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STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER

HEMATOLOGIC MALIGNANCIES, PART I

Hematologic malignancies comprise a variety of cancers of the hematopoietic and lymphatic systems, some rather common and others relatively rare. Each major type of hematologic cancer, i.e. leukemia, lymphoma and multiple myeloma, will be discussed separately in-depth in terms of worldwide epidemiology, putative mechanisms of malignancy, diagnosis and treatment status and drug development programs, in upcoming issues of FUTURE ONCOLOGY. This introduction estimates overall incidence and mortality of hematologic cancer in the USA in 1995 (see Exhibit 1) and mortality in selected world regions (see Exhibit 2).

MEETING COVERAGE

REPORT FROM THE EIGHTH EUROPEAN CANCER CONFERENCE (ECCO 8) OCTOBER 29 TO NOVEMBER 2, 1995, PARIS, FRANCE

Note: All references are from The European Journal of Cancer, November 1995, Volume 31A, Supplement 5.

TAXANES IN THE TREATMENT OF CANCER

Docetaxel

Breast cancer. In a phase II clinical trial, 51 women with anthracycline-resistant metastatic breast cancer were treated with docetaxel at 100 mg/m^2 as a one-hour IV infusion every three weeks. Oral steroids and antihistamines were given prior to docetaxel administration to minimize possible drug-induced adverse effects. In this group of women, five previously had a metastatic relapse while on adjuvant therapy, 25 had progression of disease as their best first-line therapeutic response, 16 progressed while on anthracyclines, and two were completely resistant to anthracyclines at the initiation of treatment. In 38 evaluable patients, the overall response rate was 32%, with 12 patients showing a partial response (PR). Among responders, 42% were previously anthracycline-resistant. In addition, the response rate was 44% in patients with metastases to three or more organs, a very high rate for patients so difficult to treat with chemotherapy (Guastella JP, etal, Pg S75-S76: #348).

Administration of prophylactic steroids significantly reduces incidence of docetaxel-induced edema and pleural effusion, without having any effect on the highly active chemotherapeutic action of the drug. In a phase II clinical trial, 83 women who were previously treated with one chemotherapeutic regimen for advanced metastatic breast cancer were randomly assigned to receive prophylactic antihistamines with or without methylprednisolone (40 mg on treatment days -1, 0, +1, 7, 8, and 9). All patients received docetaxel 50 mg/m^2 on days one and eight in a one hour IV infusion, for a total dose of 100 mg/m^2 every three weeks. A 35% response rate was experienced by both treatment groups, and disease stabilized in 45% of the women. In addition, there was no difference in the interval to disease progression or overall survival in the two study arms. Patients treated with steroids were, however, less likely to develop fluid retention (5% versus 32%) and took longer to develop edema (116 days versus 84 days) and pleural effusions (120 days versus 77 days) (Piccart MJ, etal, Pg S75:#347).

In a phase I study, the combination of docetaxel and doxorubicin (an anthracycline well known for its activity as first-line treatment of advanced breast cancer) demonstrated significant activity with predictable and manageable side effects. Thirty five women were enrolled in the study, 13 chemotherapy-naive, 20 who had been treated with anthracyclines previously, and two who had received adjuvant nonanthracycline-based therapy. Although maximum tolerated dose (MTD) was not reached, combined doses of IV doxorubicin (50 mg/m^2) and docetaxel (60 mg/m^2 or 75 mg/m^2), given as a one hour infusion every three weeks, were active. At these doses, 12 of 14 women with measurable disease showed an objective response, with one complete response (CR) and 11 PRs. The other two women had stable disease. There were no grade 3 or 4 adverse events observed with the exception of neutropenia. Fluid retention was mild and there were no adverse cardiac effects (Dieras V, etal, Pg S194:#935).

Combination of docetaxel with vinorelbine, a semisynthetic vinca alkaloid, has also shown both good activity and an acceptable safety profile in women with metastatic breast cancer who had failed anthracycline-based chemotherapy. In a phase I study, 28 patients with advanced metastatic breast cancer, 23 of whom had received prior chemotherapy (in 22 the therapy was anthracycline-based), were treated with docetaxel (60 mg/m^2 to 100 mg/m^2) as a one hour IV infusion, preceded by a 20-minute bolus administration of vinorelbine (20 mg/m^2), every three weeks. All patients were premedicated with corticosteroids and a "capillary protector" to minimize chemotherapy-induced side effects. Of 25 evaluable patients, 10 had measurable metastatic disease; of

Exhibit 1
Estimated Incidence and Mortality Associated with Hematologic Malignancies in the USA (1995)

Type of Cancer	Male (#)	Rate*	Female (#)	Rate*	Total (#)	Rate*
			Incidence			
Leukemia	14,700	11.4	11,000	8.2	25,700	9.8
Lymphocytic	6,700	5.2	4,300	3.2	11,000	4.2
ALL	2,316	1.8	1,617	1.2	3,933	1.5
CLL	4,247	3.3	2,156	1.6	6,403	2.4
Granulocytic	5,900	4.6	5,200	3.9	11,100	4.2
AML	3,603	2.8	2,425	1.8	6,029	2.3
CML	2,059	1.6	1,213	0.9	3,272	1.2
Other & Unspecified	2,100	1.6	1,500	1.1	3,600	1.4
Lymphoma & Other Hematologic Malignancies	41,100	31.9	30,100	22.3	71,200	27.1
Hodgkin's Disease	4,500	3.5	3,300	2.4	7,800	3.0
Non-Hodgkin's Lymphoma	29,500	22.9	21,400	15.9	50,900	19.3
Multiple Myeloma	7,100	5.5	5,400	4.0	12,500	4.8
TOTAL	55,800		41,100		96,900	
			Deaths			
Leukemia	11,100	8.6	9,300		20,400	7.8
Lymphocytic	3,500	2.7	2,900	2.2	6,400	2.4
Granulocytic	4,600	3.6	3,800	2.8	8,400	3.2
Other & Unspecified	3,000	2.3	2,600	1.9	5,600	2.1
Lymphoma & Other Hematologic Malignancies	18,120	14.1	16,330	12.1	34,450	13.1
Hodgkin's Disease	820	0.6	630	0.5	1,450	0.6
Non-Hodgkin's Lymphoma	12,000	9.3	10,700	7.9	22,700	8.6
Multiple Myeloma	5,300	4.1	5,000	3.7	10,300	3.9
TOTAL	29,220		25,630		54,850	

**Per 100,000 population*
Source: The American Cancer Society and New Medicine

these, six women experienced PRs and four showed no change. Promising responses were observed at all dose levels, with a 50% decrease in tumor size and a similar response in non-measurable tumors after only three or four cycles of chemotherapy. Further investigation of this combination is ongoing (Fumoleau P, etal, Pg S195:#938).

Non-small cell lung cancer. Combination of docetaxel and cisplatin results in significant activity in patients with metastatic or locally advanced non-small cell lung cancer (nsclc), although it does not appear to be substantially better than docetaxel alone. In a phase II trial, 47 eligible patients with metastatic or locally advanced nsclc were treated with docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) administered as one-hour IV infusion, every three weeks. Patients also received hydration, antiemetics and steroids. In 36 evaluable patients (those completing at least two cycles of chemotherapy), the overall response rate was 33%, with 12 PRs. In addition, disease stabilized in 45% of patients and progressed in 22%. Of the 12 PRs, six were confirmed by subsequent CT scans. Significant toxicities were observed, with grade 4 toxicities including febrile neutropenia (3 patients), neutropenia (31), and diarrhea (5). Ten patients experienced grade 3 or 4 nausea and vomiting (Zaleberg JR, etal, Pg S226: #1084).

Head and neck cancer. Docetaxel also has demonstrated significant activity as a single agent in the treatment of advanced head and neck cancer. Thirty-one patients with metastatic or recurrent head and neck cancer, 10 of whom had undergone prior chemotherapy, were premedicated with corticosteroids and antihistamines and treated with docetaxel (100 mg/m^2) as a one-hour IV infusion every three weeks. In 30 evaluable persons, the overall objective response rate was 47%,

Exhibit 2
Estimated Mortality Associated with Hematologic Malignancies in Selected World Regions (1995)

Region	Hematologic Cancer (#)	Rate	Leukemia (#)	Rate	Lymphoma & Others (#)	Rate
Total Europe	71,054	14.1	33,707	6.7	37,347	7.4
Western Europe-EEC	51,922	14.9	23,775	6.8	28,147	8.1
Western Europe-non EEC	6,132	18.2	2,389	7.1	3,743	11.1
Eastern Europe (excluding the former USSR)	12,999	10.7	7,542	6.2	5,457	4.5
Japan	13,552	11.0	5,666	4.6	7,886	6.4
North America	60,240	20.9	22,440	7.8	37,800	13.1
United States	54,850	20.8	20,400	7.8	34,450	13.1
Canada	5,390	21.3	2,040	8.1	3,350	13.2
TOTAL	144,846		61,813		83,033	

Source: Health and Welfare Statistics in Japan, Health and Welfare Statistics Association (1994); Centers of Disease Control and Prevention; The American Cancer Society; Canadian Cancer Statistics and New Medicine

with four CRs and 10 PRs. The median duration of response was five months. Side effects were predictable and manageable. The most frequently observed side effect was neutropenia, occasionally requiring a dose reduction. Hematopoietic growth factors might substantially mitigate this side effect (Posner M, etal, Pg S91:#421).

Other solid tumors. In a phase I study, docetaxel in combination with ifosfamide produced promising results in advanced solid tumors such as soft tissue sarcoma and malignant melanoma. Eighteen patients with a variety of advanced solid tumors (adrenal, colon, head and neck, hepatocellular and cervical tumors and leiomyosarcoma, melanoma, mesothelioma and nsclc) were treated with an dose-escalating regimen of docetaxel starting at 60 mg/m^2 as a one-hour IV infusion on day one, followed by ifosfamide (2.5 g/m^2) as a 24-hour IV infusion. All patients were pretreated with oral steroids, antiemetics, hydration, and mensa. To date, five different dose levels of docetaxel and ifosfamide were administered, 60 mg/m^2 and 2.5 g/m^2 (I); 75 mg/m^2 and 2.5 g/m^2 (II); 75 mg/m^2 and 3.0 g/m^2 (III); 75 mg/m^2 and 4.0 g/m^2 (IV); and 75 mg/m^2 and 5.0 g/m^2 (V). The dose limiting toxicity of these combinations was not reached. One patient with malignant melanoma experienced a PR at dose level III and one person with soft tissue sarcoma had a histologically proven CR at dose level II. Grade 3-4 neutropenia was common (87.1%), with 17.1% of patients experiencing neutropenic fever. With regard to non-hematologic toxicities, all individuals developed alopecia, two persons had an allergic reaction despite pretreatment, and two patients reported grade 1 or 2 asthenia. No edema was reported (Pronk L, etal, Pg S200: #961).

Paclitaxel

Ovarian cancer. A large phase II clinical trial confirmed the efficacy and tolerability of paclitaxel for the treatment of platinum-refractory advanced ovarian cancer. In this study, 306 women with advanced ovarian cancer that had relapsed after at least one platinum-based regimen were treated with paclitaxel. Those pretreated with one to two prior chemotherapy regimens (Group A) were treated with a dose of 175 mg/m^2; those pretreated with three or more chemotherapy regimens were administered a dose of 135 mg/m^2, as a three-hour IV infusion every three weeks after standard premedication with steroids, antihistamines, and H_2 blockers. Median number of cycles per patient was six. Among 295 evaluable patients, the overall objective response rate was 28.8%, with 28 CRs (9.5%) and 57 PRs (19.3%). Another 119 persons (40.3%) had stable disease, and disease progressed in the remaining patients. The main toxicity was neutropenia without severe clinical manifestations, while non-hematologic toxicities such as arthralgia, peripheral neuropathy, and hypersensitivity reaction were minimal. Three-quarters of the patients experienced grade 3 or 4 alopecia (Klaassen U, etal, Pg S105: #492).

Alternating paclitaxel and carboplatin appears to be a highly effective and well tolerated treatment for advanced ovarian cancer. In a phase II study, 30 patients with advanced ovarian cancer received as first-line treatment, five cycles of paclitaxel (175 mg/m^2) in a three-hour IV infusion on day one and carboplatin AUC (7 mg/ml/min) on day 21, with a cycle time of 49 days. Among 22 evaluable patients, overall objective response was 72%, (36% CR and 36% PR). Actuarial survival rate at 18 months was 74%. The regimen was well tolerated. Thrombocytopenia with paclitaxel was uncommon (2%) and neutropenia generally was of short duration. Non-hematologic toxicities included grade 3 alopecia (100%), myalgia (60%), arthralgia (40%), parasthesia (25%), and nausea and vomiting (21%), the majority of which were grade one or two (Adams M, etal, Pg S106: #496).

Breast cancer. Paclitaxel appears to be effective and well tolerated as first-line therapy in advanced metastatic breast cancer. In a phase II clinical trial, 121 women with metastatic breast cancer (62 who had undergone prior adjuvant or neoadjuvant therapy, 58 who had no prior chemotherapy, and one who had no prior treatment of any kind), were treated with paclitaxel (225 mg/m^2) as a three-hour IV infusion, every three-weeks. Patients were premedicated with prednisolone, dexchorpheniramine, and cimetidine to reduce drug-induced adverse effects. In 101 evaluable patients, the overall response rate was 44%, with six CRs and 37 PRs. The response rate in women with prior adjuvant therapy was 45% and in those with no prior chemotherapy 42%. The response rates in 44 patients with prior anthracycline treatment was 44%. The most common dose-limiting adverse effect was neutropenia, but only seven cycles out of 745 were delayed for this reason. No colony stimulating factors (CSFs) were administered. While a quarter of the patients had mild hypersensitivity reactions, no major reactions occurred. Alopecia was seen in 95% of cases. All other non-hematologic toxicities were mild to moderate and manageable (Bonneterre J, etal, Pg S77: #354).

Paclitaxel, administered as a 225 mg/m^2 dose without CSFs, was safe and efficacious as second line therapy in patients with metastatic breast cancer. In a phase II trial, 86 women were administered paclitaxel as a three-hour IV infusion every three weeks. Twenty-four patients were previously treated with adjuvant chemotherapy (group A) and 26 with chemotherapy (group B). Among 46 evaluable patients, the overall response rate was 28% (15% in group A and 38% in group B), with two CRs and 11 PRs; disease stabilized in 22 patients and progressed in 11. The only dose-limiting toxicity was grade 3/4 neutropenia, with febrile neutropenia reported in 3% of cycles and grade 3 anemia in 5% of cycles (Bougnoux PH, etal, Pg S82:#378).

Non-small cell lung cancer. In a phase II trial, 61 patients were administered paclitaxel as a three-hour continuous IV infusion at an initial dose of 210 mg/m^2, every three weeks. Patients were premedicated with dexamethasone, diphenhydramine, and ranitidine to alleviate possible drug-induced adverse effects. The median number of cycles administered was three. In 60 evaluable patients overall objective response rate was 31.7%, with one CR and 18 PRs. In addition, disease stabilized in 28 patients. Median duration of survival was 208.5 days (20-469+ days), with an estimated one-year survival rate of 22%. Most common toxicities were hematologic, including leukopenia and neutropenia; 73.3% of patients experienced grade 3 or 4 neutropenia. Hypersensitivity reactions, peripheral neuropathy and cardiac and pulmonary toxicities were manageable with appropriate supportive care (Furuse K, etal, S224: #1072).

Adjuvants

Amifostine (Ethyol, U.S. Bioscience), a selective cytoprotective agent that protects marrow and peripheral nervous system toxicity from alkylating agents and platinum analogs, may also be useful against paclitaxel toxicity. In an ongoing phase I trial, nine patients with a variety of advanced cancers were treated with amifostine (910 mg/m^2) as a 15-minute IV infusion 30 minutes before receiving paclitaxel. Following appropriate premedication, paclitaxel (135 mg/m^2 to 360 mg/m^2 as permitted by dose-limiting toxicities) was administered as a three-hour IV infusion to groups of three patients. In addition to routine evaluations, all individuals underwent neurological examination and functional neurologic testing at baseline and every three cycles. The nine patients treated to date received 26 cycles of paclitaxel (135, 200, and 270 mg/m^2) for a cumulative paclitaxel dose of up to 1,500 mg/m^2. Transient grade 4 neutropenia was seen in five patients, but there were no complications. Neurotoxicities of grade 2 or more were not seen in any cycle and grade 3 myalgia/arthralgia was seen in only one of 26 cycles. Regarding side effects attributed to amifostine, no patient experienced significant hypotension, and nausea and vomiting were minimal (Schuchter L, etal, Pg S199: #958). On December 8, 1995, Ethyol was approved by the FDA for use as a cytoprotective to reduce cumulative renal toxicity in ovarian cancer patients administered repeated doses of cisplatin. Subsequently, U.S. Bioscience entered into an agreement with Alza (Palo Alto, CA) under which Alza would have a five-year exclusive rights to market and sell Ethyol in the USA, while U.S. Bioscience would retain the right to co-promote the product. Alza agreed to make a $20 million upfront payment and another $15 million payment during the next few years to cover clinical development activities. European marketing rights to Ethyol are held by Schering-Plough and Canadian rights by Eli Lilly. Also, see FO V1 # 4, p 111.

NEW ANTICANCER AGENTS IN CLINICAL DEVELOPMENT

Ecteinascidin-743

Ecteinascidin (ET)-743, under development by PharmaMar [Tres Cantos (Madrid), Spain], a novel marine-derived anticancer compound isolated from the Caribbean tunicate *Ecteinascidia turbinata*, may inhibit the growth of a number of common solid tumors. ETs are isoquinoline-related compounds sharing antiviral, immunosuppressive and antitumor activity. They appear to inhibit steps in protein, DNA and RNA synthesis, as well as DNA and RNA polymerases. Increasing dosages of ET743 disorganizes microtubules with an effect similar to that seen with paclitaxel, but based on a different mechanism. *In vitro* studies have demonstrated that ET743 has considerable activity against melanoma, nsclc and ovarian and breast cancer cell lines. Significant

activity also has been confirmed in *in vivo* xenograft animal studies against these tumors. In metastatic breast cancer animal models, ET743 delivered as a 250 mg/kg bolus, results in complete remission. Furthermore, fractionating the dose appears to minimize long term liver toxicity. Based on these findings, phase I clinical trials are expected to begin soon in Europe and the USA (Faircloth G, etal, Pg S261 #109).

