

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)

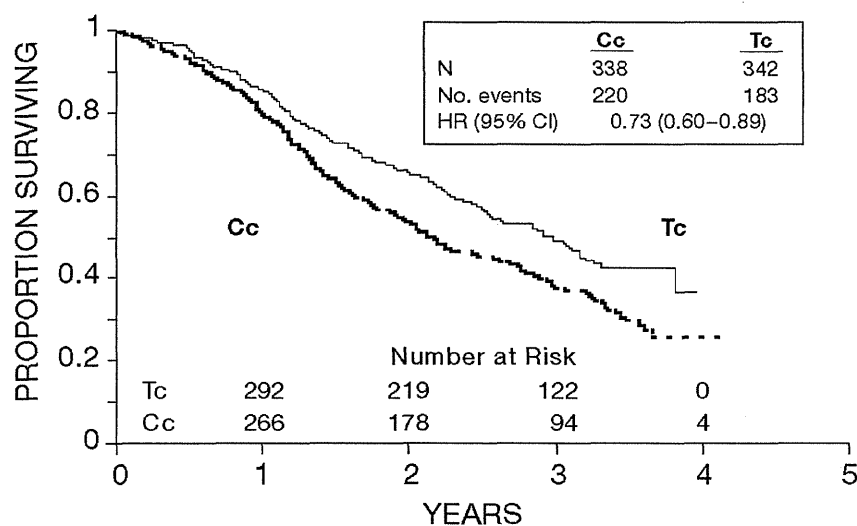
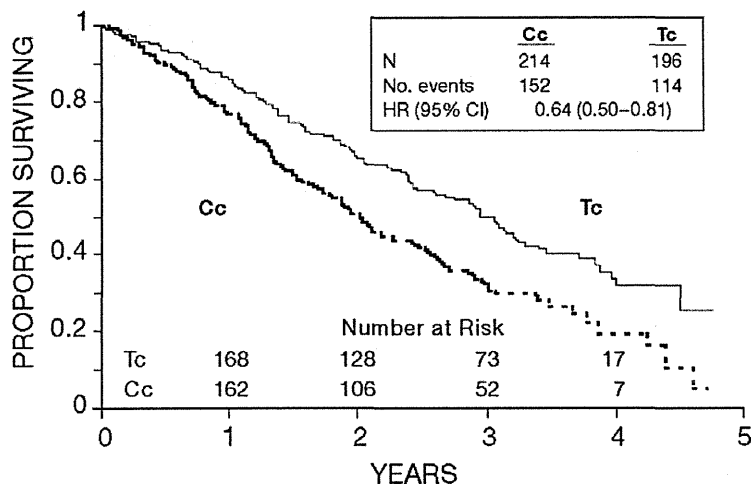


FIGURE 2
SURVIVAL: Cc VERSUS Tc (GOG-111)



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

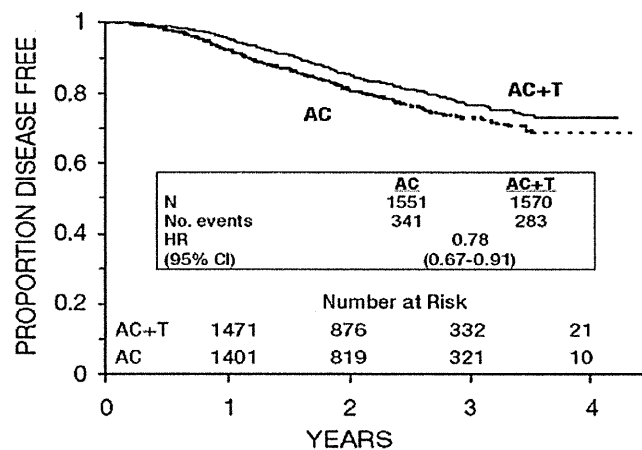
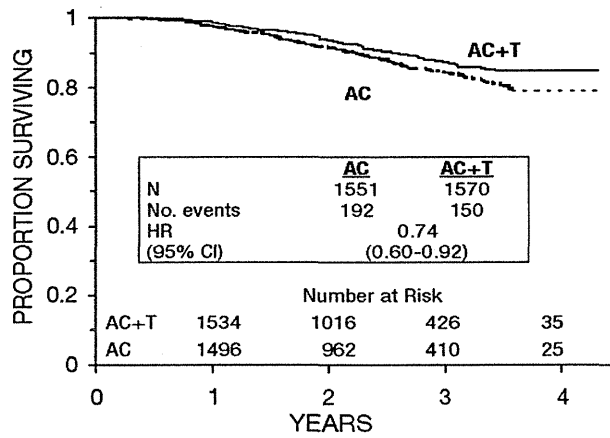


FIGURE 4
SURVIVAL: AC VERSUS AC+T



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**.

