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ANTICANCER DRUGS AND MARKETS

UPDATE ON SPINDLE POISONS — PART I TAXANES, GENERIC PACLITAXEL, AND NOVEL FORMULATIONS AND ANALOGS

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Spindle poisons represent a class of agents with potent anticancer activity. The success of one subtype of this class of agents, namely the taxanes, have spurred developers to pursue a number of avenues to either improve the performance of existing drugs, synthesize novel analogs, or identify totally different categories of agents with similar mechanisms of action. This multipart series has been designed to provide a comprehensive review of the commercial, clinical, and research status of spindle poisons as anticancer agents. Part I of this series concentrates on the commercially available taxanes, generic versions of paclitaxel, various novel formulations of commercially available taxanes, and closely related paclitaxel and docetaxel analogs. Upcoming articles will describe the clinical utility of spindle poisons, establish their opportunity based on certain indications as monotherapy or combination therapy, stressing their synergism with novel regulatory agents, and profile numerous novel spindle poisons in development.

This issue provides new and updated information on taxanes either on the market or in development. Information contained in past issues of FUTURE ONCOLOGY (pp 614-620, 635-641, 801-806, and 1025-1039) regarding this sector, is not repeated in this presentation; issues containing past articles may be purchased from NEW MEDICINE. Information about commercially available drugs and agents in development, presented in this article, has been gleaned from NEW MEDICINE's Oncology KnowledgeBASE (nm|OK) residing at www.oncologyknowledgebase.com.

CURRENT MARKETS FOR COMMERCIALLY AVAILABLE TAXANES

As stressed in previous reviews of this class of agents, taxanes will continue to be used extensively for the indications for which they have been approved to date, and expand into additional ones. However, although their clinical utility is ensured, revenues of individual drugs will fall victim to competition, as generic versions are being introduced both in the USA and abroad.

Combined global sales of taxanes were $2,300.7 million in 2001, slightly down from $2,315.8 million in 2000, which was up 13% from 1999 levels, as shown in Exhibits 1 and 2 (comparisons are in USA dollars which are converted from euros at the time of reporting). The deceleration of the dollar markets for this class of drugs is attributed to the introduction of generic paclitaxel in the USA, and does not reflect demand for these drugs as illustrated by the growth of docetaxel sales. Generic competition will continue to erode the USA market for paclitaxel. In the USA, sales of taxanes were $545.0 million in 2001, reflecting a decline of 45.0% from 2000 levels of Taxol revenues (Exhibit 3).

MECHANISM OF ACTION OF TAXANES AND SPINDLE POISONS

Spindle poisons comprise a diverse group of natural and semisynthetic and synthetic cytotoxic agents that act by interfering with microtubule function, causing mitotic arrest. These agents may be further classified in two groups, spindle poisons like taxanes that stabilize microtubule lattices or those, among them the vinca alkaloids, that preferentially form alternate lattice contacts and polymers at microtubule ends.

Microtubules are cytoskeletal components composed of various proteins, including tubulin, that are known to be a major filament of the cytoskelton in the mitotic apparatus of eucaryotic cells. Microtubules play a role in various biological functions, including mitosis, cell motility and intracellular transport. Tubulin is a guanosine triphosphate (GTP)-binding protein that is one of the major microtubular components. The polymerization and depolymerization of tubulin regulates microtubular dynamics (Fukuoka K and Saijo N, Gan To Karaku Ryoho, Sep 1997;24(11):1519-25). The structural integrity of microtubules is necessary for the execution of many basic cell functions. Microtubule-interfering agents arrest dividing cells at the G2/M phase of the cell cycle (for more about the cell cycle and cancer see FO, pp 591-600).

The exact mechanism of anticancer action, however, differs among individual spindle poisons, and may have a significant consequence in their clinical performance. In addition to determining an agent's anticancer activity, the mechanism of action is also manifested in a drug's toxicity profile. Currently, part of the effort in identifying novel spindle poisons is motivated by loss of effectiveness of the currently available drugs, attributed to drug resistance, and by their troublesome side effects.