Update on Platinum Agents

Results of clinical trials of various new platinum agents were reported during ECCO8, as well as preclinical evaluations of novel compounds. Information on compounds in human trials is presented below. For a comprehensive review of platinum-based compounds please see FO, V1 #1.

JM-216 (bis-acetatoammine-dichorocyclohexylamine platinum) is under development by Johnson Matthey Technology (Reading, Berks, UK). JM-216 for oral use, based on its oral bioavailability, low emetogenicity, lack of nephro- or neurotoxicity, and similar antitumor activity to carboplatin. JM-216 appears to be active in ovarian cancer, nsclc and mesothelioma In addition, it has a much lower resistance factor compared to carboplatin. In a phase I clinical trial of 32 patients (11 with mesothelioma), those previously treated by chemotherapy were administered 100 mg/m^2 and chemotherapy-naive patients were administered 120 mg/m^2, in a fractionated five-part daily oral dose. Evidence of anticancer activity was seen in patients with ovarian cancer (one PR), nsclc (one PR) and mesothelioma (one minor response). No nephrotoxicity or neurotoxicity was observed and emesis was easily controlled with metoclopramide. Phase II clinical trials are now underway in lung cancer (sclc and nsclc) and ovarian cancer (Judson I, etal, Pg S205: #981).

Oxaliplatin (L-OHP) is a dach platinum under development by Debiopharm (Lausanne, Switzerland). When administered in conjunction with high-dose leucovorin and 5-fluorouracil (5-FU), it is highly active in patients with pretreated metastatic colorectal cancer. In a phase II study, 40 patients with pretreated metastatic colorectal cancer who experienced disease progression on first-line therapy or after more than six months subsequent to adjuvant therapy, were administered IV oxaliplatin (100 mg/m^2) on day one and leucovorin (500 mg/m^2) over two hours, followed by 5-FU (1.5-2 g/m^2) as a 24-hour continuous infusion on days one and two, every two weeks. If there was no toxicity after 2 cycles, the 5-FU dose was increased to 2 g/m^2. The overall response rate was 49%, with one CR and 18 PRs. Disease stabilized in 17 patients and progressed in three. Nine patients (56%) who had previously progressed on the high dose leucovorin and 5-FU regimen alone, responded. Median progression free survival was 9.6 months and 12-month median survival rate was 65% (deGramont A, etal, Pg S149: #716).

Letrozole

Letrozole (CGS-20267), a novel non-steroidal selective competitive aromatase inhibitor under development by Ciba-Geigy, has shown real promise in the treatment of postmenopausal women with advanced or recurrent breast cancer. In a phase II trial, 64 postmenopausal patients with advanced or recurrent breast cancer, exposed to more than one prior treatment regimen (hormonal therapy and/or chemotherapy) were randomized between two oral regimens of letrozole for more than eight weeks. Thirty-three patients were administered letrozole daily at a dose of 0.5 mg and 31 at a dose of 1.0 mg. Overall response rates were 28% (3 CRs and 6 PRs) among 32 evaluable patients in the 0.5 mg-treated group and 39% (5 CRs and 6 PRs) among 28 patients on the 1.0 mg group. Disease stabilized for more than six months in 19% of patients in the 0.5 mg dose group and 29% in the 1.0 mg group. Adverse events were reported in 6% of patients in each of the two treatment groups. All were of a very mild nature (grade I) except for one patient who experienced grade 2 itching. Laboratory test abnormalities were either grade 0 or 1 in severity except for one person in the 0.5 mg group who had grade 2 elevations of liver function tests (Tominaga T, etal, Pg S81:#373).

Toremifene

Toremifene, a nonsteroidal antiestrogenic anticancer drug under development by Orion-Farmos (Espoo, Finland) that has clinical efficacy equal to that of tamoxifen, also has antiatherogenic properties, improving all lipoprotein indices associated with increased coronary heart disease risk. In a study of 49 postmenopausal women with early breast cancer, patients were randomized to toremifene (60 mg/kg) or tamoxifen (40 mg/kg). Total LDL, and HDL cholesterol, apolipoprotein. (A-I, A-II and B) and Lp(a) were measured before treatment and after 12 months. Both drugs significantly decreased serum total and LDL cholesterol and apo B levels. However, toremifene increased HDL levels by 14% while tamoxifen decreased HDL levels by 5%. Both cholesterol/HDL and LDL/HDL ratios fell significantly more with toremifene than with tamoxifen (Saarto T, etal, Pg S15: #65). Through an agreement with Orion, Schering-Plough has obtained marketing rights for toremifene (Fareston) in the USA. An NDA was filed in January 1995 for the treatment of advanced breast cancer.

RFT5-SMPT-DGA

The immunotoxin RFT5-SMPT-dgA, which consists of a monoclonal antibody directed against the α-chain of the interleukin-2 receptor (CD25) chemically linked to deglycosylated ricin A-chain, has shown activity against Hodgkin's disease (HD) *in vitro*, in experimental animal models, and in human patients. In a phase I trial, twelve patients with refractory HD were treated with the immunotoxin (5.0, 10, or 15 mg/m^2), administered IV over four hours, every other day, for seven days. Patients

received one to four courses of treatment. All of these individuals had been heavily pretreated with a mean of four different prior therapies, including autologous bone marrow transplantation in eight of the twelve. One patient experienced a PR and disease stabilized in five and progressed in six. Side effects generally were related to the vascular leak syndrome (edema, weight gain, hypotension, tachycardia, myalgia and weakness) and decrease in serum albumin. Two patients had grade 2 allergic reactions, with generalized urticaria and mild bronchospasm. Maximal dose has not been reached yet and enrollment continues (Schnell R, etal, Pg S193: #930).

ANTICANCER DRUG DEVELOPMENT

TAXANES

- Docetaxel and paclitaxel, the two taxanes currently in clinical use, have been proven effective in the treatment of a variety of cancers as monotherapy (see Exhibit 3) and in combination with various others chemotherapeutic agents, hematopoietic support and radiation therapy; combinations with platinum-based agents are proving particularly effective (see Exhibit 4).
- Revenues of paclitaxel, currently supplied as Taxol by Bristol-Myers Squibb (BMS), were $340 million in 1994 and are forecast to exceed $515 million in 1995. Total sales of taxanes are expected to exceed $675 million in 1996 and reach $1 billion by the end of the decade.
- BMS' exclusivity for Taxol is due to expire in 1997, presenting a very attractive opportunity for generic versions currently pursued by numerous developers (see Exhibit 5).
- Companies are working to produce synthetic analogs of currently available taxanes or to modify semi-synthetic taxanes to create new patentable versions with a more favorable clinical profile.
- For an excellent review of the status of paclitaxel in the clinical setting, see a review article by Eric K. Rowinsky, MD and Ross C. Donehower, MD, which appeared in the April 13, 1995 issue of the New England Journal of Medicine (Vol. 332, No. 15:1004-1014).

TAXANES IN DEVELOPMENT

Taxanes are a unique class of anticancer agents which inhibit cell division by acting on the cell's internal skeleton, composed of microtubules which assemble and disassemble during the cell cycle. Taxanes block the disassembly phase, preventing cancer cells from dividing, leading to cancer cell death. Discovered by National Cancer Institute researchers in the early 1960s, Taxol (now a Bristol-Myers Squibb registered trade name) was originally isolated from the bark of the Pacific (Western) yew tree (*Taxus brexifolia*). Taxol, once considered a miracle cure for ovarian cancer, has not lived up to expectations. However, administered either as single agent therapy or in combination with other chemotherapeutic agents, taxanes are joining the armentarium of treatment options for a variety of cancers.

Controversy followed initial use of the yew tree, a scarce natural resource, to produce a potentially life-saving drug, pitting women with advanced ovarian cancer against concerned environmentalists. The issue rapidly became moot when Taxol was produced by extracting paclitaxel from 10-deacetyl baccatin III (10-DAB), a precursor found in the needles of various species of yew such as the American ornamental yew tree, the European (Chinese) yew (*Taxus baccata*) and the Indian yew, among others.

Currently, alternative approaches to obtain taxanes include semi-synthesis, cellular culture production and chemical synthesis; after decades of effort (because of their molecular complexity), taxanes were finally synthesized in 1994. Although it is unlikely that synthetic Taxol requiring several complex steps to produce, will be needed to fill demand, it has allowed scientists to modify the molecule in hopes of enhancing its cytotoxic effects and modifying its toxicity profile.

Paclitaxel

Taxol. The only source of FDA-approved paclitaxel is Bristol-Myers Squibb (BMS) that sells the agent worldwide as Taxol. Paclitaxel, produced from the bark of the Pacific yew tree, was developed by BMS under an NIH Collaborative Research and Development Agreement (CRADA) in the mid-1980s. Taxol was first approved in December 1992 for the treatment of advanced refractory ovarian cancer (as 24-hour infusion monotherapy) and, in April 1994, was also approved for the treatment of advanced refractory breast cancer. The drug is also being investigated as monotherapy for a number of additional indications (see Exhibit 3).

An application to market a semi-synthetic version of Taxol, submitted in Europe in March 1994, was approved in several European countries in October 1994. This version of the drug is produced from the needles and twigs of the European yew tree in collaboration with Indena (Milan, Italy) that collects the biomass and extracts the paclitaxel precursor which is used by BMS to synthesize Taxol at its Swords, Ireland plant using technology licensed from Florida State University (Tallahassee, FL). In the USA semi-synthetic Taxol, produced in a similar fashion, was approved in December 1994. In May 1995, BMS exercised an option to license Phyton's (Ithaca, NY) cell culture process to produce Taxol and related products under a multi-year, muti-million agreement.

In October, 1995, BMS ended ongoing licensing discussions with Rhône-Poulenc Rorer (RPR) regarding royalty payments on sales of semi-synthetically-produced

Exhibit 3
Selected Clinical Trials of Taxanes as Monotherapies for Various Malignancies

Investigator/Site/Citation	Agent/Dosage	Phase/Indication	Results
		Paclitaxel	
Fennelly D/Memorial Sloan-Kettering Cancer Center/ ASCO95, Abs. 756	Taxol/24-hour infusion of 40-100 mg/m^2/week	Phase I/refractory ovarian cancer	2/9 with normalization of CA 125; significant reduction in abdominal ascites in 1 patient, 2/9 SD
Gore, ME/London Gynaecological Oncology Group, UK/ ASCO95, Abs. 747	3-hour infusion of 225 mg/m^2 IV, every 3 weeks	Phase II/stage IV epithelial ovarian cancer	1/28 CR; 8/28 PR; 7/28 SD; 8/28 PD; 9/28 (32%) overall RR; 3 responders relapsed at 6-7.5 months; 6 responders continue in PR (5+ to 18+months)
Hainsworth, JD/Sarah Cannon Cancer Center (Nashville, TN)/ ASCO95, Abs. 376	1-hour infusion of 135-200 mg/m^2	Phase I/II/refractory ovarian cancer	45% RR
		Phase I/II/refractory breast cancer	33% RR
Currow D/ASCO95, Abs. 237	3-hour infusion of 175 mg/m^2	Phase I/breast	4/11 (36%) PR
Gelmon KA/British Columbia Cancer Agency (Vancouver, Canada)/ASCO95, Abs. 226	Taxol/ 100-130 mg/m^2, bi-weekly	Phase I/II/ metastatic breast cancer	Responses to be reported when phase II is completed
Akerley W/Rhode Island Hospital/ASCO95, Abs. 1170	3-hour infusion of 100-175 mg/m^2/week	Phase I/metastatic nsclc	Ongoing study
Hainsworth JD/Sarah Cannon Cancer Center /ASCO95, Abs. 1116	1-hour infusion of 135-200 mg/m^2	Phase I/nsclc	13/53 (25%) MR; 12/53 PR, 1/53 CR, 5/53 MR; median survival was 8 months; actuarial 1 year survival was 33%
		Phase I/II/refractory nsclc	25% RR
Bringhurst C/M. D. Anderson Cancer Center/ ASCO95, Abs. 1572	Escalating 10-day infusion of 50 to 210 mg/m^2	Phase I/nsclc, sclc and head and neck, prostate, colon and skin cancer	3/16 PR (1 nsclc, 1 head and neck, 1 skin)
Gian V/U Florida (Gainsville, FL)/ASCO95, Abs. 1693	Taxol at 200 mg/m^2	Phase II/recurrent or metastatic soft tissue sarcoma or osteosarcoma	No CR or PR; 2 patients alive with PD; 1 alive with no evidence of disease after undergoing surgery and radiotherapy
Loeffler TM/Stadtische Kliniken (Dortmund, Germany)/ ASCO95, Abs. 1522	1-hour ambulatory infusion of escalating doses (40-90 mg/m^2/week) for 6 weeks, followed by a 3-week interval	Phase I/ pretreated solid tumors	Overall response: 2/50 CR, 18/50 PR, 20/50 NC, 11/50 PD
		Phase I/colon	3/8 NC, 5/8 PD
		Phase I/head & neck	3/8 PR, 4/8 NC, I/8 PD
		Phase I/esophageal	5/6 PR, 1/6 NC
		Phase I/gastric	1/3 NC, 2/3 PD
		Phase I/pancreatic	2/4 PR, 2/4 NC
		Phase I/sclc	2/4 CR, 1/4 PR, 1/4 NC
		Phase I/nsclc	3/3 NC
		Phase I/breast	3/6 PR, 3/6 NC
		Phase I/ovarian	2/5 PR, 1/5 NC, 2/5 PD
Lowenbraun S/Louisville, Kentucky/ ASCO95 Abs. 1505	Taxol/6-hour infusion (40 mg/m^2/day) for 4 days	Phase II/lung	6/17 PR; 2/17 NR; 3 months MRD
		Phase II/breast	1/17 CR; 4/17 PR; 1/17 NR; 6 months MRD
		Phase II/colon	1/17 PR; 6 months MRD
		Phase II/larynx	1/17 PR; 4 months MRD
		Phase II/larynx	1/17 PR; 2 months MRD

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Mamounas E/NSABP Headquarters (Pittsburgh, PA)/ ASCO95, Abs. 206	Taxol/3-hour infusion of 250 mg/m^2, every 3 weeks	Phase II/advanced breast cancer	17% CR, 26% PR; 43% overall RR; 22% SD, 35% PD
Mendiola C/Hospital Doce de Octubre Servicio de Oncologia Medica (Madrid, Spain)/ ASCO95, Abs. 783	Taxol/175-230 mg/m^2	Phase I/advanced ovarian cancer	4/27 CR, 7/27 PR; overall RR 41%; median survival was 7 months
Prados M/ ASCO95, Abs. 281	Taxol/3-hour infusion, of 210-240 mg/m^2	Phase II/recurrent malignant glioma	RR 35%; 27 weeks median survival
Riseberg D/NCI/ ASCO95, Abs. 1576	14-day infusion on 28-day cycles with intrapatient dose escalation as permitted (total of 32-175 mg/m^2)	Phase I/advanced malignancies (breast and rectal cancer, melanoma and other primary cancers)	Toxicity was minimal; 6/18 patients had grade 2 anemia and 3/18 had grade 2 neutropenia
Saville MW/NCI, NIH Clinical Center/ASCO95, Abs. 826	3-hour escalating infusion at 135-175 mg/m^2	Phase I/Kaposi's sarcoma	10/20 (50%) PR, 9/20 MR or SD, 1/20 NR
Seidman AD/Memorial Sloan-Kettering Cancer Center/ ASCO95, Abs. 151	96-hour infusion of 120 mg/m^2	Phase II/metastatic breast cancer	7/25 PR; median response duration is 5+ months
Swain S/Vincent T. Lombardi Cancer Research Center (Washington, DC)/ASCO95, Abs. 227	24-hour infusion of 135 mg/m^2 IV on day 1, every 3 weeks	Phase II/metastatic breast cancer	2 (11%) CR, 4 (21%) PR, 2 (42%) SD, 5 (26%) PD
Tan V/Albert Einstein Cancer Center (Bronx, NY)/ASCO95, Abs. 1122	Taxol/3-hour infusion of 175 mg/m^2 or 24-hour infusion of 135-400 mg/m^2	Phase I/nsclc	3-hour: 1/4 CR, 2/4 PD, 1/4 SD 24-hour: 5/23 PR, 7/23 SD, 11/23 PD; overall RR 6/38 (16%)
Tester W/Albert Einstein Cancer Center (Philadelphia, PA)/ ASCO95, Abs. 1189	Taxol/3-hour infusion of 200 mg/m^2 IV, every 3 weeks	Phase II/stage IV nsclc	42% RR; 5/12 PR, 2/12 SD, 5/12 PD (ongoing study)
Upadhyaya G/USC Norris Cancer Center (Los Angeles, CA)/ASCO95, Abs. 1520	3-hour infusion of 175-225 mg/m^2, every other week	Phase I/solid tumors	OR seen in 2 breast patients, 1 melanoma, 1 tongue, 1 other primary and germ cell cancer
Vaughn DJ/U Pennsylvania Cancer Center (Philadelphia, PA)/ASCO95, Abs. 530	96-hour infusion of 120-140 mg/m^2	Phase II/metastatic colorectal cancer	Of 10 evaluable patients, no OR was seen (ongoing study)
Bonneterre J/Breast Cancer French Study Group/ECCO8, Abs. 354	Taxol/3-hour infusion of 225 mg/m^2, every 3 weeks	Phase II/metastatic breast cancer	4/47 CR, 17/47 PR, 12/47 SD, 14/47 PD; RR 45%
Bougnoux P/MBC French Trialists Group/ECCO8, Abs. 378	Taxol/3-hour infusion of 225 mg/m^2, without G-CSF	Phase I/metastatic breast cancer	2/46 CR, 11/46 PR, 22/46 SD, 11/46 PD; 28% RR
Fennelly D/Memorial Sloan-Kettering Cancer Center/ECCO8, Abs. 923	Taxol/24-hour infusion of 40-100 mg/m^2, every 3 weeks	Phase I/ovarian cancer	Overall RR 3/14 (21.4%); 2/14 SD
Furuse K/National Sanatorium Kinki Central Hospital (Osaka Japan)/ECCO8, Abs. 1072	3-hour infusion of 210 mg/m^2	Phase II/nsclc	18/60 PR, 1/60 CR; overall RR 31.7%
Gianni L/Instituto Nazionale Tumori (Milan, Italy)/ECCO8, Abs. 359	Taxol/3-hour infusion of 100-125 mg/m^2	Phase I/anthracycline-resistant metastatic breast cancer	3/13 CR, 8/13 (84%,) PR/median duration of response is 5 months (2+ to 10+)
Klaassen U/West German Cancer Center, U Essen, Germany/ECCO8, Abs. 380	1-hour infusion of 70-100 mg/m^2, weekly	Phase I/advanced breast and ovarian cancer	1st level: 1/7 PR, 5/7 SD, 1/7 PD; 2nd level: 1/5 PR, 1/5 SD, 3/5 PD; 3rd level: 1/3 PR, 1/3 SD, 1/3 PD; 4th level: 1/4 PR, 3/4 unevaluable
Klaassen U/West German Cancer Center, U Essen, Germany/ ECCO8, Abs. 492	Taxol/3-hour infusion of 135-175 mg/m^2, every 3 weeks	Phase II/ovarian cancer	28/295 (9.5%) CR, 57/295 (19.3%) PR, 119/295 (40.3%) SD, 85/295 (28.8%) PD
Lhomme C/French Anti Cancer Centers/ECCO8, Abs. 507	Taxol/3-hour infusion of 135-175 mg/m^2	Phase II/ovarian cancer (platinum pretreated)	20% RR; 5% CR, 15% PR, 32% SD
Martoni A/S. Orsola-Malpighi Hospital (Bologna, Italy)/ ECCO8, Abs. 523	3-hour infusion of 135-175 mg/m^2	Phase II/advanced ovarian cancer(platinum pretreated patients)	16/34 PR, 1/34 CR; RR (50%)

