The development of severe hypersensitivity reactions (HSRs) was rare; 1% of the patients and 0.2% of the courses overall. There was no apparent dose or schedule effect seen for the HSRs. Peripheral neuropathy was clearly dose related, but schedule did not appear to affect the incidence.

Adjuvant Breast: For the Phase 3 adjuvant breast carcinoma study, the following table shows the incidence of important severe adverse events for the 3121 patients (total population) who were evaluable for safety as well as for a group of 325 patients (early population) who, per the study protocol, were monitored more intensively than other patients.

TABLE 13
FREQUENCY[a] OF IMPORTANT SEVERE[b] ADVERSE EVENTS IN THE PHASE 3 ADJUVANT BREAST CARCINOMA STUDY

	Percent of Patients			
	Early Population		Total Population	
	AC[c] (n=166)	AC[c] followed by T[d] (n=159)	AC[c] (n=1551)	AC[c] followed by T[d] (n=1570)
• ***Bone Marrow***[e]				
—Neutropenia <500/mm^3	79	76	48	50
—Thrombocytopenia <50,000/mm^3	27	25	11	11
—Anemia <8 g/dL	17	21	8	8
—Infections	6	14	5	6
—Fever Without Infection	—	3	<1	1
• ***Hypersensitivity Reaction***[f]	1	4	1	2
• ***Cardiovascular Events***	1	2	1	2
• ***Neuromotor Toxicity***	1	1	<1	1
• ***Neurosensory Toxicity***	—	3	<1	3
• ***Myalgia/Arthralgia***	—	2	<1	2
• ***Nausea/Vomiting***	13	18	8	9
• ***Mucositis***	13	4	6	5

[a] Based on worst course analysis.

[b] Severe events are defined as at least Grade III toxicity.

[c] Patients received 600 mg/m^2 cyclophosphamide and doxorubicin (AC) at doses of either 60 mg/m^2, 75 mg/m^2, or 90 mg/m^2 (with prophylactic G-CSF support and ciprofloxacin), every 3 weeks for 4 courses.

[d] TAXOL (T) following 4 courses of AC at a dose of 175 mg/m^2/3 hours every 3 weeks for 4 courses.

[e] The incidence of febrile neutropenia was not reported in this study.

[f] All patients were to receive premedication.

The incidence of an adverse event for the total population likely represents an underestimation of the actual incidence given that safety data were collected differently based on enrollment cohort. However, since safety data were collected consistently across regimens, the safety of the sequential addition of TAXOL (paclitaxel) following AC therapy may be compared with AC therapy alone. Compared to patients who received AC alone, patients who received AC followed by TAXOL experienced more Grade III/IV neurosensory toxicity, more Grade III/IV myalgia/arthralgia, more Grade III/IV neurologic pain (5% vs 1%), more Grade III/IV flu-like symptoms (5% vs 3%), and more Grade III/IV hyperglycemia (3% vs 1%). During the additional 4 courses of treatment with TAXOL, 2 deaths (0.1%) were attributed to treatment. During TAXOL treatment, Grade IV neutropenia was reported for 15% of patients, Grade II/III neurosensory toxicity for 15%, Grade II/III myalgias for 23%, and alopecia for 46%.

The incidences of severe hematologic toxicities, infections, mucositis, and cardiovascular events increased with higher doses of doxorubicin.

Breast Cancer After Failure of Initial Chemotherapy: For the 458 patients who received single-agent TAXOL in the Phase 3 breast carcinoma study, the following table shows the incidence of important adverse events by treatment arm (each arm was administered by a 3-hour infusion).

TABLE 14

FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 STUDY OF BREAST CANCER AFTER FAILURE OF INITIAL CHEMOTHERAPY OR WITHIN 6 MONTHS OF ADJUVANT CHEMOTHERAPY

		Percent of Patients	
		175/3[b] (n=229)	135/3[b] (n=229)
• ***Bone Marrow***			
—Neutropenia	<2000/mm^3	90	81
	<500/mm^3	28	19
—Thrombocytopenia	<100,000/mm^3	11	7
	<50,000/mm^3	3	2
—Anemia	<11 g/dL	55	47
	<8 g/dL	4	2
—Infections		23	15
—Febrile Neutropenia		2	2
• ***Hypersensitivity Reaction***[c]			
—All		36	31
—Severe[†]		0	<1
• ***Peripheral Neuropathy***			
—Any symptoms		70	46
—Severe symptoms[†]		7	3
• ***Mucositis***			
—Any symptoms		23	17
—Severe symptoms[†]		3	<1

[a] Based on worst course analysis.