Mechanism of Action of Taxanes

The mechanism of action of taxanes has been studied intensely and much has been discovered about their cytotoxic effects. The interaction of paclitaxel with the microtubule polymer results in the formation of stable bundles of cellular microtubules that are resistant to depolymerization. Paclitaxel promotes the polymerization of microtubules, inhibits microtubule disassembly, arrests eukaryotic cell division, and causes DNA fragmentation, leading to apoptosis signaling that initiates destruction of proliferating tumor cells. The paclitaxel-binding site on β-tubulin has been identified both by electron crystallography, showing paclitaxel bound on the of β-tubulin dimer (Nogales E, etal, Nature, 8 Jan 1998;391(6663):199-203), and by photoaffinity labeling, which has identified amino acids 1-31 and 217-233 as important areas for paclitaxel binding (Rao S, etal, J Biol Chem 1994; 269, 3132-3134).

The αβ tubulin heterodimer is the structural subunit of microtubules; β-tubulin is a GTPase, whereas α-tubulin

Exhibit 1
Worldwide Sales of Taxanes in 1999 and 2000

Drug	WW Sales in 1999 ($ mil.)	WW Sales in 2000 ($ mil.)	Change (%)	USA Sales in 1999 ($ mil.)	USA Sales in 2000 ($ mil.)	Change (%)	ROW Sales in 1999 ($ mil.)	ROW Sales in 2000 ($ mil.)	Change (%)
Taxol	1,481.0	1,592.0	7.5	935.0	987.0	5.6	545.0	605.0	11.0
Taxotere*	568.5	688.8	21.2	218.6	338.9	55.0	349.9	470.2	34.4
Onxol	NA	35.0		NA	35.0		NA	NA	
Total	2,049.5	2,315.8	13.0	1,153.6	1,360.9	18.0	1,015.2	954.9	20.1

**Sales take into account currency fluctuations in translating euros to dollars*
Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), February 2002

has no enzyme activity. Each tubulin monomer binds a guanine nucleotide, which is nonexchangeable when it is bound in the α subunit, or N-site, and exchangeable when bound in the β subunit, or E-site. The α- and β-tubulins share 40% amino-acid sequence identity, both exist in several isotype forms, and both undergo a variety of post-translational modifications. The structures of α- and β-tubulin are basically identical with each monomer formed by a core of two β-sheets surrounded by α-helices. The monomer structure is very compact, but can be divided into three functional domains, the amino-terminal domain containing the nucleotide-binding region, an intermediate domain containing the paclitaxel-binding site, and the carboxy-terminal domain, which probably constitutes the binding surface for motor proteins (Nogales E, etal, *ibid*).

Microtubule-interfering agents such as paclitaxel, docetaxel, vinblastine, vincristine, nocodazole, and colchicine, also activate the c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK)-signaling pathway in a variety of human cells in a dose-dependent and time-dependent fashion. These agents also activate both Ras and apoptosis signal-regulating kinase (ASK1); coexpression of dominant negative Ras and dominant negative ASK1 exert individual and additive inhibition of JNK/SAPK activation by these agents (Wang TH , etal, J Biol Chem, 27 Feb 1998; 273(9):4928-36).

In order to investigate the possible predictive value of microtubule-associated parameters (MTAP) in patients treated with docetaxel, 41 eligible patients (evaluable for response with available pretreatment paraffin-embedded tumor tissue), among 54 women with metastatic breast cancer who had been treated with docetaxel, were evaluated in a retrospective study. The majority of these patients had been treated with at least 1 prior chemotherapy regimen. Samples of primary and/or metastatic tumor were evaluated by immunohistochemistry for such MTAP as α- and β-tubulin, class II, III and IV β-tubulin isotypes, and τ protein. Clinical response was correlated with MTAP status. The PR rate was 54%, and disease stabilized in 29% and progressed in 17%. No correlation with docetaxel activity was possible because α- and β-tubulin and class IV β-tubulin isotype were strongly expressed in the majority of samples. Of the 4 patients with τ-negative tumors, 2 did not experience an objective response. Also, an inverse correlation was found between class II expression and docetaxel activity, but outcome was similar in the two groups regarding class III expression. Although the small number of patients in this analysis tempers conclusions, according to these preliminary data, the evaluation of τ protein and class II β-tubulin deserves further investigation as potential predictive markers for docetaxel activity (Bernard C, etal, European Journal of Cancer, Oct 2001:37(Suppl 6):182).