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Schutte W/Martin-Luther-U (Halle, Germany)/ECCO8, Abs. 1107	3-hour infusion of 200 mg/m^2	Phase II/advanced nsclc	28% PR, 36% NC, 36% PD
Voravud N/Chulalongkorn U Hospital (Bangkok, Thailand)/ ECCO8, Abs. 1111	24-hour infusion of 200 mg/m^2, every 3 weeks	Phase II/nsclc	6 (26.1%) PR, 4 (17.4%) SD, 13 (56.5%) PD; median time to response and duration of response were 8 weeks and 16 weeks, respectively
Patel SR/ M. D. Anderson Cancer Center/ AACR95, Abs. 1438	24-hour infusion of 175 mg/m^2, every 3 weeks	Phase II/osteosarcoma	1/15 achieved mixed response; 14/15 PD
Sarosy G/National Cancer Institute (Bethesda, MD)/ AACR95, Abs. 3786	250 mg/m^2; one patient received an additional 750 mg/m^2 of cyclophosphamide	Patients who relapsed after initial treatment	1/5 PR, 3/5 SD, 1/5 PD
Gill PS/U Southern California School of Medicine (Los Angeles, CA)/ASH95, Abs 1516	Taxol/3-hour infusion of 100 mg/m^2	Phase I/advanced AIDS-related Kaposi's sarcoma	59% RR; 1/27 CR, 15/27 PR, 11/27 (41%) SD
Miller H/Evanston Hospital, Northwestern U (Evanston, IL)/ ASH95, Abs 738	250 mg/m^2 infusion, every 3 weeks	Muliple myeloma	30% objective RR; dose used in study produced unacceptable toxicity
Younes A/U Texas M.D. Anderson Cancer Center (Houston, TX)/ ASH95, Abs 3293	Taxol/96-hour infusion of 140 mg/m^2, every 3 weeks	Phase II/ non-Hodgkin's lymphoma	8/12 (67%) PD, 3/12 (25%) SD, 1/12 (8%) MR
Goldberg SL/Bone Marrow Transplant Program, Temple U Cancer Center (Philadelphia, PA)/ASH95, Abs 3238	3-hour infusion of 135 mg/m^2	Phase II/relasped non-Hodgkin's lymphoma	1/3 CR, 1/3 PR
	Docetaxel		
Abbruzzese JL/M. D. Anderson Cancer Center/ ASCO95, Abs. 561	75-100 mg/m^2 IV, every 3 weeks	Phase II/pancreatic adenocarcinomas	2/10 PR
Bedikian A/M. D. Anderson Cancer Center/ASCO95, Abs. 1304	1-hour infusion of 100 mg/m^2, every 3 weeks	Phase II/advanced melanoma	1/26 CR, 3/26 PR;
Dreyfuss A/Dana-Farber Cancer Institute (Boston, MA)/ ASCO95, Abs. 875	1-hour IV of 100 mg/m^2, every 3 weeks	Phase II/head and neck cancer	4/23 CR, 7/23 PR, 7/23 SD; 1/23 deaths
Einzig AI/Eastern Cooperative Oncology Group (Denver, CO)/ ASCO95, Abs. 441	1-hour IV of 100 mg/m^2, every 3 weeks	Phase II/gastrointestinal cancer	1/22 CR, 2/22 PR, 4/22 SD, 15/22 PD; 10 patients required dose reduction because of toxicity
Erazo-Valle A/Taxotere Cooperative Group (Mexico City, Mexico)/ASCO95, Abs. 244	1-hour IV of 100 mg/m^2, every 3 weeks	Phase II/advanced breast cancer	26% CR, 61% PR, 6.5% SD; 6.5% PD/median survival time had not been reached
Fujii H/National Cancer Center Hospital East (Japan)/ASCO95, Abs. 859	1-hour IV of 60 mg/m^2, every 3-4 weeks	Phase II/head and neck cancer	4 PR (17.4%); median survival time was 4 months
Lira-Puerto V/ Taxotere Cooperative Group (Mexico City, Mexico)/ASCO95, Abs. 1186	100 mg/m^2, every 3 weeks	Phase II/advanced nsclc	22/41 (53.6%) PR, 9/41 (22%) SD, 10/41 (24.3%) PD; median survival time had not been reached
McCaffrey J/Memorial Hospital (NY, NY)/ASCO95, Abs. 607	1-hour IV of 100 mg/m^2, every 3 weeks	Phase II/advanced transitional cell cancer	20% RR
Rios M/Centre A. Vautrin (Nancy, France)/ASCO95, Abs. 87	97.6-994.5 mg/m^2	Phase II/metastatic and advanced breast cancer	2/37 CR, 23/37 PR, 8/37 NC, 4/37 PD; 67.6% RR; median duration of response not reached (9+-36+ weeks)
Valero V/M. D. Anderson Cancer Center/ECCO8, Abs. 384	100 mg/m^2, every 3 weeks	Pilot study/Taxol-resistant metastatic breast cancer	1/10 MR, 4/10 NC, 4/10 PD
Valero V/M. D. Anderson Cancer Center/ASCO95, Abs. 77	1-hour IV of 100 mg/m^2, every 3 weeks	Phase II/anthracycline (doxorubicin) and anthracedione (mitotoxantrone)-resistant advanced breast cancer	56% RR with median duration of 27 weeks; median survival time was 10 months

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Blackstein ME/National Cancer Institute of Canada, Toronto/ ECCO8, Abs. 848	1-hour IV of 100 mg/m^2, every 3 weeks	Phase II/metastatic or recurrent soft tissue sarcoma	2/13 PR, 6/13 SD
Chahine A/Hôpital Paul Brousse (Villejuif, France)/ECCO8, Abs. 382	70-100 mg/m^2, every 3 weeks	Phase I/metastatic breast cancer	1/22 MR, 4/22 PR, 7/22 PD; 1 2 early deaths
Guastalla JP/Hopital Saint-Louis (Paris, France)/ ECCO8, Abs. 348	1-hour IV of 100 mg/m^2, every 3 weeks	Phase II/anthracycline resistant metastatic breast cancer	RR in intent-to-treat analysis was 29.4%; 15 (31.6%) PR
Posner M/Dana Farber Cancer Institute/ECCO8, Abs. 421	100 mg/m^2 IV, every 3 weeks	Phase II/head and neck cancer	50% RR; 4/28 CR, 10/28 PR

Abbreviations

Clinical responses: RR (response rate), MR (major response), OR (objective response), CR (complete response), PR (partial response), SD (stable disease), PD (progressive disease), NC (no change), MRD (median response duration)

Citations: 31st Annual Session of the American Society of Clinical Oncology, Los Angeles, California, May 20-23, 1995 (ASCO95) 86th Annual Meeting of the American Association for Cancer Research (AACR95); Eighth European Cancer Conference, Paris, France, October 29 to November 2, 1995 (ECCO8); 37th Annual Meeting of the American Society of Hematology (ASH95)

Taxol and filed for a declaratory judgment in Manhattan federal court stating that its Taxol manufacturing process does not infringe on patent rights owned by RPR. Subsequently, RPR filed a patent infringement suit in U.S. District Court (Wilmington, DE) against BMS, alleging that BMS is infringing on RPR's patent rights to intermediates and processes used in manufacturing taxoids for Taxol. These patent rights are not related to Taxotere.

To date, Taxol has been approved for the treatment of refractory ovarian and breast cancer in North America and over 40 countries worldwide, including most European countries (Sweden, Austria, Denmark, Germany, Luxembourg, Greece, Belgium, Portugal, Spain, Switzerland, the Netherlands, Norway, the UK, Russia), South Africa, New Zealand and Australia, Israel, and Brazil; it was launched in France in February 1994. Worldwide sales of Taxol are estimated to exceed $515 million in 1995, representing about 65,000 treatment regimens worldwide, based on costs per treatment estimated in Exhibit 6. Taxol's patent expires at the end of 1997 in the USA.

Generic paclitaxel is under development by numerous manufacturers (see Exhibit 5) worldwide to take advantage of Taxol's imminent patent expiration. One formulation of paclitaxel, Anzatax, was approved for marketing in several overseas markets. Generic paclitaxel is also available in China.

Docetaxel

Docetaxel (Taxotere; Rhône-Poulenc Rorer) is a semisynthetic taxoid derived from an extract of the needles of the European yew tree. The drug has been studied widely in phase II trials in Europe and in the USA as monotherapy in a range of solid tumors (see Exhibit 3) and is currently in phase III clinical trials for many of these indications. Most studies use the standard regimen of 100 mg/m^2 given as a 1-hour IV infusion, every 3 weeks but other lower-dose regimens are also under evaluation.

Docetaxel has been shown to have strong activity in anthracycline-resistant advanced metastatic breast cancer, a finding of some significance because of the poor prognosis of patients with such cancers. In July 1994, RPR submitted an NDA for the treatment of locally advanced or metastatic breast cancer refractory to first-line therapies that included anthracyclines, unless contraindicated, and for the treatment of locally advanced or metastatic non-small cell lung cancer refractory to platinum-based chemotherapy. In December 1994, FDA's Oncologic Drugs Advisory Committee (ODAC) voted not to recommend Taxotere for either indication preferring to await results of phase III clinical trials in progress. The review involved results from phase II trials of 1,600 patients. Results of several of these trials, presented at the November 1995 meeting of the Eighth European Cancer Conference (ECCO8) are summarized in pages 170-173 of this issue. As of late 1995 docetaxel was studied in at least 35 clinical trials involving 2,500 patients worldwide.

ODAC reversed its decision on October 17, 1995, and recommend Taxotere for approval for the narrow indication of locally advanced or metastatic breast carcinoma which progressed during anthracycline-based therapy, or relapsed during anthracycline-based adjuvant therapy. ODAC voted to recommend approval only for patients with normal liver function tests. The drug is contraindicated in women with elevated liver enzymes (transaminases at, or greater than, 1.5 times upper limit of normal and alkaline phosphatases at, or greater than, 2.5 times normal) because this condition was a complicating factor in many of the deaths attributed to the drug's toxicity. Also, patients with enzyme abnormalities experienced a substantially higher incidence of such side effects as febrile neutropenia, infections, thrombocytopenia and stomatitis than patients with normal liver function. FDA is expected to study the link between Taxotere's toxicity

Exhibit 4
Selected Combination Regimens of Taxanes and Platinum-based Drugs in Clinical Trials

Investigator/Site/ Abstract Citation	Agent/Combination (Dosage)	Phase/Indication	Results
Browne MJ/Brown U Clinical Oncology Group (Providence, RI)/ASCO95, Abs. 245	24-hour infusion of Taxol (135 mg/m^2), followed by 1-hour infusion of cisplatin (75 mg/m^2), every 3 weeks	Phase II/metastatic breast cancer	2/13 (15%) CR, 5/13 (38%) PR
Douillard JY/Centre Rene Gauducheau (Nantes, France)/ ECCO8, Abs. 1096	Docetaxel (75 mg/m^2) + cisplatin (100 mg/m^2)	Phase II/advanced nsclc	1/48 CR, 13/48 (29%) PR
Le Chevalier T/Centre Rene Gauducheau/ASCO95, Abs. 1059	Docetaxel (75 mg/m^2) + cisplatin (100 mg/m^2) on days 1, 21, 42 and then every 6 weeks	Phase II/advanced nsclc	6/24 PR (25%), lasting 15+ to 31+ weeks
Giaccone G/EORTC-LCCG/ ASCO95, Abs. 1082	Cisplatin (80 mg/m^2 day 1) + teniposide (100 mg/m^2 on days 1, 3, 5) versus cisplatin (80 mg/m^2) + 3-hour infusion of Taxol at 175 mg/m^2 on day 1	Phase II/nsclc	Teniposide + cisplatin: 3/28 (11%) PR; paclitaxel + cisplatin: 1/31 (3%) CR, 6/31 (19%) PR
Zalcberg JR/ Heidelberg Repatriation Hospital (Melbourne, Australia)/ECCO8, Abs. 1084	Docetaxel + cisplatin (1-hour infusion of each at 75 mg/m^2)	Phase II/nsclc	12/36 (33%) PR, 16/36 (44%) SD, 8/36 (22%) PD
Evans WK/Ottawa Regional Cancer Center, Canada/ASCO95, Abs. 1156	1-hour infusion of Taxol (175 mg/m^2), followed by carboplatin	Phase II/nsclc	1/11 (9%) MR, 4/11 (36%) PR, 4/11 (36%) SD, 2/11 (18%) PD
Langer CJ/Fox Chase Cancer Center (Philadelphia, PA)/ ASCO95, Abs. 1080	Taxol (24-hour infusion of 135-215 mg/m^2), followed by carboplatin	Phase II/advanced nsclc	OR was 63%; 9% CR; MDR was 6 months (range 1-15+ months), with 17% remaining free from progression (6-15+ months); 1-year survival projected in 51%
Paul D/Vanderbilt U/ASCO95, Abs. 1103	24-hour infusion of paclitaxel (135-175 mg/m^2) + carboplatin, initially given at a fixed dose (300 mg/m^2) then determined by AUC	Phase II/nsclc	12/47 (25.5%) PR; overall RR (26%)
Cole JT/Ochsner Cancer Institute (New Orleans, LA)/ ASCO95, Abs. 1087	1-hour docetaxel (75-85 mg/m^2) IV, every 3 weeks + 30-min. IV cisplatin (75-100 mg/m^2) with mannitol, on days 1, 22 and then every 3 weeks	Phase I/II/nsclc	Major response were seen in 46%; too early to estimate survival; 4/22 (18%) deaths (ongoing study)
Belli L/Institut Gustave Roussy (Villejuif, France)/ ASCO95, Abs. 1058	3-hour infusion of Taxol (135-225 mg/m^2) followed by cisplatin (100-120 mg/m^2), every 3 weeks	Phase I/II/advanced nsclc	38% PR, lasting 1 to 7+ months
Vafai D/ USC Norris Cancer Center/ASCO95, Abs. 1067	3-hour infusion of Taxol (150-250 mg/m^2) + a fixed dose of carboplatin	Phase I/II/nsclc	63% RR; 2/27 (7%) CR, 15/27 (55.5%) PR
Natale RB/USC Norris Cancer Center/AACR95, Abs. 1493	Taxol (3-hour infusion of 150-250 mg/m^2) + carboplatin	Phase I/II/nsclc	65% RR; 2/23 (8.7%) CR, 13/23 (57%) PR
Georgiadis MS/NCI-Navy Medical Oncology Branch (Bethesda, MD)/ ASCO95, Abs. 1072	Paclitaxel (100-140 mg/m^2 4-day continuous infusion), followed by cisplatin (60-80 mg/m^2)	Phase I/advanced nsclc and sclc	Nsclc: overall RR 56%; 1/16 (6%) CR, 8/16 (50%) PR, 6/16 (4%) SD, 1/16 (6%) PD Sclc: 4/6 (66%) PR; 1/6 (17%) SD, 1/6 (17%) PD
Klastersky J/Institut Jules Bordet (Brussels, Belgium)/ AACR95,Abs. 1423	Taxol (3-hour infusion of 135-200 mg/m^2) + cisplatin (30-minute infusion of 100-120 mg/m^2)	Phase I/nsclc	8/17 (47%) OR
Belani CP/U Pittsburgh Cancer Institute, U Pittsburgh, PA/ ASCO95, Abs. 381	Paclitaxel (24-hour infusion of 135-200 mg/m^2) + carboplatin	Phase I/advanced and metastatic nsclc	9/21 (43%) PR, 9/21 (43%) SD
Rowinsky EK/The Johns Hopkins Oncology Center (Baltimore, MD)/ ASCO95, Abs. 1075	3-hour paclitaxel (175-225 mg/m^2) + carboplatin (404-417 mg/m^2)	Phase I/nsclc	5/10 (50%) PR
Hainsworth JD/Sarah Cannon Cancer Center/ASCO95, Abs. 1197	1-hour infusion of paclitaxel (135 mg/m^2) + carboplatin + etoposide, alternating 50 mg and 100 mg orally on days 1-10	sclc	10/22 (45%) CR (6 limited, 4 extensive), 11/22 (50%) PR