TABLE 4
SUBSET ANALYSES—ADJUVANT BREAST CARCINOMA STUDY

| Patient Subset | No. of Patients | Disease-Free Survival | | Overall Survival | |
|--------------------------------|-----------------|-----------------------|-----------------------|------------------|-----------------------|
| | | No. of Recurrences | Hazard Ratio (95% CI) | No. of Deaths | Hazard Ratio (95% CI) |
| • No. of Positive Nodes | | | | | |
| 1–3 | 1449 | 221 | 0.72 (0.55–0.94) | 107 | 0.76 (0.52–1.12) |
| 4–9 | 1310 | 274 | 0.78 (0.61–0.99) | 148 | 0.66 (0.47–0.91) |
| 10+ | 360 | 129 | 0.93 (0.66–1.31) | 87 | 0.90 (0.59–1.36) |
| • Tumor Size (cm) | | | | | |
| ≤2 | 1096 | 153 | 0.79 (0.57–1.08) | 67 | 0.73 (0.45–1.18) |
| >2 and ≤5 | 1611 | 358 | 0.79 (0.64–0.97) | 201 | 0.74 (0.56–0.98) |
| >5 | 397 | 111 | 0.75 (0.51–1.08) | 72 | 0.73 (0.46–1.16) |
| • Menopausal Status | | | | | |
| Pre | 1929 | 374 | 0.83 (0.67–1.01) | 187 | 0.72 (0.54–0.97) |
| Post | 1183 | 250 | 0.73 (0.57–0.93) | 155 | 0.77 (0.56–1.06) |
| • Receptor Status | | | | | |
| Positive ^a | 2066 | 293 | 0.92 (0.73–1.16) | 126 | 0.83 (0.59–1.18) |
| Negative/Unknown ^b | 1055 | 331 | 0.68 (0.55–0.85) | 216 | 0.71 (0.54–0.93) |

^a Positive for either estrogen or progesterone receptors.

^b Negative or missing for both estrogen and progesterone receptors (both missing: n=15).

These retrospective subgroup analyses suggest that the beneficial effect of TAXOL (paclitaxel) is clearly established in the receptor-negative subgroup, but the benefit in receptor-positive patients is not yet clear. With respect to menopausal status, the benefit of TAXOL is consistent (see TABLE 4 and FIGURES 5–8).