[b] TAXOL dose in mg/m^2/infusion duration in hours.

[c] All patients received premedication.

[†] Severe events are defined as at least Grade III toxicity.

Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m^2.

First-Line NSCLC in Combination: In the study conducted by the Eastern Cooperative Oncology Group (ECOG), patients were randomized to either TAXOL (T) 135 mg/m^2 as a 24-hour infusion in combination with cisplatin (c) 75 mg/m^2, TAXOL (T) 250 mg/m^2 as a 24-hour infusion in combination with cisplatin (c) 75 mg/m^2 with G-CSF support, or cisplatin (c) 75 mg/m^2 on day 1, followed by etoposide (VP) 100 mg/m^2 on days 1, 2, and 3 (control).

The following table shows the incidence of important adverse events.

TABLE 15
FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 STUDY FOR FIRST-LINE NSCLC

		Percent of Patients		
		T135/24[b] c75 (n=195)	T250/24[c] c75 (n=197)	VP100[d] c75 (n=196)
• ***Bone Marrow***				
—Neutropenia	<2000/mm^3	89	86	84
	<500/mm^3	74[e]	65	55
—Thrombocytopenia	< normal	48	68	62
	<50,000/mm^3	6	12	16
—Anemia	< normal	94	96	95
	<8 g/dL	22	19	28
—Infections		38	31	35
• ***Hypersensitivity Reaction***[f]				
—All		16	27	13
—Severe[†]		1	4[e]	1
• ***Arthralgia/Myalgia***				
—Any symptoms		21[e]	42[e]	9
—Severe symptoms[†]		3	11	1
• ***Nausea/Vomiting***				
—Any symptoms		85	87	81
—Severe symptoms[†]		27	29	22
• ***Mucositis***				
—Any symptoms		18	28	16
—Severe symptoms[†]		1	4	2
• ***Neuromotor Toxicity***				
—Any symptoms		37	47	44
—Severe symptoms[†]		6	12	7
• ***Neurosensory Toxicity***				
—Any symptoms		48	61	25
—Severe symptoms[†]		13	28[e]	8
• ***Cardiovascular Events***				
—Any symptoms		33	39	24
—Severe symptoms[†]		13	12	8

[a] Based on worst course analysis.
[b] TAXOL (T) dose in mg/m^2/infusion duration in hours; cisplatin (c) dose in mg/m^2.
[c] TAXOL dose in mg/m^2/infusion duration in hours with G-CSF support; cisplatin dose in mg/m^2.
[d] Etoposide (VP) dose in mg/m^2 was administered IV on days 1, 2, and 3; cisplatin dose in mg/m^2.
[e] $p<0.05$.
[f] All patients received premedication.
[†] Severe events are defined as at least Grade III toxicity.

Toxicity was generally more severe in the high-dose TAXOL treatment arm (T250/c75) than in the low-dose TAXOL arm (T135/c75). Compared to the cisplatin/etoposide arm, patients in the low-dose TAXOL arm experienced more arthralgia/myalgia of any grade

and more severe neutropenia. The incidence of febrile neutropenia was not reported in this study.

Kaposi's Sarcoma: The following table shows the frequency of important adverse events in the 85 patients with KS treated with 2 different single-agent TAXOL (paclitaxel) regimens.

TABLE 16

FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE AIDS-RELATED KAPOSI'S SARCOMA STUDIES

		Percent of Patients	
		Study CA139-174 TAXOL 135/3[b] q 3 wk (n=29)	Study CA139-281 TAXOL 100/3[b] q 2 wk (n=56)
• ***Bone Marrow***			
—Neutropenia	<2000/mm^3	100	95
	<500/mm^3	76	35
—Thrombocytopenia	<100,000/mm^3	52	27
	<50,000/mm^3	17	5
—Anemia	<11 g/dL	86	73
	<8 g/dL	34	25
—Febrile Neutropenia		55	9
• ***Opportunistic Infection***			
—Any		76	54
—Cytomegalovirus		45	27
—Herpes Simplex		38	11
—*Pneumocystis carinii*		14	21
—*M. avium intracellulare*		24	4
—Candidiasis, esophageal		7	9
—Cryptosporidiosis		7	7
—Cryptococcal meningitis		3	2
—Leukoencephalopathy		—	2
• ***Hypersensitivity Reaction***[c]			
—All		14	9
• ***Cardiovascular***			
—Hypotension		17	9
—Bradycardia		3	—
• ***Peripheral Neuropathy***			
—Any		79	46
—Severe[†]		10	2
• ***Myalgia/Arthralgia***			
—Any		93	48
—Severe[†]		14	16
• ***Gastrointestinal***			
—Nausea and Vomiting		69	70
—Diarrhea		90	73
—Mucositis		45	20
• ***Renal (creatinine elevation)***			
—Any		34	18
—Severe[†]		7	5
• ***Discontinuation for drug toxicity***		7	16

[a] Based on worst course analysis.