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Fraci G/National Tumor Institute (Naples, Italy)/ ECCO8, Abs. 968	Cisplatin (25-30 mg/m^2/week) + paclitaxel (45-65 mg/m^2/week)	Phase I/lung; ovarian, and other cancers	Ongoing study
Adams M/Velindre Hospital NHS Trust (Cardiff, UK)/ ECCO8, Abs. 496	3-hour infusion of paclitaxel (175 mg/m^2 day 1) + carboplatin (day 21)	Phase II/advanced ovarian cancer	36% CR, 36% PR; actuarial survival is 74% at 18 months
Connelly E/Cleveland Clinic Foundation/ ASCO95, Abs. 777	3-hour infusion of Taxol (135-175 mg/m^2) followed by cisplatin (75 mg/m^2)	Phase I/ovarian, peritoneal and endometrial cancer	Ongoing study
Paraiso D/Salpetriere Hospital, (Paris, France)/ ASCO95, Abs. 803	1-hour infusion of Taxol (175 mg/m^2) + cisplatin (80 mg/m^2) + cyclophosphamide (600 mg/m^2)	Pilot study/ovarian cancer	3/10 (30%) pathologic CR
McGuire WP/Gynecologic Oncology Group (Buffalo, NY)/ ASCO95, Abs. 771	Cytoxan (500-750 mg/m^2) + cisplatin (75 mg/m^2) versus Taxol (100-135 mg/m^2) + cisplatin (75 mg/m^2)	Phase I/ovarian cancer	In 218 evaluable patients RR was seen in 64 % and 77% treated by cytoxan + cisplatin and Taxol + cisplatin, respectively; median progression-free survival was 12.9 months and 18 months, respectively; median survival was 24.4 months and 37.5 months, respectively
Bolis G/U Milan, Italy/ASCO95, Abs. 748	Paclitaxel (escalating 3-hour infusion of 150-250 mg/m^2) + carboplatin (fixed 1-hour infusion of 300 mg/m^2)	Advanced ovarian cancer	86.7% RR
Lhomme C/France/ ASCO95, Abs. 798	3-hour infusion of taxol (110-225 mg/m^2) + carboplatin (400 mg/m^2)	Phase I/ovarian cancer	Ongoing study
ten Bokkel Huinink WW/The Netherlands Cancer Institute, Amsterdam/ASCO95, Abs. 746	Carboplatin (300-600 mg/m^2) + 3-hour infusion of Taxol (125-225 mg/m^2)	Advanced ovarian cancer	7/27 (26%) CR, 10/27 (37%) PR, 6/27 (22%) NC, 2/27 (7%) PD
Zamagni C/S. Orsola-Malpighi Hospital (Bologna, Italy)/ ECCO8, Abs. 510	Taxol (3-hour infusion of 125-150 mg/m^2), followed by 30-minute infusion of carboplatin (250-300 mg/m^2)	Phase I/advanced ovarian cancer	Ongoing study
Bookman MA/Gynecologic Oncology Group (GOG; Philadelphia, PA)/ASCO95 Abs. 755	Paclitaxel (3-hour & 24-hour infusion of 135-225 mg/m^2) + carboplatin for 14-35 cycles	Phase I/advanced epithelial ovarian cancer	16 CR + 6 PR (75%); median survival was not reached at >60 weeks
Siddiqui N/Newcastle General Hospital, UK/ASCO95/Abs. 752	3-hour infusion of paclitaxel (150-200 mg/m^2), followed with AUC-based 30-minute infusion of carboplatin	Phase I/epithelial ovarian cancer	1 patient discontinued study due to peripheral neuropathy; all patients had alopecia; maximum tolerated dose was not reached (ongoing study)
Cummings FJ/Roger Williams Medical Center, Brown U (Providence, RI)/ASCO95, Abs. 1379	24-hour paclitaxel (135 mg/m^2 IV) before cisplatin (50-75 mg/m^2 at 1 mg/min IV, or IA), every 3-4 weeks	Phase I/colon, rectum, breast, esophageal, lung, stomach, ovarian, head and neck and unknown primary site cancer and melanoma	PRs were seen in hepatic metastasis from colorectal breast and lung cancer; CR in 1 melanoma patient
Dunphy F/Saint Louis U, MO/ASCO95, Abs. 869	Paclitaxel (3-hour infusion of 150-175 mg/m^2) + Paraplatin	Phase I/II/head and neck cancer	OR was 40% at primary site and 60% at regional lymph nodes
Creaven PJ/Rosewell Park Cancer Institute (Buffalo, NY)/ASCO95, Abs. 874	Escalating 3-hour infusion of paclitaxel (100-230 mg/m^2), followed by a fixed dose of carboplatin	Phase I/head and neck cancer	PR in 3/3 of pretreated patients
Ajani JA/M. D. Anderson Cancer Center/ASCO95, Abs. 489	Taxol (3-hour infusion of 175 mg/m^2) + cisplatin (20 mg/m^2 day 1-5 + 5-FU (750-1000 mg/m^2/d, on days 1-5)	Phase II/esophageal cancer	Overall RR was 44%; 5/39 (13%) MR, 1/30 (3%) CR, 16/39 (41%) PR

and elevated liver enzymes before it acts on RPR's application. It may still be possible to treat women with elevated enzymes by decreasing Taxotere dosage because patients with elevated liver enzymes have, on average, 25% decreased Taxotere clearance so they may be safely treated with a 25% reduction of the starting dose. At this reduced dose level they should be at the same risk for toxicities as patients with normal liver function. Studies are ongoing using doses of 60 mg/m^2 and 75 mg/m^2. Other options are also under investigation to allow inclusion of patients with hepatic dysfunction.

Approval for Taxotere in refractory breast cancer is being sought in over 30 countries. Applications were filed in Japan (5/94) and the centralized European regulatory agency (8/94) which approved the drug in November 1995; Taxotere was approved in Norway in October 1995. Outside Europe and the USA, Taxotere has been-launched in Canada, South Africa, Mexico (11/94), Brazil

Exhibit 5
Generic Taxanes in Development

Developer/ Supplier	Comments
Aphios (Woburn, MA)	Aphios' proprietary patented process (Super-Fluids) produces Taxol using twigs and needles of the ornamental yew tree (acquired from cultivator Zelinka Nurseries, Grand Haven, MI). A plan to establish a plant in Michigan as Orisa Pharmaceuticals was scrapped. Pilot quantities are produced at Aphios and the company is seeking marketing partners.
ESCAgenetics and its subsidiary, PHYTOpharmaceuticals	PHYTOpharmaceuticals developed a plant cell fermentation process to produce paclitaxel (also see Samyang Genex). In mid-1994 PHYTOpharmaceuticals, in collaboration with Children's Hospital (Oakland, CA), isolated four bioactive toxoid compounds that may be used as alternatives to paclitaxel or intermediates for its production. In June 1995 ESCAgenetics and PHYTOpharmaceuticals liquidated their biotechnology facility in San Carlos, CA.
Bio-Technology General (Iselin, NJ)	In July 1994 BTG received exclusive marketing rights in most major world regions (North America, Europe, and the Pacific Rim) and non-exclusive rights in China, to a generic version of paclitaxel from the Chinese manufacturer, Shenzhen Boda Natural Product Co. Ltd. Under the 17-year agreement, Shenzhen Boda will manufacture paclitaxel for BTG.
Biolyse Pharmacoppée Internationale (Port Daniel, Quebec, Canada)	Biolyse is extracting paclitaxel from the twigs and needles of the yew species *Taxus canadensis.* In mid-1995 BMS filed a complaint against Biolyse for allegedly misrepresenting its formulation of paclitaxel as being the same as Taxol. Biolyse's paclitaxel is in phase II clinical trials.
Cytoclonal Pharmaceutics (Dallas, TX)	Cytoclonal holds an exclusive worldwide license from the Research and Development Institute at Montana State University (Bozeman, MT) to use patented technology (issued in 1994) to synthesize paclitaxel from yew biomass using a combination of extraction and microbial fermentation techniques. A paclitaxel-producing fungus, *Taxomyces andreanae,* originally isolated from the Pacific yew tree, has been adapted to grow independently by using fermentation processes. This fungus produces paclitaxel that is equivalent to that resulting from other processes based on chemical analysis. It also produces other taxanes such as docetaxel.
Florida State University (FSU; Tallahassee, FL)	BMS has licensed technology from FSU to produce its version of semi-synthetic Taxol. Also, Robert Holton, PhD, at FSU, who reported the chemical synthesis of paclitaxel in February 1994, is working independently to develop synthetic analogs of paclitaxel.
Hafslund Nycomed (HN; Oslo, Norway)	HN has entered into a joint venture (Yew Tree Pharmaceuticals) with OPG/Pharmachemie (Haarlem, The Netherlands) to produce generic paclitaxel.
Hauser Chemical Research (Boulder, CO)	Hauser began manufacturing paclitaxel in 1989, entering a supply contract with BMS in 1991 which expired in March 1995. Hauser has also achieved paclitaxel semi-synthesis from natural taxanes without using 10-DAB routes. In October 1994, FDA approved Hauser's process to manufacture paclitaxel. In May 1994 Hauser entered into an agreement with Lederle Laboratories (American Home Products) to jointly commercialize paclitaxel and to develop taxane analogs. The agreement guarantees a minimum payment of $8 million to Hauser over the first three years of the contract. The two companies will share development expenses. Under the agreement Hauser is to supply bulk paclitaxel to Lederle and Immunex (Seattle, WA) for international and domestic markets, respectively.
Indena (Milan, Italy)	Indena signed an agreement with BMS in June 1992 to extract from the needles and twigs of the European species of the yew tree the paclitaxel precursor used by BMS to synthesize Taxol at its Swords, Ireland plant.
NaPro BioTherapeutics (Boulder, Colorado)	NaPro uses a proprietary extraction, isolation and purification (EIP) process to produce paclitaxel from the bark of the Pacific yew tree obtained from private sources. The company has adapted its EIP technology to also extract paclitaxel from renewable parts of various species of yews and has contracted with Pacific Biotechnologies (a subsidiary of Pacific Generation Technologies, a Canadian reforestation company) to cultivate yew species with favorable characteristics.
NaPro BioTherapeutics/ F. H. Faulding (Parkside, SA, Australia)	NaPro has granted Faulding the exclusive rights to its paclitaxel in ten countries, including Australia, New Zealand and much of Southeast Asia (Singapore, Hong Kong, South Korea, Indonesia, Thailand and Malaysia, among others). In January 1995 Faulding received marketing approval for Anzatax, its paclitaxel formulation for the treatment of refractory advanced breast and ovarian cancer, in Australia, New Zealand and eight other countries in Southeast Asia and certain Middle Eastern markets. Faulding manufactures and packages Anzatax at its David Bull Labs (Mulgrave, Victoria, Australia) facility using the glass vial system Oncotain. In early 1995 BMS sought an injunction to prevent Faulding from continuing to market Anzatax in Australia. BMS launched Taxol in Australia in 1994; at that time Faulding took legal action against BMS, seeking to invalidate patents held by BMS.
NaPro BioTherapeutics/ Baker Norton Pharmaceuticals (Ivax)	NaPro has granted Ivax marketing rights to its paclitaxel in North America, Europe, Japan and the rest of the world not covered by the agreement with Faulding, and non-exclusive rights in the former Soviet Union, China, certain countries in the Middle East and the Vatican, where Ivax has been granted non-exclusive rights. (Simultaneously upon entering into the agreement, Ivax purchased approximately 19.8% of NaPro's then outstanding common stock). Ivax is in phase III trials with paclitaxel in ovarian, breast and lung cancer.

— continued on next page

NeXstar Pharmaceuticals	In 1993 NeXstar (then Vestar) invested in TPL Phytogen (formerly Towers Phytochemicals; Vancouver, BC, Canada) which owned rights to the bark of certain Pacific yew trees in Canada. TPL has agreed to provide paclitaxel to a joint venture established with NeXstar to supply paclitaxel to the Canadian market. As of early 1995, the joint venture had completed the construction of a bulk extraction facility and produced 30 grams of clinical grade paclitaxel.
Phyton (was Phyton Catalytic; Ithaca, NY)	In May 1995, BMS exercised an option to license Phyton's cell culture process to produce Taxol and related products under a multi-year, multi-million agreement; the two companies have been collaborating in this area since 1991 and in 1993 agreed to scale-up production of paclitaxel. Phyton emerged from research conducted at Cornell University (Ithaca, NY) with the mandate to develop and supply high value plant-derived compounds. Phyton will produce paclitaxel at its German subsidiary in Ahrensburg.
Samyang Genex (formerly Sun Hill Glucose; Seoul, South Korea)	In April 1994 PHYTOpharmaceuticals finalized an agreement to collaborate with Sun Hill Glucose to scale-up production of paclitaxel using its plant cell fermentation technology (now used at a pilot plant in Inchon, South Korea) and in July 1995 signed an agreement with Samyang Genex that included an option to license the former's paclitaxel production process. In September 1995, ESCAgenetics and its subsidiary, PHYTOpharmaceuticals, sold all interest in paclitaxel and other toxoids to Samyang Genex.
SepraChem (Sepracor; Marlborough, MA)	SepraChem, a subsidiary of Sepracor, set up a joint venture (InNova Pharmaceuticals) with Dabur (Delhi, India) to manufacture paclitaxel in Windsor, Nova Scotia, Canada, using material imported from India. The company produces semi-synthetic pharmaceutical-grade final dosage form paclitaxel, starting from the raw material such as leaves and needles of the Himalayan yew tree.
Scripps Research Institute (La Jolla, CA)	K. C. Nicolaou, PhD, a chemist at Scripps Research Institute, reported the chemical synthesis of Taxol in February 1994. Subsequently this technology was licensed to Ivax that is now developing analogs using various approaches to modify the molecule.
Wex Technologies (Vancouver, BC, Canada)	Wex plans to produce and sell raw paclitaxel to pharmaceutical companies. Wex established a manufacturing operation, Nanning Maple Leaf Pharmaceutical Company (Nanning, Guangxi, People's Republic of China), as part of a 51%-49% joint-venture with the Chinese Pharos Pharmaceutical Company.

(1/94) and Uruguay for both refractory breast cancer and nsclc. In Japan, RPR is developing Taxotere jointly with Chugai Pharmaceuticals (Tokyo, Japan). Phase III clinical trials in the USA and abroad began in July 1994 in refractory breast cancer and in November 1994 in advanced/refractory nsclc. In early 1995, RPR completed a £10 million facility in the UK to manufacture Taxotere.

CLINICAL STATUS

Paclitaxel and docetaxel are being evaluated as monotherapy for a variety of cancers (see Exhibit 3).

Taxol versus Taxotere

Although Taxol and Taxotere share a similar mechanism of action, they are neither identical nor interchangeable. Their differences, however, are subtle, vary from indication to indication and are not fully defined. In anthracycline-resistant breast cancer several studies showed that the response rate of the two drugs was comparable. Response rates as high as 48% have been reported in anthracycline-resistant disease treated by Taxol compared to response rates of 41% to 49% reported with Taxotere. In a phase II study, 68 patients with advanced breast cancer who had failed or relapsed on doxorubicin or mitotoxantrone, experienced an overall response rate of 56% when treated with Taxotere (100 mg/m^2) as a one-hour infusion every three weeks. There were 35 (51.5%) PRs and three (4.4%) CRs and disease stabilized in 15 patients (22%); median survival time was 10 months. Remarkably, patients with visceral metastases and those with >3 involved organs experienced a response rate of 53% and 50%, respectively (Valero V, ASCO95, Abs. 77).

Preliminary data also indicate that some patients who no longer respond to Taxol respond to Taxotere. RPR is sponsoring a phase III trial comparing Taxotere (175 mg/m^2) to Taxol (100 mg/m^2) in breast cancer. Another phase III trial is studying Taxotere in breast cancer patients who have failed Taxol. Approximately 60 centers are expected to enroll patients for these two breast cancer trials.

Taxanes are associated with serious side effects (see Exhibit 7). The incidence of serious side effects is generally higher with Taxotere than with Taxol. However, techniques have been developed to lessen side effects, making the toxicity profile of both drugs comparable.

Combination Therapies

Various combination chemotherapy and multimodality therapies with taxanes have shown promise in a variety of cancers. One of the most active taxane-containing combination chemotherapy against a variety of solid tumors involves platinum-based drugs (see Exhibit 4). Other combinations of taxanes with other chemotherapeutic agents and radiation therapy are also under investigation (taxanes were shown to sensitize tumor cells to ionizing radiation *in vitro*). Taxol is also being evaluated in combination with multidrug resistance reversing agents

Exhibit 6
Taxol Treatment Costs

Location	AWP	Regimen	Average Cost of Treatment (range)
USA	$182.63 for 30 mg (6 mg/ml, 5 ml) or $6.06 per gram/ml*	135 mg/m2 repeated two to five times, every three weeks (average 3.5 cycles)	$8,590 ($4,860-$12,150)
		175 mg/m2 repeated two to five times, every three weeks (average 3.5 cycles)	$11,025 ($6,300-$15,750)
France	FFr 942 ($160) for 30 mg (6 mg/ml, 5 ml); a 175 mg/m^2 dose costs Fr 8,478 ($1,410)	175 mg/m^2 dose, repeated two to five times, every three weeks	FFr 50,000/$8,333

** These prices are discounted for various purchasers eligible for mandated discounts such as Medicaid, public hospitals, the Veteran's Affairs Department and others with special supply arrangements.*

such as Sandoz' SDZ PSC 833 (Fracasso PM, ASCO95, Abs. 1585 and Collins HL, ASCO95, Abs. 406) and R-verapamil (Riseberg D, ASCO95, Abs. 403) and in combination with amofistine (Ethyol; U.S. Bioscience) in breast cancer (Schuchter L, ECCO8, Abs. 958). If shown effective in comparative trials, oncologists may initiate taxane-based therapies during earlier stages of cancer.