FIGURE 5
DISEASE-FREE SURVIVAL—RECEPTOR STATUS NEGATIVE/UNKNOWN
AC VERSUS AC+T

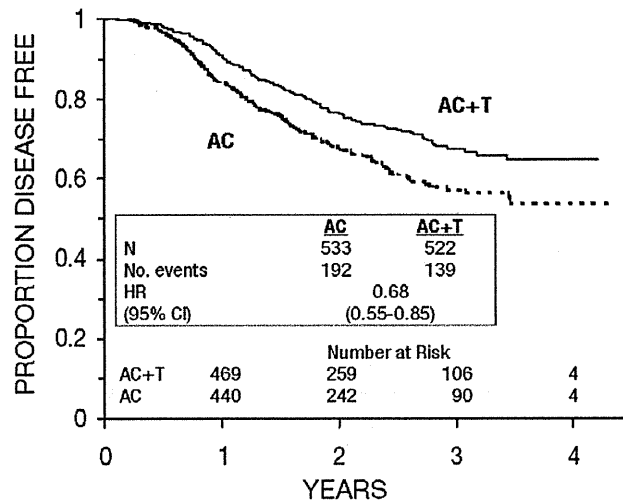


FIGURE 6
DISEASE-FREE SURVIVAL—RECEPTOR STATUS POSITIVE
AC VERSUS AC+T

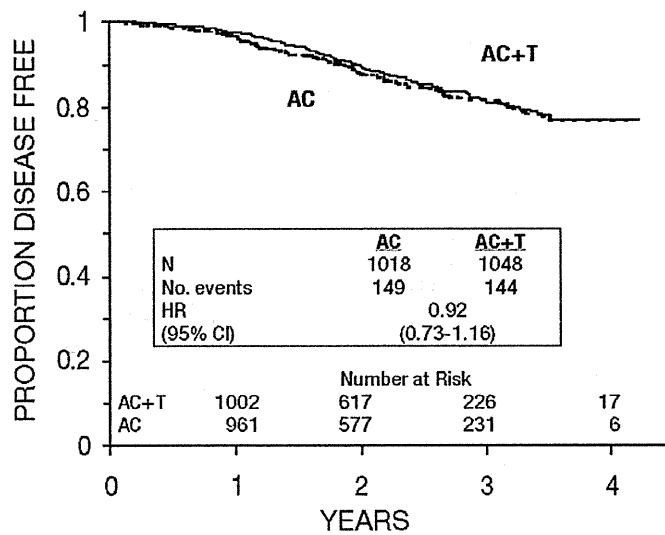


FIGURE 7
DISEASE-FREE SURVIVAL—PREMENOPAUSAL
AC VERSUS AC+T

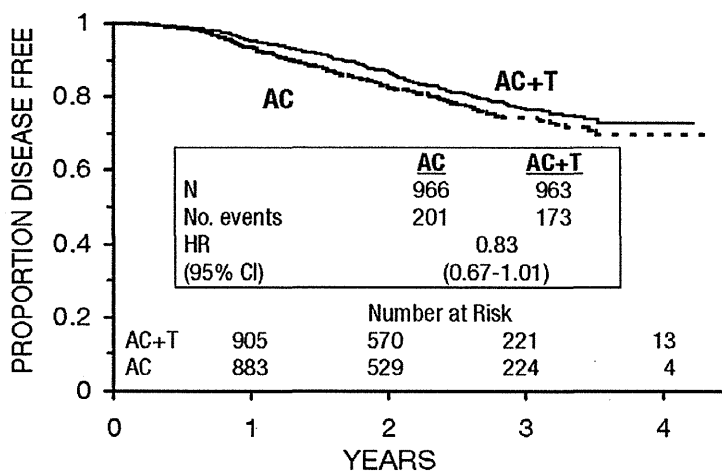
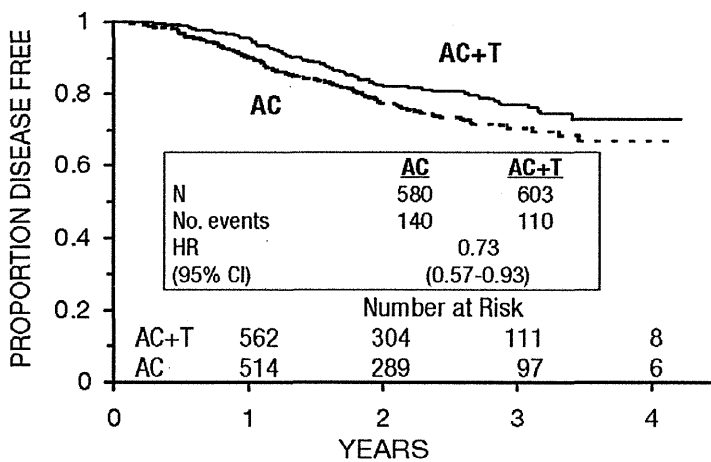


FIGURE 8
DISEASE-FREE SURVIVAL—POSTMENOPAUSAL
AC VERSUS AC+T



The adverse event profile for the patients who received TAXOL subsequent to AC was consistent with that seen in the pooled analysis of data from 812 patients (TABLE 10) treated with single-agent TAXOL in 10 clinical studies. These adverse events are described in the **ADVERSE REACTIONS** section in tabular (TABLES 10 and 13) and narrative form.