[b] TAXOL dose in mg/m^2/infusion duration in hours.

[c] All patients received premedication.

[†] Severe events are defined as at least Grade III toxicity.

As demonstrated in this table, toxicity was more pronounced in the study utilizing TAXOL (paclitaxel) at a dose of 135 mg/m^2 every 3 weeks than in the study utilizing

TAXOL at a dose of 100 mg/m^2 every 2 weeks. Notably, severe neutropenia (76% vs 35%), febrile neutropenia (55% vs 9%), and opportunistic infections (76% vs 54%) were more common with the former dose and schedule. The differences between the 2 studies with respect to dose escalation and use of hematopoietic growth factors, as described above, should be taken into account. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma**.) Note also that only 26% of the 85 patients in these studies received concomitant treatment with protease inhibitors, whose effect on paclitaxel metabolism has not yet been studied.

Adverse Event Experiences by Body System

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent TAXOL in clinical studies. Toxicities that occurred with greater severity or frequency in previously untreated patients with ovarian carcinoma or NSCLC who received TAXOL in combination with cisplatin or in patients with breast cancer who received TAXOL after doxorubicin/cyclophosphamide in the adjuvant setting and that occurred with a difference that was clinically significant in these populations are also described. The frequency and severity of important adverse events for the Phase 3 ovarian carcinoma, breast carcinoma, NSCLC, and the Phase 2 Kaposi's sarcoma studies are presented above in tabular form by treatment arm. In addition, rare events have been reported from postmarketing experience or from other clinical studies. The frequency and severity of adverse events have been generally similar for patients receiving TAXOL for the treatment of ovarian, breast, or lung carcinoma or Kaposi's sarcoma, but patients with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections (including opportunistic infections, see **TABLE 16**), and febrile neutropenia. These patients require a lower dose intensity and supportive care. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma**.) Toxicities that were observed only in or were noted to have occurred with greater severity in the population with Kaposi's sarcoma and that occurred with a difference that was clinically significant in this population are described. Elevated liver function tests and renal toxicity have a higher incidence in KS patients as compared to patients with solid tumors.

Hematologic: Bone marrow suppression was the major dose-limiting toxicity of TAXOL. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in the Phase 3 second-line ovarian study with a 3-hour infusion, neutrophil counts declined below 500 cells/mm^3 in 14% of the patients treated with a dose of 135 mg/m^2 compared to 27%

at a dose of 175 mg/m^2 (p=0.05). In the same study, severe neutropenia (<500 cells/mm^3) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

In the study where TAXOL was administered to patients with ovarian carcinoma at a dose of 135 mg/m^2/24 hours in combination with cisplatin versus the control arm of cyclophosphamide plus cisplatin, the incidences of grade IV neutropenia and of febrile neutropenia were significantly greater in the TAXOL plus cisplatin arm than in the control arm. Grade IV neutropenia occurred in 81% on the TAXOL plus cisplatin arm versus 58% on the cyclophosphamide plus cisplatin arm, and febrile neutropenia occurred in 15% and 4% respectively. On the TAXOL/cisplatin arm, there were 35/1074 (3%) courses with fever in which Grade IV neutropenia was reported at some time during the course. When TAXOL followed by cisplatin was administered to patients with advanced NSCLC in the ECOG study, the incidences of Grade IV neutropenia were 74% (TAXOL 135 mg/m^2/24 hours followed by cisplatin) and 65% (TAXOL 250 mg/m^2/24 hours followed by cisplatin and G-CSF) compared with 55% in patients who received cisplatin/etoposide.

Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all patients and 9% of all courses; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. In the Phase 3 second-line ovarian study, infectious episodes were reported in 20% and 26% of the patients treated with a dose of 135 mg/m^2 or 175 mg/m^2 given as 3-hour infusions, respectively. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. In the immunosuppressed patient population with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, 61% of the patients reported at least one opportunistic infection. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma**.) The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia. (See **DOSAGE AND ADMINISTRATION**.)

Thrombocytopenia was reported. Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm^3 at least once while on treatment; 7% had a platelet count <50,000 cells/mm^3 at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients, but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the TAXOL dose and schedule. In the Phase 3 second-line ovarian study, bleeding episodes were