Platinum-based drugs. In a phase I/II of 25 chemotherapy-naive patients with advanced nsclc (stage IIIb or IV), Taxotere, in combination with cisplatin, resulted in a 50% overall response rate. Treatment regimen consisted of 75 mg/m^2 of Taxotere every three weeks and 75 mg/m^2 or 100 mg/m^2 of cisplatin on days 1, 22 and then every six weeks. Major responses occurred in 12 of 24 evaluable patients; median survival was 11 months. Granulocytopenia was the only dose-limiting toxicity (Cole J, ASCO95, Abs. 1087). Although this regi-men did not involve administration of colony stimulating factors, several other platinum-based combinations used such agents to prevent life-threatening neutropenias (see Exhibit 6).

INDICATIONS FOR TAXANES

Taxanes are being actively evaluated against a variety of solid tumors such as ovarian, breast, lung, head and neck and uterine cancers, melanoma and sarcoma and hematologic malignancies. To date, the three approved indications for taxanes as monotherapy are as second-line therapies involving refractory, advanced stage cancers of the ovary, breast and lung. Future approvals may be as first-line treatment and as a part of combination therapies.

Ovarian Cancer

Paclitaxel has been approved and launched as second-line therapy in refractory ovarian cancer worldwide. In the USA, Taxol received approval for this indication which affects approximately 13,000 women, in 1992. Currently, various studies are ongoing in ovarian cancer to evaluate the effectiveness of taxanes as monotherapy and combination therapy (see Exhibits 3 and 4) and by escalating doses in conjunction with or without colony-stimulating factors.

Breast Cancer

Both paclitaxel and docetaxel have been approved as second-line therapies in advanced metastatic breast cancer refractory to first-line therapy using anthracyclines. In the USA, Taxol was affirmed in April 1994 and Taxotere in October 1995. Numerous studies of taxanes in breast cancer are ongoing. It is anticipated that taxanes will play a role in treating earlier stages of breast cancer as monotherapy and/or adjuvant therapy.

Lung Cancer

Taxanes have demonstrated activity in lung cancer, primarily nsclc. Docetaxel has been approved for the treatment of advanced nsclc in various countries outside the USA. Currently, an ongoing phase III trial is comparing Taxotere in nsclc patients who have failed platinum-based chemotherapy with best supportive care. A randomized trial in previously untreated patients has also been recommended to assess the drug's effectiveness in advanced nsclc.

Other Cancers

Taxanes have shown activity in various solid tumors (see Exhibit 3).

Kaposi's sarcoma. In a NCI-sponsored clinical trial, Taxol (135 mg/m^2 over three hours, every 3 weeks), clinically evaluated in 20 HIV+ immunocompromised patients with advanced, poor prognosis KS, resulted in a PR rate of 65% (13 of 20); six patients experienced stable disease, and one patient progressed (Yarchoan R, etal, Lancet, July 1st, 1995, p 26).

Non-Cancer Indications

Taxol is also being evaluated as therapy for congenital polycystic kidney disease (which accounts for 10% of all patients on kidney dialysis) and for malaria.

Exhibit 7
Dosage, Treatment Regimens and Side Effects of Taxanes

Dosage	Side Effects
	Paclitaxel
Original recommended dose (for refractory ovarian cancer) was 135 mg/m^2 infused over 24 hours; subsequently, 135 mg/m^2 of 175 mg/m^2 infused over 3 hours was approved by the FDA in June 1994, allowing for outpatient administration of Taxol	• hypersensitivity reactions (current dosage regimens and standard premedication have reduced incidence to less than 5%) • neutropenia, a major dose-limiting toxicity, is severe with dosage levels exceeding 200 mg/m^2, but is reversible; in previously-treated patients, or administration of high doses paclitaxel may necessitate use of colony stimulating factors • other hematologic toxicity is generally mild • peripheral neuropathy is unlikely to occur at prevailing dose levels • cardiac toxicity, manifested as disturbances in cardiac rhythm (usually transient asymptomatic bradycardia), was reported in small numbers of patients • alopecia develops in most patients • infection (incidence rate is up to 23%) • gastrointestinal side effects are infrequent
	Docetaxel
Recommended dose is 100 mg/m^2 infused over one hour every 3 weeks; one phase III study, started in 1995, is using a 75 mg/m^2 dose in anthracycline-resistant breast cancer and a similar Japanese study used a 60 mg/m^2 dose	• toxic death rate is between 1% and 2% • fluid retention (weight gain, peripheral edema or pleural effusion) incidence (ranging from 37% to 74%) is related to cumulative dose (roughly 400 mg/m^2); the pathophysiology of fluid retention has not been elucidated; premedication with corticosteroids was beneficial in breast cancer patients allowing patients to complete treatment regimen (approximately 1.9% of patients discontinued treatment because of fluid retention) • neutropenia incidence was 99% in anthracycline-resistant cancer, with febrile neutropenia at 22% • GI disturbances • skin rash • hypersensitivity • alopecia • infection occurred in 25% of patients but severe cases were rare, except in patients with liver dysfunction

MECHANISMS IN MALIGNANCY

ANGIOGENESIS IN MALIGNANCY

- The relationship between angiogenesis and tumor growth has been well documented and this mechanism was shown to be involved in carcinogenesis in many tumor types (see Exhibit 8).
- Inhibition of angiogenesis as an anticancer strategy will undoubtedly prove very challenging because numerous molecules act as mediators of angiogenesis, and inhibiting one may be insufficient to interfere with the process.
- If successful, angiogenesis inhibitors are expected to be applied in a variety of ways, as monotherapy for certain types of cancer, in combination therapy to enhance the effects of other anticancer agents and/or as chemopreventives in the chronic management setting.
- Based on observations first reported by Dr. Judah Folkman in a seminal paper in 1971, angiogenesis inhibitors have recently entered clinical trials in cancer applications; also, numerous agents based on a variety of novel approaches are in preclinical development (see Exhibits 10 and 11).
- This report was prepared in collaboration with the Angiogenesis Foundation, with contributions from Richard Casey, MD, William W. Li, MD and Vincent W. Li, MD.

TOWARDS AN UNDERSTANDING OF THE ROLE OF ANGIOGENESIS IN CANCER

Angiogenesis (the development of new blood vessels from pre-existing vessels) is a complex biologic process which is governed by a net excess of stimulatory compared to inhibitory molecules. Stimulation or inhibition of angiogenesis is the result of the interaction of a variety of mediators, including growth factors and cell adhesion molecules in the milieu of the extracellular matrix (ECM), activated by various signal transduction pathways. During angiogenesis vascular capillary endothelial cells are activated to proliferate, migrate, cross cell matrices and form new intercellular adhesions and tubular conduits for enhanced blood flow (Microvasc. Res., 14:53-65, 1977). Under normal physiologic conditions the process of angiogenesis is strictly controlled, vascular endothelial cells are maintained in a quiescent state and turnover is extremely low. In the normal state the process is only

Exhibit 8
Association of Microvessel Intensity with Poor Prognosis

Tumor Type	Selected References
Breast cancer	NEJM 324:1-8, 1991; Hum. Pathol. 23:755-61, 1992; Lancet 340:1120-24, 1992; J NCI 84:1875-87, 1992; Internatl. J Cancer 55:341-74, 1993; J Clinc. Oncol. 12:454-66, 1994;
Prostate cancer	Am J Pathol 143:401-9, 1993; Cancer 73:678-87, 1994
Lung cancer (nsclc)	Lancet 340: 145-56, 1992; Cancer 74:2245-51, 1994
Brain cancer	Lancet 334:82-86, 1994
Melanoma	Eur. J Cancer Clinc. Oncol. 22:1205-9, 1986; Lab. Invest. 67:331-37, 1992
Ovarian cancer	Am. J Pathol., 1995
Head & neck cancer	Internatl. J Cancer 55:1-6,1993; Am. J Surg. 168:373-80, 1994 (squamous) cancer
Rectal cancer	Dis. Colon Rectum 37:921-26, 1994
Testicular cancer	Cancer Res. 54:2800-802, 1994
Bladder cancer	J NCI, Vol. 87, No. 21, Nov 1, 1995, pp 1603-12; J Urology, 1995
Gastric cancer	J Clinc. Oncol. 13:477-871, 1995
Pancreatic cancer	Nature 339:58-61 (1989)
Multiple myeloma	Brit. J Hematol. 87:503-8,1994

activated during wound healing and endometrial hypertrophy associated with ovulation. However, in pathologic states such as tumor growth, the regulatory balance is shifted and new vascular channels are formed.

Solid tumors have long been observed to possess extensive vascular channels, but it was assumed for many years that tumor vasculature was merely a product of inflammatory mediators acting on pre-existing vessels resulting in vasodilation. This theory was challenged by Folkman who observed that melanoma cells when implanted into isolated, perfused thyroid glands demonstrated severely restricted growth but when implanted into animals, these small tumors quickly became vascularized and grew exponentially (Cancer, 16:453, 1963). This finding suggested that tumor growth might be arrested when held in an avascular or pre-vascular state. Subsequent investigation by Folkman led to the hypothesis that solid tumors are angiogenesis-dependent, i.e. tumor growth must be preceded by capillary proliferation and vessel formation (NEJM, 285: 1182, 1971). During the past 25 years, significant contributions were made toward a better understanding of the role of angiogenesis in cancer that may result in the development of effective cancer therapies through inhibition of angiogenesis.

The early phase (pre-vascular) of tumor growth, characterized by limited cell populations with small tumor cell mass, is not angiogenesis-dependent. Early, *in situ* carcinomas have been observed to contain fewer than 10^6 cells (J NCI 82:4-6, 1990). Tumors implanted in the avascular cornea grow slowly and at a linear rate but switch to exponential growth after vascularization reaches the implanted specimen. In addition, tumors suspended in the aqueous fluid of the anterior chamber of the eye remain viable, avascular, and limited in size (<1 mm^3) but, when implanted on the iris vessels, they induce angiogenesis and grow rapidly, reaching 16,000 times their original volume within two weeks. Therefore, there is a pre-vascular and neovascular phase of tumor growth with the greatest expansion of tumor cell population occurring during the latter.

MEDIATORS OF ANGIOGENESIS

A number of physiologic and pathologic mediators of angiogenesis, termed "angiogenic factors", have been identified that are released directly from tumor cells, or from host cells (e.g. macrophages, mast cells) recruited by the tumor, or from the surrounding ECM, or from endothelial cells, themselves. Angiogenesis is only one of the many steps involved in tumor growth and metastasis which also involves ECM interactions and cell adhesion. Selected positive mediators of angiogenesis are listed in Exhibit 9.

Growth Factors and their Role in Tumor Growth

More than a dozen factors that promote angiogenesis have been identified, their complete amino acid sequence determined, and their genes cloned; bFGF was the first such molecule purified in 1984. Others include the FGF family (FGF 1-5), TNF-α, TGF-β, PDGF, PD-ECGF, VEGF)/VPF, HGF/scatter factor, proliferin, G-CSF, angiogenin, pleiotrophin and IL-8. Several other growth factors suspected of being mediators of angiogenesis are currently under investigation. Angiogenic factors stimulate vascular endothelial cells to undergo the complex sequence of events necessary for new blood vessel formation, and may simultaneously serve to recruit mast cells to sites of neovascularization. In murine models, PDGF-AB, VEGF and bFGF each cause directed migration of mast cells at picomolar concentrations in a dose-responsive manner. PD-ECGF also appears to promote chemokinesis of mast cells, whereas TNF-α, a weak angiogenic factor, is less effective and epidermal growth factor (EGF), which exhibits minimal angiogenic properties, is ineffective. Genistein effectively dampens chemotactic responses (Gruber BL, etal, Blood, 1995 Oct 1, 86(7):2488-93).

bFGF is a heparin-binding growth factor that is angiogenic *in vivo.* It induces an increase in protease production, causes motility and cell proliferation in cultured epithelial cells and modulates integrin expression in microvascular endothelial cells. The biological activity of bFGF may be potentiated by its binding to heparan sulfate proteoglycans in the ECM. Several oncogenic characteristics of bFGF have been elucidated. It is synthesized by hepatomas, rhabdomyoblastomas, retinoblas-

tomas and many other tumor types (PNAS 83:2448-2452, 1986). Importantly, bFGF-associated angiogenesis is not accompanied by inflammation. Strategies to inhibit bFGF include small molecules and monoclonal antibodies (MAbs).

ProsCure (Cambridge, MA) was formed in 1993 as a subsidiary of Glycan Pharmaceuticals (Cambridge, MA), to develop inhibitors of angiogenic growth factors for cancer applications. These inhibitors are small molecules based on a novel readily synthesized pharmacophore which is a structural and functional homolog of the two sulfated sugar building blocks that make up heparan sulfate. The potent anti-growth factor properties of these compounds resides in their ability to interfere with signal transduction pathways by preventing binding of bFGF or VEGF to cell surface glycoaminoglycan chains. ProsCure has identified and synthesized two structurally-related lead compounds, GL5-6 and GL14.2, by using technology that combines proprietary, high volume screening assays with combinatorial chemistry libraries created in-house. These compounds have shown antitumor activity in syngeneic and xenogeneic models of cancer without causing any serious toxicity. The lead compound, GL14.2, is being developed for the treatment of hormone refractory prostate cancer. Glycan, which shares its facilities, officers and some staff with ProsCure, is concentrating in the areas of inflammation and neurobiology and has alliances with Pfizer and Glaxo Wellcome.

Glycomed (Alameda, CA), a subsidiary of Ligand Pharmaceutical (San Diego, CA) acquired in May, 1995, is evaluating a sulfated oligosaccharide molecule (GM1306/GM1474) which inhibits binding of bFGF to its key cofactor, heparan sulfate. In animal models this agent inhibited the growth and metastasis of orthotopic human lung, renal and colorectal tumors. Glycomed is also developing Galardin(GM6001), a matrix metalloproteinase inhibitor, for both cancer and ophthalmic applications. Glycomed has also identified several MMPI analogs such as carboxylic analogs (GM1489) and N-terminal (P3') modified versions (GM2487 and GM2679).

3-Dimensional Pharmaceuticals (Exton, PA), a private company established in 1993, is using its patented DirectedDiversity automated combinatorial chemistry technique to create libraries of virtual compounds which are robotically synthesized, analyzed using structure activity models, and stored. The company plans to license its technology and has also initiated an in-house pilot program to identify small molecule antagonists of bFGF as angiogenesis inhibitors in cancer and retinopathy.

VEGF/flk-1. Other angiogenic factors are believed to work alone or in concert with bFGF to coordinate the angiogenic response. Vascular endothelial growth factor (VEGF), also referred to as vascular permeability factor (VPF), represents a family of dimeric glycoproteins that affect capillary permeability, stimulate endothelial cell growth *in vitro* and angiogenesis *in vivo.* VEGF is specifically mitogenic for vascular capillary endothelial cells only and is also involved in the regulation of tumor angiogenesis. Neutralizing antibodies against VEGF have been demonstrated to suppress tumor growth *in vivo.* Several tumor lines, among them human A673 rhabdomyosarcoma, G55 glioblastoma multiforme and the SK-LMS-1 leiomyosarcoma, express VEGF mRNA and release VEGF into cell culture media. These tumor cell lines are also tumorigenic in nude mice. However, when tumor-injected nude mice received anti-VEGF MAbs biweekly, tumor growth was dramatically inhibited. The magnitude of the effect was greater in the rhabdomyosarcoma compared to the glioblastoma because of the greater proliferative activity and angiogenic dependency of the former (Nature 362: 841-844, 1993). VEGF expression has been shown to be upregulated by hypoxia. This may represent one mechanism of angiogenesis where the expanding mass exceeds the diffusion distance for the adequate delivery of nutrients and oxygen necessary for tumor cell metabolism.

The VEGF receptors flk-1 and flt-1 are two of four endothelial cell-specific receptor tyrosine kinases (RTKs) that have been isolated and characterized. Flk-1 is exclusively expressed on endothelial cells. It is also an important link in the RTK-mediated signal transduction process which results in endothelial cell activation. Alteration of this receptor, as in the case of the flk-1 TM mutant produces an inactive VEGF/flk-1 TM mutant receptor/ligand system. When this strategy was employed using the encoded defective receptors onto the vascular endothelial cells of C6 glioblastoma cells which had been implanted into nude mice, the defective receptors blocked VEGF-stimulated tumor growth when compared with control tumors with normal flk-1 receptors (Nature 367:576-579, 1994).

The function of the other two RTKs, Tie-1 and Tie-2, has not been fully elucidated but deficiency of these RTKs *in vivo* resulted in abnormal blood-vessel structure during embryogenesis. These two RTKs seem to have distinct functions; Tie-1 is related to endothelial cell differentiation and establishment of blood vessel integrity and Tie-2 participates in angiogenic processes of endothelial cells (Nature, Vol. 376, 6 July 1995). Several companies are developing VEGF/flk-1 and/or flt-1 antagonists, among them Hybridon (Worcester, MA), Sugen (Redwood City, CA), Genentech (South San Francisco, CA), Daiichi Pharmaceutical (Tokyo, Japan), Merck, ProsCure, etc.