After Failure of Initial Chemotherapy

Data from 83 patients accrued in 3, Phase 2 open-label studies and from 471 patients enrolled in a Phase 3 randomized study were available to support the use of TAXOL in patients with metastatic breast carcinoma.

Phase 2 open-label studies: Two studies were conducted in 53 patients previously treated with a maximum of 1 prior chemotherapeutic regimen. TAXOL was administered in these 2 trials as a 24-hour infusion at initial doses of 250 mg/m² (with G-CSF support) or 200 mg/m². The response rates were 57% (95% CI, 37–75%) and 52% (95% CI, 32–72%), respectively. The third Phase 2 study was conducted in extensively pretreated patients who had failed anthracycline therapy and who had received a minimum of 2 chemotherapy regimens for the treatment of metastatic disease. The dose of TAXOL was 200 mg/m² as a 24-hour infusion with G-CSF support. Nine of 30 patients achieved a partial response, for a response rate of 30% (95% CI, 15–50%).

Phase 3 randomized study: This multicenter trial was conducted in patients previously treated with 1 or 2 regimens of chemotherapy. Patients were randomized to receive TAXOL (paclitaxel) at a dose of either 175 mg/m² or 135 mg/m² given as a 3-hour infusion. In the 471 patients enrolled, 60% had symptomatic disease with impaired performance status at study entry, and 73% had visceral metastases. These patients had failed prior chemotherapy either in the adjuvant setting (30%), the metastatic setting (39%), or both (31%). Sixty-seven percent of the patients had been previously exposed to anthracyclines and 23% of them had disease considered resistant to this class of agents.

The overall response rate for the 454 evaluable patients was 26% (95% CI, 22–30%), with 17 complete and 99 partial responses. The median duration of response, measured from the first day of treatment, was 8.1 months (range, 3.4–18.1+ months). Overall for the 471 patients, the median time to progression was 3.5 months (range, 0.03–17.1 months). Median survival was 11.7 months (range, 0–18.9 months).

Response rates, median survival and median time to progression for the 2 arms are given in the following table.

TABLE 5
EFFICACY IN BREAST CANCER AFTER FAILURE OF INITIAL
CHEMOTHERAPY OR WITHIN 6 MONTHS OF ADJUVANT CHEMOTHERAPY

| | 175/3 (n=235) | | 135/3 (n=236) |
|------------------------------|------------------|-------|------------------|
| • Response | | | |
| —rate (percent) | 28 | | 22 |
| —p-value | | 0.135 | |
| • Time to Progression | | | |
| —median (months) | 4.2 | | 3.0 |
| —p-value | | 0.027 | |
| • Survival | | | |
| —median (months) | 11.7 | | 10.5 |
| —p-value | | 0.321 | |

The adverse event profile of the patients who received single-agent TAXOL in the 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 breast carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (**TABLES 10** and **14**) and narrative form.

Non-Small Cell Lung Carcinoma (NSCLC)

In a Phase 3 open-label randomized study conducted by the ECOG, 599 patients were randomized to either TAXOL (T) 135 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m², TAXOL (T) 250 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m² with G-CSF support, or cisplatin (c) 75 mg/m² on day 1, followed by etoposide (VP) 100 mg/m² on days 1, 2, and 3 (control).

Response rates, median time to progression, median survival, and 1-year survival rates are given in the following table. The reported p-values have not been adjusted for multiple comparisons. There were statistically significant differences favoring each of the TAXOL plus cisplatin arms for response rate and time to tumor progression. There was no statistically significant difference in survival between either TAXOL plus cisplatin arm and the cisplatin plus etoposide arm.

TABLE 6
EFFICACY PARAMETERS IN THE PHASE 3 FIRST-LINE NSCLC STUDY

| | T135/24 c75 (n=198) | T250/24 c75 (n=201) | VP100 ^a c75 (n=200) |
|------------------------------|---------------------------|---------------------------|--------------------------------------|
| • Response | | | |
| —rate (percent) | 25 | 23 | 12 |
| —p-value ^b | 0.001 | <0.001 | |
| • Time to Progression | | | |
| —median (months) | 4.3 | 4.9 | 2.7 |
| —p-value ^b | 0.05 | 0.004 | |
| • Survival | | | |
| —median (months) | 9.3 | 10.0 | 7.4 |
| —p-value ^b | 0.12 | 0.08 | |
| • 1-Year Survival | | | |
| —percent of patients | 36 | 40 | 32 |

^a Etoposide (VP) 100 mg/m² was administered IV on days 1, 2, and 3.