Drug Resistance

Like with most chemotherapeutics derived from natural sources, drug resistance by tumor cells limits the clinical utility of taxanes. In order for cytotoxic agents to be effective against tumor cells, they must:

- be transported into the cell
- be metabolized into an active form
- interact with target molecules
- initiate apoptosis

Tumor cells overcome the effects of cytotoxic agents at one or more of these levels. Drug pumps that lower the intracellular concentration of chemotherapeutic agents by actively extruding drug from the cell, represent the classic causes of multidrug resistance (MDR). The most prevalent pumps are the large glycosylated plasma membrane proteins, P-glycoproteins (P-gp), expressed by the mdr1 gene, and multidrug resistance-associated proteins (MRP). Whereas P-gp extrudes unmodified hydrophobic drugs, MRP extrudes drugs conjugated to glutathione (GSH), glucuronic acid, or sulphate. Important questions remain as to how and whether such transport systems can be specifically measured and effectively targeted to improve therapeutic outcomes.

P-gp is a 170-kilodalton drug-transporting membrane protein that is abundantly present in biliary ductal cells and epithelial cells lining the gastrointestinal tract. P-gp acts as an ATP-dependent efflux pump reducing the intracellular accumulation of anthracyclines, vinca alkaloids,

epipodophyllotoxins, actinomycin D, and paclitaxel among other natural cytotoxics. Among pharmacologic approaches to reverse P-gp-mediated MDR are drugs which overcome MDR by inhibiting efflux, thus allowing chemotherapeutic agents to accumulate within resistant tumor cells. These resistance-modifying agents, include calcium channel blockers, calmodulin antagonists, local anesthetics, membrane-active agents, steroids and hormonal agents, and cyclosporins. However, these resistance modulators have yet to succeed in mitigating MDR in most chemotherapeutics, including the taxanes.

Also, inhibition of P-gp in the blood-brain barrier (BBB) may increase transport to the brain of many chemotherapeutics, thus expanding paclitaxel's utility to the treatment of brain tumors. Results show that increased paclitaxel uptake in the brain of wild type mice was observed with cyclosporin A, PSC833, and GF120918 P-gp inhibitors, but levels were lower than the brain levels of paclitaxel in P-gp knock out mice. The rank order of the inhibitors in their efficacy to increase the brain levels of paclitaxel was cyclosporin A<<PSC833<GF120918. In addition to increasing paclitaxel levels in the brain, both cyclosporin A and PSC833 significantly increased, 6-and 4-fold, respectively, plasma AUC levels of paclitaxel, whereas only a 1.5-fold increase was possible with GF120918. These results indicate that increased brain levels of paclitaxel by GF120918 are mainly attributed to inhibition of P-gp in the BBB, whereas the increased paclitaxel plasma levels affected by cyclosporin A and PSC833, also contribute to the higher penetration of paclitaxel in the brain. Because it is anticipated that dose reductions of paclitaxel will be required when it is used in combination with cyclosporin A or PSC833, the degree of the drug's penetration to the brain may be adversely affected. The most favorable therapeutic index was achieved with GF120918. Paclitaxel brain levels reached at clinically achievable plasma levels of GF120918 were about 80-90% of those in P-gp knock out mice (Kemper M, etal, 21st AGM meeting, 21-23 June 2001).

Numerous studies have attempted to assess the importance of various other potential mechanisms for the development of MDR. As yet, there is no conclusive evidence that any of these play a pivotal role in drug resistance. It is most likely that multiple mechanisms lead to the development of chemoresistance in various cancers, making a standardized approach to preventive treatment impossible. Rather, it is likely that chemoresistance would have to be addressed in each individual treatment setting as it arises. Therefore, there is a unique opportunity for the development of chemoresistance assays that would predict a tumor's susceptibility to various cytotoxics including spindle poisons.

Expression of certain oncogenes may also confer endogenous MDR. Abnormalities in the apoptosis-related genes can prevent cells from undergoing apoptosis, thus favoring a malignant phenotype. Poor prognosis cancers include those that have excess Bcl-2 or p53 mutations; abnormalities in these genes often cause apoptosis-inducing cancer therapies to fail. Also, expression of certain oncogenic proteins such as HER2 and a mutant form of epidermal growth factor receptor (EGFrvIII), render ovarian cancer cells more resistant to taxane chemotherapy.