Exhibit 9
Positive Mediators of Angiogenesis

Factor	Comments/Reference
Angiogenin	Biochem 24, 5480-5486, 1985
Angiotropin	J Cell Physiol., 1987
Fibroblast growth factor (FGF) family (FGF 1-5); basic fibroblast growth (bFGF) was the first such molecule purified	Science 223:1296-1299, 1984
G-CSF	J Clin. Invest., 1991
Gangliosides	Internat. Review of Cytology, 159:113-60, 1995
Haptoglobin	J Clin.Invest. 91, 977-985, 1993
Hepatocyte growth factor (HGF)/scatter factor	PNAS 1993
Hyaluronic acid fragments	Science 228, 1324-1326, 1985
Interleukin-8 (IL-8)	Science 258, 1798-1801, 1992
Okadaic acid (phosphatase inhibitors)	Prostaglandins, Leukotrienes, Essent. Fatty Acids 47, 11-115, 1992
Platelet-derived endothelial cell growth actor (PD-ECGF)	Biochem 1987
Platelet-derived growth factor (PDGF)	J Clin. Invest. 91, 1822-1829, 1993
Pleiotropin	J Biol. Chem. 1992
Proliferin (placental growth factor)	Science 1994
Transforming growth factor-α (TGF-α)	Science 1986
Transforming growth factor-β (TGF-β, *in vivo*)	PNAS USA (1986) 83, 4167-71; TGF-β is a potent chemoattractant for macrophages; TGF-β-induced neovascularization is associated with an inflammatory process
Tumor necrosis factor-α (TNF-α, extralumenal)	Nature (1987) 329, 630-632; PNAS 1987; antibodies to TNF-α have been shown to neutralize angiogenic activity
Vascular endothelial growth factor (VEGF)/vascular permeability factor (VPF)	Science 246, 1309-1311, 1989

Hybridon has identified specific sequences on the VEGF messenger RNA as targets for chemically-modified antisense oligonucleotides and has synthesized oligonucleotides that inhibit the expression of the VEGF gene in *in vitro* and tissue culture assays. Hybridon currently is evaluating these compounds in an animal model. The company is also synthesizing chemically-modified antisense oligonucleotides designed to inhibit the expression of the VEGF gene in retinal cells.

The Extracellular Matrix and its Role in Angiogenesis

The extracellular matrix (ECM) plays an important role in the maintenance of endothelial cells and in the formation of new blood vessels. ECM influences cell growth by mediating attachment and, thus, altering cell shape. Anchorage-dependent cells typically proliferate more rapidly in response to mitogens as the cells become more extended compared to the rounded configuration.

Endothelial cells, cultured on layers of gelled basement membrane (Matrigel) *in vitro,* organize into networks which resemble capillaries (J Cell Biol. 107:1589-1598, 1988). Matrigel contains laminin, type IV collagen, and fibronectin but lacks type I collagen. A variety of ECM components which include type I collagen, basement membrane matrix, laminin, and fibronectin can activate endothelial cells to an angiogenic phenotype *in vitro.* The mechanism governing the regulatory activity of these endothelial cells is likely mediated through chemical signaling and binding interactions with cytoskeletal proteins.

Fibronectins are high molecular mass adhesive glycoproteins present in ECM. They participate in various biological processes such as establishment and maintenance of normal cell morphology, cell migration, homeostasis and thrombosis and angiogenesis. Fibronectin comprises several structurally and functionally different isoforms resulting from the alternative splicing of three regions (IIICS, ED-A, ED-B) of the fibronectin primary transcript as well as from post-translational modifications. In cell culture studies, the influence of ECM fibronectin and cell shape can supersede that of soluble angiogenic factors. In the presence of saturating amounts of bFGF, endothelial cell proliferation is enhanced in direct proportion to the concentration of fibronectin (PNAS 87:3579-3583, 1990). Increased amounts of fibronectin is associated with a greater degree of cell membrane extensions. This promotion of cell spreading, in turn, enhances the mitogenic activity of bFGF. Thus, there is an apparent connection between endothelial cell shape and proliferation rates.

Antisoma (London, UK) obtained, in August 1995, exclusive worldwide licensing rights from the Italian National Institute of Cancer Research (Genoa, Italy) to a murine MAb directed against an antigen of fibronectin domain ED-B believed to be uniquely expressed on tumor blood vessels. The MAb was effective in detecting and destroying tumors in pilot tests. Antisoma is conducting preclinical studies with the MAb, in collaboration with the Institute for Molecular Medicine (Oxford, UK), and has converted it into functional fragments, in anticipation of human clinical trials. In addition to its potential application in cancer diagnosis and therapy, the MAb will be tested in other angiogenesis-related disorders, such as inflammation and abnormal blood vessel growth on the retina.

Laminin is a major ECM component associated with endothelial cell alignment and capillary tube formation. Two domains of this molecule are important in this process. The YIGSR sequence in the B1 chain induces a ring-shaped orientation to endothelial cells which resembles a capillary lumen, while the RGD-containing sequence binds an endothelial cell surface integrin receptor for cell attachment (Cell 58:7-802, 1989). Synthetic peptides at two sites in the laminin B1 chain (the RGD and YIGSR sequences) inhibit angiogenesis, whereas a third site in the A chain, designated SIK-VAV stimulates vessel and tumor cell growth (Path. Res. and Practice, 1994 Oct, 190(9-10):854-63). SIK-VAV is responsible for inducing endothelial cell migration and invasion *in vitro* and is a potent stimulator of angiogenesis *in vivo* (J Cell Phys. 153: 614-625, 1992).

Sequus Pharmaceuticals (Menlo Park, CA) has attached a small peptide inhibitor of angiogenesis to polyethylene glycol (PEG) on the surface of the long-circulating Stealth liposomes. Designated YIGSR/SPI-42, this pentapeptide inhibits laying down of laminin. Liposome delivery is used to improve the agent's pharmacokinetics by preventing its rapid clearance and, by presenting it on a multivalent array on the surface of the liposome, it enhances its opportunity to interact with its target.

Proteases and ECM Turnover

During capillary formation, activated endothelial cells must degrade and migrate through the basement membrane and ECM toward the interstitium. The secretion of proteases necessary for this migratory effort is, thus, a vital component of the angiogenic process. A similar process is essential for tumor cell invasion in metastatic cancer. The degradative enzymes involved include the serine proteases, in particular the plasminogen activator/plasmin system and the matrix metalloproteinases (MMPs).

Matrix metalloproteinases. At least nine different MMPs have been identified, including collagenases which degrade fibrillar interstitial collagens, stromelysins which hydrolyze proteoglycans and ECM glycoproteins, and gelatinases (type IV collagenases) which degrade basement membranes and denatured collagens (J Biol. Chem. 269:2032-2040, 1994). Gelatinase A (also known as 72K gelatinase or MMP2), which is frequently overexpressed in stromal cells of malignant tumors, degrades collagen types IV and V, elastin and laminin.

In addition, there is increasing evidence that plasma membrane-bound proteolytic enzymes or membrane-type MMP (MT-MMP) localize matrix destruction to the vicinity of the cell surface and may play a role in the amplification of ECM turnover by activating other enzymes (Nature 370:14-15, 1994). Cytokines can also influence protease activity. For example, both bFGF and VEGF enhance ECM degradation by increasing synthesis of proteolytic enzymes (J Cell Phys. 161:1-14, 1994). The addition of anti-recombinant bFGF IgG abolishes this protease up-regulation and blocks *in vitro* angiogenesis. The enzymatic activity of the MMPs can also be mitigated by the tissue inhibitors of MMPs, TIMP-1 and TIMP-2 (Molec. Carcinog. 10: 207-215, 1994). Thus, homeostatic regulatory control of ECM turnover is a balance between MMP and TIMP production which significantly influences tumor growth.

Celltech (Slough, Berks, UK) announced in October 1995 that it had entered into a collaborative agreement with Zeneca Group to develop gelatinase inhibitors as anticancer agents. Celltech, which has developed and patented several such compounds, will receive up to £10 million to identify suitable candidates. Zeneca will fund the clinical development of the suitable candidate and retain exclusive worldwide marketing rights while Celltech will receive royalties on future sales.

Endothelial Cell Adhesion Molecules

Vascular endothelial cells are anchorage-dependent and can be induced to undergo apoptosis when detached from substrate (J Cell Biol. 124:619-626,1994). During angiogenesis, endothelial cells proceed through a complex sequence of events which are mediated through cell-ECM and cell-cell attachment/detachment interactions. Transmembrane adhesion molecules, primarily responsible for vascular endothelial cell attachment to ECM, include the integrins, a family of molecules formed from the non-covalent association of α and β subunits. Combinations of particular α and β subunits confer receptor specificity to a given membrane-bound adhesion molecule for particular components of the surrounding matrix. ECM components recognized by the integrins include vitronectin, fibronectin, laminin, and denatured collagen.

αvβ3 integrin or vitronectin receptor (VNR) is an RGD-dependent receptor responsible for a number of endothelial cell-ECM adhesion interactions. It is the most promiscuous of all integrins because of its affinity for a variety of ECM components, including vitronectin, fibronectin, fibrinogen, von Willebrand factor, osteopontin, laminin, and denatured collagen (PNAS 84:6471-6475, 1987). This integrin is expressed on a small group of cells which include proliferating endothelial cells, smooth muscle cells, and some malignant neoplastic cells such as melanoma and glioblastoma. High levels of VNR are expressed on newly formed endothelial cells during angiogenesis (Science 264:569-571, 1994) but not on nonproliferating endothelium. VNR is, therefore, an excellent potential anti-angiogenesis target. Attachment of VNR-expressing cells to ECM proteins containing an RGD tripeptide sequence is preventable by RGD peptides and by LM609, a murine MAb that blocks the specific function of the αvβ3 complex. LM609 prevents the migration and proliferation of endothelial cells in response to bFGF, VEGF, TNF-α and tumor-secreted growth factors during angiogenesis. LM609 prevents angiogenesis and inhibits tumor growth and metastasis in animal models by inducing apoptosis of primary endothelial cells caused by detachment of proliferating endothelial cells to the substratum through the αvβ3 integrin. Inhibition of angiogenesis by LM609 or a cyclic peptide antagonist of VNR, leads to tumor shrinkage and complete necrosis. LM609 also inhibits new blood vessel growth in various angiogenesis models.

Ixsys (San Diego, CA) is developing Vitaxin, the humanized version of MAb LM609, under a licensing agreement with Scripps Research Institute (La Jolla, CA). According to a presentation by Judith A. Varner, PhD, at ASCO 95, Vitaxin was humanized at Ixsys by sequencing the cDNA for the murine antibody, identifying complementarity determining regions (CDRs) and grafting the murine CDRs onto a human immunoglobulin backbone, using Ixsys' patented codon-based synthesis procedure to vary framework residues which have been found to be critical to the maintenance of antibody specificity and activity. The full length humanized MAb displays the same affinity and anti-adhesive and antiangiogenic properties as the murine LM609. Efficacy studies, safety studies for both IV and intraocular routes of admin-istration and tissue crossreactivity studies are being conducted in animal models. Clinical trials in Kaposi's sarcoma, astrocytoma, melanoma or breast, prostate and colon cancer, are being planned. Ixsys is also developing patented high affinity, cyclic non-RGD peptide antagonists of VNR which exhibit extreme specificity for VNR.

Other adhesion molecules. Studies of inflammatory models of angiogenesis also support the role of adhesion molecules as key components of new blood vessel formation. Leukocyte invasion of inflamed tissue requires adhesion to endothelial cells. This is mediated by an increased expression of the endothelial adhesion molecules E-selectin and vascular-cell-adhesion molecule-1 (VCAM-1). Recombinant human soluble E-selectin and VCAM-1 are chemotactic for endothelial cells *in vitro*. Antibodies directed against these molecules significantly reduced angiogenesis *in vitro* and *in vivo* (Nature 376:517-519, 1995).

THE ROLE OF ANGIOGENESIS IN CANCER METASTASIS

Vascular channels within tumors serve as the major route for malignant cells to travel to distant sites. Once tumor cells reach the remote location, several possible growth patterns may arise. Micrometastases may immediately grow or they may become dormant. Dormant metastases can grow along with the primary tumor or remain undetected until after the primary tumor is surgically removed. In the latter case, the latency period can be short (weeks to months) or of several years duration. Folkman's hypothesis regarding "dormant metastases" invokes a switch to the angiogenic phenotype that is controlled in part by the balance of angiogenic stimulators and inhibitors secreted by the primary tumor (Nature Medicine 1:27-31, 1995). Positive regulators which promote tumor growth by inducing angiogenesis must be increased, while negative angiogenic regulators are decreased. The primary tumor is, therefore, capable of inhibiting the growth of metastases by up-regulating the production of angiogenic inhibitors such as thrombospondin or angiostatin. This type of regulation has been demonstrated in an experimental mouse Lewis lung carcinoma model. Angiogenesis and tumor growth was observed in metastatic lesions following removal of the primary tumor. This correlated with a decline in angiostatin levels detected in the circulation. EntreMed (Rockville, MD) has cloned, scaled-up production and purified angiostatin, in anticipation of upcoming clinical trials. In preclinical evaluations the agent was found to inhibit both primary tumors and tumor metastases.

Why is angiogenesis correlated with increased recurrence or metastatic risk? In the multistep model of malignant progression, angiogenesis is independent of other steps in tumorigenesis. Tumor cells rarely escape into the circulation before the primary tumor is well-vascularized, and micrometastases cannot grow to any significant degree until they become vascularized (Cancer Treat. Res. 40:223-38, 1988; Biochem. Biophys. Acta 1032:89-118, 1990). Folkman has proposed that angiogenesis intensity, as evidenced by increased number of microvessels, may indicate greater areas of focal "hot spots" that comprise subclones of highly angiogenic cells (J Clin. Oncol. 12: 441-443, 1994). This heterogeneity in tumors has also been shown in transgenic mice models (Nature 339:58-61, 1989; Cell 66:1095-1104, 1991). When a higher proportion of neoplastic cells express this

phenotype there is a greater likelihood of tumor vascularization and shedding of these cells from the primary tumor. Moreover, neovascularization enlarges the total surface area of endothelium by which tumors can escape into the circulation (Cancer Res. 34:997-1004, 1974). Detection of angiogenic peptides in the circulation might indicate a "high output" from angiogenic cells, especially given that released molecules are diluted within the circulatory space, and normally are rapidly metabolized (Growth Factors 1:157-64, 1989). Presence of angiogenic stimulators may overwhelm the physiologic quiescent state of the endothelium (which depends on endogenous inhibitors such as thrombospondin or TIMP, or tumor-secreted inhibitors such as angiostatin), and thus permit micrometastases to grow.

ANGIOGENESIS IN CLINICAL ONCOLOGY

Angiogenesis research is beginning to yield new avenues for the diagnosis, prognosis and treatment of cancer. A large body of experimental work has shed light on the molecular and cellular steps of tumor angiogenesis, with each step representing a potential target for antiangiogenic therapy (Biologic Therapy of Cancer 1991: 743-753, Lippincott, Philadelphia). Strategic approaches for antiangiogenic therapy are shown in Exhibit 10.

Inhibition of Angiogenesis

In two decades of effort, angiogenesis inhibitor molecules have been identified, purified and synthesized and are currently being developed for clinical use. The first angiogenesis inhibitors were discovered in extracts from naturally avascular tissues, such as cartilage and vitreous humor from the eye. Subsequently, virtually all inhibitors were discovered by serendipity or by random screening of natural compounds. One notable exception is the identification and purification of angiostatin (Cell 79:1-20, 1994). At this writing, over 200 compounds have been reported to possess angiostatic properties *in vitro* and/or i*n vivo*. Many of these inhibitors occur physiologically, originate in the natural world, can be synthesized, or are drug compounds already in clinical use (e.g., methotrexate, paclitaxel, D-penicillamine, bleomycin) for which angiogenesis inhibition is a newly identified feature (Pharmac. Ther. 63:265-311, 1994).

Physiological inhibitors of angiogenesis. Angiogenesis inhibitory molecules have been found in healthy as well as diseased tissues (Molec. Med. 1(2):120-122, 1995). There are many inhibitors which appear to play a physiological role in suppressing neovascularization, among them the interferons which inhibit release of angiogenic factors; platelet factor-4 and heparinases which inhibit binding of angiogenic cytokines to endothelium; proteinase inhibitors, such as TIMP, cartilage-derived inhibitor (CDI) and plasminogen activator inhibitor (PAI) which interfere with ECM remodeling processes; and a number of other endogenous molecules (thrombospondin, angiostatin, proliferin-related protein, tetrahydrocortisol S) which directly suppress endothelial cell activity. Expression and activity of these molecules may play a role in rendering healthy tissues resistant to tumor invasion as well as suppressing the growth of primary tumors and their metastases (Nature Med. 1: 27-31, 1995). For example, the wild-type p53 tumor suppressor gene regulates the expression of thrombospondin in healthy cells. In Li-Fraumeni patients with a familial tendency to develop multi-organ malignancies, mutation of p53 down-regulates thrombospondin production resulting in the acceleration of angiogenesis and tumor growth (Cold Spring Harbor Symposia on Quantitative Biology, Vol. LIX: 483-489, 1994).

Angiogenesis inhibitors derived from natural sources. Angiogenesis inhibitors are also found outside of the human body in compounds derived from the natural world (Pharmac. Ther. 63:265-311, 1994). Natural sources of antiangiogenic compounds such as ginseng (ginsenoside), licorice root (isoliquiritin), soy product (genistein) and shark tissue (squalamine), have been long used in traditional healing practices as primary or preventative therapy against certain conditions now known to be angiogenesis-dependent.

Antiangiogenic activities have also been reported in a number in antimicrobial agents such as fumagillin, eponemycin, erbstatin, staurosporine, as well as in bacterial wall components from the *Arthrobacter* species such as tecogalan sodium (J Biochem. 92:1775-1784, 1982) and from Group B Streptococcus such as CM101 (J Cancer Res. Clin. Oncol. 120:63-70, 1993). Naturally-derived chemotherapeutic compounds, such as paclitaxel (Arteriosclerosis 10:215-222, 1990) and bleomycin (Chem. Pharm. Bull. 38:1790-92, 1990) also possess angiostatic activity that may, in part, explain their efficacy in antitumor therapy. Magnosalin, an extract from the bark of magnolia trees, is another natural compound that inhibits angiogenesis *in vitro* (Int. Arch. Allergy Appl. Immuno. 93:365-370, 1990).