^b Compared to cisplatin/etoposide.

In the ECOG study, the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire had 7 subscales that measured subjective assessment of treatment. Of the 7, the Lung Cancer Specific Symptoms subscale favored the TAXOL 135 mg/m²/24 hour plus cisplatin arm compared to the cisplatin/etoposide arm. For all other factors, there was no difference in the treatment groups.

The adverse event profile for patients who received TAXOL in combination with cisplatin in this study was generally 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 NSCLC study are described in the **ADVERSE REACTIONS** section in tabular (**TABLES 10 and 15**) and narrative form.

AIDS-Related Kaposi's Sarcoma

Data from 2, Phase 2 open-label studies support the use of TAXOL (paclitaxel) as second-line therapy in patients with AIDS-related Kaposi's sarcoma. Fifty-nine of the 85 patients enrolled in these studies had previously received systemic therapy, including interferon alpha (32%), DaunoXome[®] (31%), DOXIL[®] (2%), and doxorubicin containing chemotherapy (42%), with 64% having received prior anthracyclines.

DaunoXome[®] is a registered trademark of Gilead Sciences, Inc.

DOXIL[®] is a registered trademark of ALZA Corporation.

Eighty-five percent of the pretreated patients had progressed on, or could not tolerate, prior systemic therapy.

In Study CA139-174, patients received TAXOL at 135 mg/m² as a 3-hour infusion every 3 weeks (intended dose intensity 45 mg/m²/week). If no dose-limiting toxicity was observed, patients were to receive 155 mg/m² and 175 mg/m² in subsequent courses. Hematopoietic growth factors were not to be used initially. In Study CA139-281, patients received TAXOL at 100 mg/m² as a 3-hour infusion every 2 weeks (intended dose intensity 50 mg/m²/week). In this study patients could be receiving hematopoietic growth factors before the start of TAXOL therapy, or this support was to be initiated as indicated; the dose of TAXOL was not increased. The dose intensity of TAXOL used in this patient population was lower than the dose intensity recommended for other solid tumors.

All patients had widespread and poor-risk disease. Applying the ACTG staging criteria to patients with prior systemic therapy, 93% were poor risk for extent of disease (T₁), 88% had a CD4 count <200 cells/mm³ (I₁), and 97% had poor risk considering their systemic illness (S₁).

All patients in Study CA139-174 had a Karnofsky performance status of 80 or 90 at baseline; in Study CA139-281, there were 26 (46%) patients with a Karnofsky performance status of 70 or worse at baseline.

TABLE 7
EXTENT OF DISEASE AT STUDY ENTRY
Percent of Patients

| | Prior Systemic Therapy (n=59) |
|---|----------------------------------|
| Visceral ± edema ± oral ± cutaneous | 42 |
| Edema or lymph nodes ± oral ± cutaneous | 41 |
| Oral ± cutaneous | 10 |
| Cutaneous only | 7 |

Although the planned dose intensity in the 2 studies was slightly different (45 mg/m²/week in Study CA139-174 and 50 mg/m²/week in Study CA139-281), delivered dose intensity was 38 to 39 mg/m²/week in both studies, with a similar range (20–24 to 51–61).

Efficacy: The efficacy of TAXOL was evaluated by assessing cutaneous tumor response according to the amended ACTG criteria and by seeking evidence of clinical benefit in

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/mm³ or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm³.

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 H₂ 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/mm³ (<1000 cells/mm³ 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/mm³ (>1000 cells/mm³ for patients with KS) and platelets recover to a level >100,000 cells/mm³.

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/m² 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/m² 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/m²) and cisplatin (50 or 75 mg/m²) 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.

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Hematology: TAXOL therapy should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm³. 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/mm³ and platelets recover to a level >100,000 cells/mm³. In the case of severe neutropenia (<500 cells/mm³ 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/mm³.

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 H₂ 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/m² 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/m² to 420 mg/m². 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.