Immunotoxins against the vasculature of solid tumors. Another approach to deprive tumors of blood supply is denudation of the endothelial lining of capillaries in the tumor which in turn causes coagulation and formation of occlusive thrombus blocking blood flow and resulting in necrosis of the tumor parenchyma (J Cont. Rel., 28:195-202, 1994 and PNAS USA, 90:8996-9000, 1994). Immunotoxins constructed with plant or bacterial ribosome-inactivating proteins, targeted to markers unique to the tumor vasculature and not internalized by quiescent endothelial cells, are attractive therapeutic agents because of their exceptional potency and ability to kill non-dividing cells. Other targeting approaches that modulate endothelial cell functions but do not kill the cells, with potential therapeutic activity in solid tumors, include conjugates or fusion proteins of antibodies and procoagulant factors. In addition, because endothelial cells are amenable to genetic modification *in situ*, it may

Exhibit 10
Strategic Approaches for Antiangiogenic Therapy

Disruption of the Release of Angiogenic Stimuli by Inhibiting Release of Angiogenic Factors from Local Tissues or from Tumors

- Interferons

  IFN-α and IFN-β downregulate the expression of bFGF

- Antisense oligonucleotides to bFGF mRNA (AIDS 11(S1): S96, 1995)

Disruption of the Release of Angiogenic Stimuli by Inhibiting Release of Angiogenic Factors from Local Tissues or from Tumors

- Antibodies to block bFGF (Cancer Research 51:6180-84, 1991)
- Sulfated polysaccharide-peptidoglycan complex (Cancer Research 49:6727-30, 1989)
- Pentosan polysulfate (J NCI 84:1716-24, 1992)
- Neutralization of heparin or interference with the heparin-binding moiety of angiogenic factors

  Suramin (Cancer Research 52:5073-75, 1992)

  Small molecule heparin sequence mimics

  Recombinant platelet factor-4 (Science 247:77-79, 1990)

  Lavendustin A, a protein tyrosine kinase (Brit. J Pharmac., 1995 Jan, 114 (2):262-8)

Disruption of Endothelial Cell Receptor-mediated Intracellular Signaling

- Inhibition of protein kinases (PKC).

  Eponemycin (Biochem. Biophys. Res. Commun. 181:1070-76, 1991). In 1990, Bristol-Myers Squibb Research Institute (Tokyo, Japan) reported that eponemycin exhibited specific *in vivo* antitumor effect against B16 melanoma (Sugawara K, etal, Journal of Antibiotics, 1990 Jan, 43(1):8-18) and in 1992 reported that an actinomycete strain produced a novel compound, epoxomicin, closely related to eponemycin, which exhibited *in vivo* antitumor activity (Hanada M, etal, Journal of Antibiotics, 1992 Nov, 45(11):1746-52).

  Staurosporine (J Antibiotics 45:1155-60, 1992b). Researchers at Ciba-Geigy (Basle, Switzerland) reported isolating a nitro analogue of staurosporine and other minor metabolites from the staurosporine-producing *Streptomyces longisporoflavus* strain that inhibited protein kinase C with IC50 values in the nanomolar range (Cai Y, etal, Journal of Antibiotics, 1995 Feb, 48(2):143-8).

  Erbstatin produced a dose-dependent inhibitory action on embryonic angiogenesis and affected the proliferation of vascular endothelial cells in a dose-dependent fashion (Oikawa T, etal, Journal of Antibiotics, 1993 May, 46(5):785-90).

- Rendering endothelial cell surface receptors insensitive to angiogenic cytokines

  Phorbol esters (Cell Biology 104:679-87, 1987)

- Inhibition of GTP-binding proteins

  Octreotide acetate (Patel PC, Surgery 116(6):1148-52, 1994)

Interference with Basement Membrane Degradation, ECM Remodeling, and Basement Membrane Biosynthesis
(required steps during the directional migration of endothelial cells, as well as during capillary tube formation)

- Metalloproteinase inhibitors (Eur. Respiratory J 7:2062-72, 1994)
- Cartilage-derived inhibitors (Science 248:1408-10, 1990)
- Minocycline (Cancer Research 51:672-75, 1991). Researchers at Pharmacia & Upjohn (Kalamazoo, MI) found that the tetracycline analogs minocycline and doxycycline that are inhibitors of MMPs, potently inhibit angiogenesis in an *in vitro* model of aortic sprouting in fibrin gels (Gilbertson-Beadling S, etal, Cancer Chemotherapy and Pharmacology, 1995, 36(5):418-24). In animal models, local treatment with minocycline by a controlled-release polymer implanted at the time of tumor implantation extended median survival time by 530% compared to controls. When treatment was begun 5 days after tumor implantation, minocycline delivered locally or systemically had no effect on survival. However, after tumor resection, treatment with locally-delivered minocycline resulted in a 43% increase in median survival time compared to controls. Treatment with locally-delivered minocycline and systemic BCNU 5 days after tumor implantation resulted in a 93% extension of median survival time compared to BCNU alone. Minocycline affects tumor growth when delivered locally and suggest that minocycline may be a clinically effective modulator of intracranial tumor growth when used in combination with a chemotherapeutic agent and surgical resection (Weingart JD, etal, Journal of Neurosurgery, 1995 Apr, 82(4):635-40)
- Chitin (Cancer Research 50(12):3631-37, 1990) is a cellulose-like biopolymer found in various organisms. Inhibition of lung tumor metastasis by sulfated chitin derivatives (SCM-chitin III) may in part be due to the inhibition of tumor-associated angiogenesis (Murata J, etal, Cancer Research, 1991 Jan 1, 51(1):22-6).
- Angiostatic steroids (Endocrinology 119:1768-75, 1986) such as medroxyprogesterone (PNAS USA 78(2):1176-80, 1981). The inhibitory activities of medroxyprogesterone acetate (MPA)-related compounds (II-VI) were evaluated using bFGF (Yamamoto T, etal, International Journal of Cancer, 1994 Feb 1, 56(3):393-9).
- Plasminogen activator inhibitor (J Cell Biol. 105:2543-2549, 1987)
- Inhibitors of basement membrane collagen biosynthesis

  Tricyclodecan-9-yl-xanthate (D609) (J Pharmacol. Exp. Ther. 252(2):753-757, 1990)

— *continued on next page*

Inhibition of Endothelial Cell Migration and Proliferation

- Nicardipine (Stroke 23:1637-42, 1992)
- TGF-β (PNAS 84:5600-4, 1987)
- Suramin (Brit. J Cancer 68:932-938, 1993)
- Paclitaxel (Arteriosclerosis 10:2504-12, 1990). See this issue (pp 175-185) for a detailed review of the status of taxanes as anticancer agents
- Interferons (Science 208:516-18, 1980)
- 16 KDa fragment of prolactin (Endocrinology 133:1292-1299, 1993)
- Angiostatic steroids (Annals of Surgery 206:374-84, 1987)
- Retinoids (Microvascular Research 41: 47-62, 1991)
- Vitamin D3 (Eur. J Pharmacol. 178:247-250, 1990)
- Genistein, an isoflavonoid, is a dietary-derived angiogenesis inhibitor present in the urine of humans ingesting soy bean-based foods (PNAS USA 90:2690-94, 1993). It is a tyrosine kinase inhibitor of VEGF-promoted proliferation of endothelial cells and tyrosine phosphorylation of SH2 domain containing signaling molecules (Guo D, etal, Journal of Biological Chemistry, 1995 Mar 24, 270(12): 6729-33). Although the biochemical targets of genistein action remain obscure, the concept of dietary chemoprevention of tumors via antiangiogenic compounds is under current investigation. Genistein may contribute to the chemopreventive effect of plant-based diet on solid tumors, by inhibiting neovascularization and tumor cell proliferation (Fotsis T, etal, Journal of Nutrition, 1995 Mar, 125(3 Suppl):790S-797S).
- SPARC (J Cell Biochem 49:272-83, 1992). SPARC (selected protein acidic and rich in cysteine), also known as osteonectin and BM-40, is a metalloprotein belonging to a group of anti-adhesive proteins, including thrombospondin-1 and tenascin. SPARC diminishes the number of focal contacts in cultured epithelial cells and regulates synthesis of several ECM proteins such as plasminogen activator inhibitor-1 (PAI-1). Proteolysis of SPARC produces fragment KGHK which stimulates angiogenesis.
- Nitric oxide (J Clinical Investigation 94:2036-44, 1994)
- Fumagillin analog TNP-470 (Nature 348:555-57, 1990)
- Inhibitors of prostaglandin synthesis (Invasion Metastases 3:151-59, 1983)
- Thrombospondin (Biochem. Biophys. Res. Commun. 170:867-72, 1990)
- High molecular weight hyaluronan (Int. J Radiat. Biol. 60:55-60, 1991)
- Roquinimex (LS-2616, Linomide) (Cancer Research 53:1833-37, 1993)
- Angiostatin (Cell 79:1-20, 1994) is a novel circulating angiogenesis inhibitor that mediates suppression of metastases.
- Triterpene acids, ursolic acid (UA) and oleanolic acid (OA), effectively inhibited proliferation of bovine aortic endothelial cells in a concentration-dependent manner (Sohn KH, etal, Cancer Letters, 1995 Aug 1, 94(2):213-8).
- Gold thiomalate (J Clin. Investigation 79:1440-46, 1987)

Inhibition of Cell-adhesion Interactions Required for Capillary Tube Three-dimensional Organization

- Castanospermine (Cancer Research 55:2920-2926, 1995)
- Arg-Gly-Asp (RGD)-containing peptide Gly-Arg-Gly-Asp-Ser (GRGDS) (Am. J Pathology 138:829-833, 1991)
- 1-deoxymannojirimycin (J Biological Chemistry 267:26157-65, 1992)
- Antibodies against vitronectin (VNR) and fibronectin receptors (J Cell Biochem. 51:206-218, 1993)
- Antibodies to E-selectin (Nature 365:267-2369, 1993)

Interference with Angiogenic Co-factors (such as copper)

- D-penicillamine (J Clinical Investigation 83(1):158-67, 1989)

Inhibition of Inflammatory Cells such as Lymphocytes which can Themselves Elaborate Cytokines

- Cyclosporin (Archives of Ophthalmology 110:405-7, 1992)
- Cortisone acetate plus heparin (J NCI 78(3):581-585, 1987)

Induction of Endothelial Cell Apoptosis

- Monoclonal antibodies against αvβ3 integrin (Science 264:569-571, 1994)
- Retinoids

Induction of Other Angiogenesis Inhibitors

- Interferon-γ induces interleukin 12 (J NCI 87(8):581-86, 1991)

Direct Injury to Proliferating Endothelial Cells

- Group B Streptococcus-derived CM101 (J Cancer Res. Clin. Oncol. 120:63-70, 1993)
- TEC-11 immunotoxin (Thorpe, PE, etal, ASCO95)

be possible to use antibodies to target DNA to tumor endothelial cells to endow them with proinflammatory, immunoregulatory or tumor growth regulatory functions.

Peregrine Pharmaceuticals (Princeton, NJ) has characterized an immunotoxin (TEC 11-A) which consists of a murine IgM MAb, TEC-11, which recognizes endoglin and may be suitable for targeting tumor vessels, linked by means of a disulfide bond to the isolated A chain of the plant toxin ricin. TEC-11 stains endothelial cells in a broad range of solid tumors but weakly stains endothelial cells in the majority of healthy adult tissues. Antibody binding correlates with neoplastic progression in the breast; benign fibroadenomas and early *in-situ* carcinoma bind low levels of TEC-11 whereas late stage intraductal carcinomas and invasive carcinomas bind high levels.

Angiogenesis inhibitors in clinical development. Clinical application of antiangiogenic therapy was pioneered by Carl White, MD, and his colleagues in Denver, who successfully regressed a case of pulmonary hemangiomatosis in a child by administration of recombinant interferon α-2a (NEJM 320:1197-1200, 1989). The child suffered from a type of benign tumor, hemangioendothelioma, comprised almost exclusively of abnormal clusters of proliferating endothelial cells. Because neovascularization is a necessary but not sufficient step for progressive tumor expansion and metastasis, angiogenesis inhibitors will most likely be applied as adjunctive therapy in conjunction with other approaches (e.g., chemotherapy or ionizing radiation) that are directly cytotoxic to tumor cells. Nonetheless, angiostatic agents possess several distinct advantages over conventional cancer chemotherapeutics, including drug selectivity against intratumoral neovascularization and non-toxicity. To date, clinical trials of several angiostatic drugs support the experimental finding that antiangiogenic agents exhibit low toxicity. Another advantage may be lack of drug resistance. Because virtually all capillary endothelial cells lack the multidrug resistance (MDR) gene, antiangiogenic agents may eventually be used for long-term maintenance therapy to prevent tumor recurrence or to suppress metastatic growth.

Specific antiangiogenic agents may also contribute antitumor effects beyond the disruption of tumor vasculature. Interleukin-12, for example, which inhibits neovascularization in Lewis lung carcinoma-bearing mice (J NCI 87:581-586, 1995), also possesses immunomodulatory properties (induction of natural killer cells and activation of cytotoxic T lymphocytes) that contribute to its antitumor effects (J Exp. Med. 178:1223-1230, 1993). Antagonists to specific angiogenic molecules may also serve to enhance or potentiate the efficacy of other cytotoxic drugs. It has been shown, for example, that bFGF transfected into transformed cell lines (NIH 3T3 fibroblasts) decreases the sensitivity of these cells to conventional chemotherapeutics (Oncogene 9:491-499, 1994). Therefore, an anti-bFGF strategy might render tumor cells more susceptible to chemotherapeutic agents, or permit use of lower doses of such drugs. Antagonists to VEGF/VPF may also decrease VEGF/VPF-induced peritumoral edema in critical organs adjacent to the tumor.

British Biotech (Oxford UK) is clinically evaluating two MMPIs, batimastat, an injectable agent currently in phase III clinical trials in malignant pleural effusions, and marimastat (BB-2516), an orally-delivered agent in phase II clinical in advanced solid tumors. Development of batimastat was delayed when trials were suspended in early 1995 because most of 150 patients with advanced ovarian cancer, enrolled in a phase III trial, reported pain and discomfort following injection of the drug. The problem was attributed to a new manufacturing process to scale-up production which has been subsequently modified and trials resumed in June 1995. In mid-1995 British Biotech shifted its development efforts to marimastat, now in phase II clinical trials in advanced cancers of the ovary, prostate, colon and pancreas.

CarboMed (Brentwood, TN), a private company founded in 1990, is developing biopharmaceuticals for the intervention and inhibition of neovascularization in cancer and other diseases. The company's lead anticancer compound, CM101 (was also known as GBS toxin), is a polysaccharide exotoxin produced by group B Streptococcus. CM101 selectively binds to developing blood vessels of tumors and induces a severe inflammatory reaction that leads to destruction of the neovasculature and tumor necrosis without harming healthy tissues. A phase I clinical trial, managed by ClinTrials (Nashville, TN) and conducted at Vanderbilt University School of Medicine (Nashville, TN), was completed in December 1994. This trial enrolled 15 patients with refractory malignancies such as ovarian, colon, biliary, esophageal, duodenal, renal, hepatocellular and prostate cancer and leiomyosarcoma. CM101, infused at 7.5-25 mg/kg over a 15-minute period, three times for one week, induced an acute inflammatory response that was also associated with elevation of soluble E-selectin levels indicating endothelial involvement. Results indicate that CM101 is a potent inducer of cytokine production *in vivo.* CM101 demonstrated antitumor activity and a favorable safety profile with no long-term or cumulative toxicities observed. In December 1994 CarboMed entered into a collaborative agreement with the NCI to clinically evaluate CM101 in phase II and III clinical trials. In animal studies, CM101 induced a strong inflammatory response in the lung associated with pulmonary sequestration of granulocytes and extensive capillary endothelial damage. A similar inflammatory response was observed

in mice when picomole quantities of CM101 were infused in the developing vasculature of transplanted tumors shortly after tumor implantation. Optimum treatment with CM101 caused the majority of tumors to regress and the animals remained tumor-free for over 5 months but some regressed tumors recurred after treatment was stopped (J Cancer Res. and Clin. Onc., 1994, 120(8):479-84).

Daiichi Pharmaceutical (Tokyo, Japan) has initiated a clinical trial with tecogalan sodium (DS-4512) against solid tumors. The company is also collaborating with the NCI to evaluate this agent against Kaposi's sarcoma.

EntreMed (Rockville, MD) is developing thalidomide analogs as angiogenesis inhibitors. Orally administered thalidomide is a potent teratogen probably because of its angiogenic properties (PNAS USA, 1994 Apr 26, 91(9):4082-5). Thalidomide is currently under clinical evaluation by Celgene (Warren, NJ) as an anti-HIV agent and for the treatment of cachexia and aphthous stomatitis in AIDS patients.

Pharmacia Oncology Immunology (Lund, Sweden) is clinically evaluating roquinimex (LS-2616, Linomide), an antiangiogenic agent (Cancer Research 53:1833-37, 1993), for the treatment of prostate cancer (Hartley-Asp B and Borgstrom Per, Modern Developments in Cancer Therapeutics, joint meeting of the Institute of Biomedical Science and the AACR, Taipei, Taiwan, November 7-11, 1994, Abs. P33).

Repligen (Cambridge, MA) is in phase I/II with recombinant platelet factor-4 (rPF4), a genetically-engineered version of a naturally-occurring human protein, in Kaposi's sarcoma, renal and colon cancer and malignant melanoma. Although rPF4 induced tumor shrinkage in a phase II clinical trial in Kaposi's sarcoma, intralesional delivery was suboptimal and systemic delivery is problematic because the protein is rapidly neutralized by adsorption to heparin in the blood stream (ASCO94, Abs. DS 3).

Sugen has initiated phase I clinical trials with its PDGF RTK antagonist, SU101, in malignant glioma. In August 1995, the company finalized a CRADA with the NCI to carry SU101 through phase III clinical trials for various indications, including ovarian cancer.

Takeda/Takeda Abbott Pharmaceuticals (Osaka, Japan and TAP; Deerfield, IL) is evaluating in phase II clinical trials, a fumagillin analog, TNP-470/AGM-1470, which inhibits endothelial cell proliferation (as well as that of other cell types) by blocking the G0 to G1 transition (Cancer Research 54:2073-76, 1994). Although AGM-1470 has displayed antiangiogenic activity in animal models, it has been marginally effective in phase I clinical trials and may be associated with retinal, hepatic, and brain toxicities.

Warner-Lambert, in collaboration with NIH through a CRADA, is evaluating suramin in phase III clinical trials in prostate cancer. In a phase I/II clinical trial, continuous infusion of suramin (175 mg/ml) had modest activity against hormone-refractory prostate cancer with acceptable toxicity (ASCO95, Abs. 624). Suramin delivered intermittently in combination with total androgen blockade in 42 patients resulted in 1 CR, 29 PRs, 9 SDs and 3 PDs (ASCO95, Abs 617).

Prognostic and Diagnostic Applications of Angiogenesis

Investigation of the mechanism of angiogenesis is beginning to yield useful biologic markers that may assist oncologists in delineating the "pre-vascular phase" from the "vascular phase" of tumor growth. Because the pre-vascular phase is associated with restricted tumor growth (early cancer) while the vascular phase is associated with rapid tumor growth and metastases (invasive cancer), angiogenesis-based diagnostic and prognostic tools may provide important clinical information about the biologic aggressiveness of a patient's tumor. The extent of tumor vascularization can have a significant influence on patient survival.

It has been suggested that the key requirement of a prognostic indicator is to possess "clear biological significance" (J NCI 83:154-55, 1991). Although numerous tumor markers (carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), human chorionic gonadotropin (HCG) among others) have been identified, their biological significance remains obscure. In contrast, angiogenesis does have a clear biological role in malignancies and the body of evidence for using microvessel count or detection of circulating angiogenic molecules as a prognostic indicator in solid tumors is clearly mounting. Although a few medical centers are beginning to employ these tools, many oncologists are still unaware of their potential.

The prognostic value of angiogenesis has not as yet been fully assessed. It is possible that every biopsy would be sent to a pathologist for routine microvessel analysis or that kits would be developed for early detection of cancer available in every physician's office. Panels of tests for multiple angiogenic factors by which cancer patients may be monitored for early recurrence may be also developed. It is still too early to establish the prognostic and diagnostic value of angiogenesis. Additional large cohort, multivariate analysis clinical studies would

Exhibit 11
Angiogenesis Inhibitors in Development

Primary Developer/ Affiliate	Generic Name/ Number/Brand Name	Drug type/Target/ Mechanism/Delivery	Status/Location/ Indication	Comments
3-Dimensional Pharmaceuticals		bFGF antagonists	Research/USA	
Antisoma/National Institute of Cancer Research (Genoa, Italy)		MAb directed against antigen ED-B, an extra domain of fibronectin which is uniquely expressed on tumor blood vessels	Preclin/Europe	
Anutech/John Curtin School of Medical Research (Australia)	Castanospermine	Inhibitor of glucosidases that convert protein N-linked high mannose carbohydrates to complex oligosaccharides	Preclin/Australia	In development as an anti-arthritic and immunological agent
Aronex (was Oncologix)	OLX-514, OLX-501; OLX-516	Dioxopiperazines	Research/USA/ solid tumors	No development reported as of 11/95
British Biotech	Batimastat/BB-94	Matrix metalloproteinase inhibitor (MMPI)/IP, IV	Phase II/III/UK/malignant ascites; phase III/UK,USA/malignant pleural effusions	
British Biotech	Marimastat/BB-2516	MMPI with similar antitumor activity to batimastat/PO	Phase II/III/UK, USA/ advanced solid tumors (colorectal, ovarian, pancreatic and prostate)	
CarboMed	CM101 (previously called GBS toxin)	Polysaccharide exotoxin produced by Group B Streptococcus	Phase I (completed 12/94)/USA/solid tumors; phase II (to start in 1996 in collaboration with the NCI/USA/lung cancer	Does not inhibit wound healing in murine models (Quinn TE, etal, Journal of Cancer Research and Clinical Oncology, 1995, 121(4): 253-6); also see ASCO95, Abs. 1591, 1592
Cell Therapeutics	CT-2584	Small molecule/regulates tumor phospholipase-D (PLD) enzyme activity and phosphaditic acid production	Phase I/Ib/UK/ solid tumors	In collaboration with Christie Hospital (Manchester, UK) under the sponsorship of the Cancer Research Campaign (CRC; London, UK)
Celltech/Zeneca		Small molecule/MMPI, gelatinase inhibitor	Preclin/UK	
Daiichi Pharmaceutical	Tecogalan sodium; D-gluco-d-galactan sulfate/DS-4152	Bacteria-derived sulfated poly-saccharide/inhibits bFGF, VEGF, and bFGF + VEGF-stimulated proliferation, migration, and tube formation by choroidal endothelial cells *in vitro*; inhibits growth and chemotaxis of cells stimulated by bFGF and prevents binding of bFGF to cells at both its low and high affinity binding sites	Phase I/solid tumors; phase I/Kaposi's sarcoma in collaboration with the NCI	
EntreMed	Thalidomide analogs	Blocks TNF-α formation	Phase II/USA/prostate, breast, brain and skin cancer	In collaboration with the NCI
EntreMed	Angiostatin	Natural protein/prevents metastasis	Preclin/USA	
Fujisawa	FR-111142	Natural product/ isolated from *Scolecobasidium arenarium* F-2015 fungus/IP, IV	Preclin/Japan	
Genentech		MAbs and soluble receptors/ VEGF inhibitors	Preclin/USA	

— continued on next page

Genetics Institute (cross-licensed with Hoffmann-La Roche)/ Wyeth-Ayerst (ww except Japan; Yamanouchi in Japan)	Recombinant interleukin-12/rhIL-12	Enhances the immune system's killing ability and may trigger production of other immune system regulatory proteins that may initiate an adaptive immune response	Phase I/II (suspended 5/95 due to deaths)/ USA	In preclinical models of a variety of cancers, rhIL-12 either caused tumors to shrink or entirely eliminated them; also see FO, V1, #2/3 p 52
Glycomed (Ligand Pharmaceuticals)	GM-1306, GM-1474	Sulfated oligosaccharide compounds/block bFGF binding to heparan sulfate	Preclin/USA/ solid tumors	
Glycomed (Ligand Pharmaceuticals)	GM-6001/Galardin	Matrix metalloproteinase inhibitor	Preclin/USA	In phase III in ophthalmic topical applications (corneal ulcer
Hoffmann-La Roche	Interleukin-12 (IL-12)		Phase I/USA	See Genetics Institute
Hybridon	Phosphorothioate antisense oligonucleotide	Antisense oligonucleotide/ VEGF mRNA inhibitors	Research/USA	
Ivax	Pentosan polysulfate		Preclin/USA	Launched in the USA as Elmiron for the treatment of interstitial cystitis
Ixsys		Non-RED peptides/ VNR antagonists	Research/USA	
Ixsys/ Scripps Research Institute (licensor)	LM609/Vitaxin	Humanized MAb/VNR antagonist	Preclin/USA/ solid tumors	
Kyowa Hakko Kogyo	7-hydroxystaurosporine/ UCN-01, UCN-02	Natural product derived from Streptomyces sp./selective protein kinase C inhibitor	Preclin/Japan	Akinaga, S, etal, Cancer Chemotherapy and Pharmacology, 1993, 32(3):183-9
Magainin Pharmaceuticals	Squalamine	Aminosterol isolated from the dogfish shark, *Squalus acanthas;* cationic steroid/antibacterial	Research/USA	
Merck		Soluble flt-1 VEGF receptor	Preclin/USA	
Pharmacia Oncology Immunology (Pharmacia & Upjohn)	Roquinimex/LS-2616/ Linomide	Quinoline-3-carboxamide/ immunomodulator/PO	Phase II/Europe/ renal cancer; preclin/ Sweden/prostate cancer	No significant toxicity was observed
Pharmacia Oncology Immunology (Pharmacia & Upjohn)	Minocycline	Semisynthetic tetracycline/ inhibits tumor-induced angiogenesis/local delivery with a controlled-release polymer or systemically by IP	Preclin/USA/ intracranial9L glioma alone and with 1, 3-bis (2-chloroethyl)-1-nitrosourea (BCNU) *in vivo*	Department of Neurological Surgery, Johns Hopkins University School of Medicine
Peregrine Pharmaceuticals (Princeton, NJ)	TEC 11-A	Immunotoxin; TEC-11 MAb linked to ricin A toxin/targets endoglin on epithelium of vessels supplying tumors	Preclin/USA	
ProsCure (Glycan Pharmaceuticals)	GL14.2 and GL5-6	Small molecules/inhibit binding of bFGF and/or VEGF to heparan sulfate on tumor cells	Preclin/USA	
Repligen/New York University; Centocor	Recombinant platelet factor 4 (rPF4)	Recombinant protein/IV, SC and intralesional	Phase II/USA/brain, colon, renal cell and breast cancer, Kaposi's sarcoma and melanoma	
Sandoz	Ocreotide	Somatostatin analog	Clinical/USA	Launched in the treatment of carcinoid syndrome
Schering-Plough Research Institute		Small molecules/αvβ3 integrin antagonists	Preclin/USA	
Sequus Pharmaceuticals	YIGSR/SPI-42	Small molecule/ PEG-liposome delivery	Preclin/USA	
SmithKline Beecham		αvβ3 integrin antagonists	Preclin/USA	
Sugen	SU101	Small molecule/signal transduction inhibitor; PDGF antagonist/IV	Phase I/USA	Being developed under an NCI CRADA; orphan drug
Sugen		Small molecule/ flk-1 antagonist	Preclin/USA/ solid tumors	

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Takeda/Takeda Abbott Pharmaceuticals (TAP)	TNP-470 (AGM-1470)	Synthetic analog of the antibiotic fumagillin	Phase I/II/USA	Phase I clinical trials for Kaposi's sarcoma are ongoing at the Dana-Farber Cancer Institute in collaboration with the NCI (ASCO, May 1995, Abstract # 794)
Takeda	TAN-1120	Natural product isolated from *Streptomyces triangulatus*	Preclin/Japan/ solid tumors	Suspended as reported by Takeda (11/95)
USC Norris Comprehensive Cancer Center, Dept. of Biochemistry and Molecular Biology	Contortrostatin	Snake venom disintegrin/ antiangiogenic, anti-platelet agent	Preclin/USA/ metastatic melanoma, breast cancer	
Warner-Lambert	CI-994; PD-130636	May be antiangiogenic	Phase I/UK/solid tumors, colon and breast cancer	
Warner-Lambert/ NIH (developer)	Suramin		Phase III/USA/ prostate cancer	ASCO95, Abs. 40, 617, 624, 685, 1490, 1516

be extremely compelling if they continue to confirm all the evidence to date. Evaluation of tumor angiogenesis may help to identify those patients who are at highest risk for recurrence and metastases in order to facilitate early and aggressive treatment. For example, although node-negative breast cancer patients as a group benefit from adjuvant chemotherapy (NEJM 320:485-90, 1989), it would be useful to identify, in advance, the fraction (approximately 25%) of patients at risk for recurrence, in order to eliminate unnecessary morbidity and cost of treating the remaining 75%. Furthermore, such patients may be treated with angiogenesis inhibitors.

Moreover, although presence of angiogenic peptides does not always correlate with presence of tumor, their detection in body fluids generally indicates disease in all studies published to date. Thus, monitoring circulating angiogenic factors may provide an adjunctive means for the early detection of cancer. For example, analysis of blood or urine might one day become a cost-effective and simple aid to identify patients at high risk for cancer. Detection of angiogenic peptides might also help in diagnostically difficult cases where conventional blood tests and imaging techniques are ambiguous. For some cancer patients (e.g., brain tumors), who are at extremely high risk of local recurrence, regular sampling (by lumbar punctures, for example), instead of costly imaging technology or invasive brain biopsy, might detect early recurrence before onset of clinical symptoms.

Methods for detecting and quantifying angiogenesis in patients. The intensity of tumor angiogenesis can be measured by counting microvessels in histologic specimens or by detecting angiogenic peptides in body fluids. Both techniques were shown to have prognostic importance in a number of cancer studies. Other assays are also available to test and quantify specific components of the angiogenic process. For example, even before angiogenic molecules were fully characterized, *in vitro* assays were used to test body fluids for their ability to stimulate endothelial cell proliferation, chemotaxis, migration and capillary tube formation.

Gene expression for angiogenic molecules may be detected by techniques such as Northern blot analysis, *in situ* hybridization, and by polymerase chain reaction (Neurosurgery 35:439-49, 1994). Direct measurement of endothelial proliferation may be accomplished by labeling DNA synthesis with tritiated thymidine or bromodeoxyuridine (Neurosurgery 25:715-19, 1989). Confocal microscopy uses a laser scanning microscope to examine the three-dimensional nature and distribution of blood vessels within specimens (J Clin. Invest. 93:2357-64, 1994). Methods to indirectly assess the presence of angiogenesis include magnetic resonance imaging (MRI) with gadolinium enhancement which indicates increased vascularity (Radiol. Clin. North America 26:873-87, 1988), and color Doppler ultrasound which can detect tumor blood flow (Cancer 73:1251-56, 1994).

Cancer prognosis by the quantification of microvessels in solid tumors. As early as 1972, Brem, etal, suggested that the density of intratumoral vessels might correlate with tumor aggressiveness (J NCI 48:347-56, 1972) and created a microscopic angiogenesis grading system (MAGS) to evaluate such pathologic features as vascular density, endothelial cell hyperplasia, and cytology. Noel Weidner and colleagues performed a landmark retrospective study in 1991, using antibodies against factor VIII-related antigen (FVIIIra, an endothelial marker) to count microvessels within invasive breast carcinoma (NEJM 324:1-8, 1991). Intratumoral microvessel density was evaluated within so-called "hot spots" of intense neovascularization. In biopsies collected at the time of diagnosis, an increased microvessel count in the cancerous tissue corresponded with a rise in the occurrence of future metastases. Significantly, 100% of patients went on to develop distant metastases when microvessel

counts exceeded 100 (per 200x field). A blinded study between two independent research groups compared microvessel count in 165 patients to such commonly-used prognostic indicators as axillary lymph node status, tumor size, histologic grade, DNA ploidy, flow cytometry, c-erbB2, pre-cathepsin-D and hormone receptor status, among others (J NCI 84:1857-87, 1992). Using uni- and multi-variate analysis, the authors concluded that decreased microvessel intensity was associated with overall and relapse-free survival in all patients, and was the only significant predictor of survival among node-negative women. Several reports have since confirmed the association between microvessel density and risk of metastases in invasive breast carcinoma. A few studies have reported lack of prognostic relevance of tumor microvessel count in breast cancer (Eur. J Cancer 90A:1141-45, 1993 and Surg. Oncol. 1:223-29, 1992) but counting techniques employed by the authors did not appear to adhere to recommended detailed protocol.

Other than FVIIIra, a variety of endothelial markers have been used including CD31, CD34, and *Ulex europaeus* lectins (Am. J Pathol. 143:99-104, 1993). CD-31 is considered by some to be the most sensitive marker for endothelial cells (J Clin. Oncol. 13:765-82, 1995). MAbs against endothelial cell-proliferation antigens, such as E-9 (Int. J Cancer 54:363-70, 1993) or TEC-11 (PNAS USA 90:8996-9000, 1993), under development have the potential to be specific markers for neovascularization.

Detection of angiogenic peptides in body fluids of cancer patients. Enzyme-linked immunoassays (EIA) can detect and quantify specific angiogenic peptides in body fluids. A time-resolved immunofluorimetric assay for VEGF has been developed with a sensitivity of 200 pg/ml (Clin. Chem. 38:71, 1992). A sandwich-type immunoassay for bFGF, with a sensitivity of 30 pg/ml, developed at Takeda Chemical Industries (Osaka, Japan), was used to detect bFGF in serum of patients with renal cell carcinoma (Biochem Biophys. Res. Commun. 175:229-35, 1991). In another study using this EIA, no bFGF was detected in the serum of over 200 normal blood donors but was elevated in a subset of cancer patients (Mol. Biol. Cell 3:234a, 1992). Using an assay developed by R&D Systems (Minneapolis, MN) with a sensitivity of 1 pg/ml, it was recently shown that bFGF is present in serum of patients with cervical cancer (Cancer Letters 94:227-31, 1995).

Pilot studies have detected elevated bFGF in serum of breast cancer patients (Mol. Biol. Cell 3:234a, 1992 Proceedings of ASCO 12:113, 1993). This serum also stimulated endothelial cell proliferation *in vitro.* Proliferative activity and bFGF had independent prognostic value which increased significantly when both were considered jointly. Elevated levels of bFGF, detected in the urine of bladder cancer patients, was associated with extent and status of disease (J NCI 86:356-61, 1994). In a prospective study of CSF from children with brain tumors, the presence of bFGF was corelated with biological activity, increased intratumoral angiogenesis, and poor prognosis (Lancet 344:82-6, 1994). Because bFGF lacks a signal peptide for secretion, it is not clear how bFGF is released into body fluids. However, the switch to the angiogenic phenotype in a transgenic mouse model does correlate with the export of bFGF from within tumor cells (Cell 66:1095-104, 1991).

It is likely that there are multiple angiogenic factors in the body fluids of cancer patients. While angiogenesis is a common pathway in malignancy, different tumors may elaborate different angiogenic factors or a mixture of factors. Detection by immunoassay would be a particularly practical method in the hospital-setting because only small specimen volumes are required. Early reports, showing an association between specific angiogenic molecules and clinical outcome, will likely provide a driving force for the development of a wide range of immunoassays that will enable further studies to be conducted.

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