Numerous clinical trials (Exhibit 4) are ongoing, testing combinations of various novel regulatory agents and taxanes. It is still too early to speculate on the results of such attempts in enhancing the effectiveness of taxane-based chemotherapies, which will only be established after results from phase III comparative clinical trials become available. However, one such successful combination of a regulatory agent, trastuzumab (Herceptin; Genentech) and paclitaxel, was approved for clinical use in September 1998 (See FO, p 1101).

In March 2001, final results from the pivotal phase III trial of 469 women with metastatic breast cancer, showed that those treated weekly with Herceptin and standard cycles of chemotherapy (anthracycline and cyclophosphamide, or paclitaxel), as a first-line therapy, experienced a 24% increase in median overall survival, almost 5 months longer, from 20.3 months to 25.1 months, compared to women treated with chemotherapy alone. This increased efficacy with Herceptin was observed in both the Herceptin plus chemotherapy combinations. The combination of Herceptin and chemotherapy compared to chemotherapy alone improved the overall response rate from 32% to 50%, prolonged the time-to-disease progression (TTP) from 4.6 to 7.4 months and increased median duration of response from 6.1 to 9.1 months.

Also, defects in the mitotic checkpoint may contribute to the sensitivity of certain tumors to mitotic spindle inhibitors. One such checkpoint protein, MAD2, a member of a class of mitotic checkpoint proteins, was identified in 1996, by Drs. Robert Benezra and Yong Li of MSKCC (Li Y and Benezra R, Science, 11 Oct 1996;274(5285):246-8). Recently, researchers at Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY) genetically engineered a mutation in the MAD2 gene in human cancer cells to eliminate a checkpoint essential to normal cell division (Michel LS, etal, Nature, 18 Jan 2001;409(6818):355-9). MAD2 is required to arrest cells in mitosis when chromosomes are unattached to the mitotic spindle. Presence of a single, lagging chromosome is sufficient to activate the checkpoint, causing a delay at the metaphase-anaphase transition until the last spindle attachment is made. Complete loss of the mitotic checkpoint results in embryonic lethality in various organisms attributable to chromosome missegregation. Deletion of one MAD2 allele results in a defective mitotic checkpoint in both human cancer cells and murine primary embryonic fibroblasts. Checkpoint-defective cells show premature sister-chromatid separation in the presence of spindle inhibitors such as the taxanes, and an elevated rate of chromosome missegregation events in the absence of these agents. Furthermore, MAD2± mice develop lung tumors at high rates after long latencies, implicat-

Exhibit 2
Estimated Worldwide Quarterly Sales of Taxanes in 2001

Drug	WW Sales in 1Q01 ($ mil.)	WW Sales in 2Q01 ($ mil.)	WW Sales in 3Q01 ($ mil.)	WW Sales in 4Q01 ($ mil.)	WW Sales in 2001 ($ mil.)	Change (%)
Taxotere	194.8	213.4	236.6	241.9	886.7	28.7
Taxol	330.0	336.0	279.0	252.0	1,197.0	(24.8)
Onxol	50.0	77.0	45.0	45.0	217.0	520.0
Total	574.8	626.4	560.6	538.9	2,300.7	(0.6)

Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), February 2002

ing defects in the mitotic checkpoint in tumorigenesis (Michel LS, etal, Nature, 18 Jan 2001;409(6818):355-9).

Interestingly, in humans, low levels of MAD2 have been observed in breast tumor cell lines. Although loss of one copy of MAD2 causes only subtle decreases in the amount of MAD2 protein levels, it has a great impact on the cell's genetic behavior. In this case, tumors became genomically highly unstable and continued to grow even in the presence of taxane-based chemotherapy. Uniquely, this mutation resulted in a high frequency of lung carcinomas despite the fact that these genes are found in every cell of the body, and the disease is extremely rare in most mice. It is not clear why the lung tissue is specifically affected, but it does show that disruption of this process somehow correlates with the development of cancer. Because of this observation, an assay detecting changes in this genetic pathway in human cancers could be used to predict disease progression. The researchers also found that small changes in the MAD2 protein level result in a partial loss of the mitotic checkpoint. When the cell was missing half a dose, it became resistant to taxane drugs. This was a surprise since the yeast results suggested the exact opposite. This could have implications as to why a cancer cell suddenly develops drug resistance and needs further investigation.

Understanding the linkage between microtubule dynamics, mitotic block, and resistance to paclitaxel promises to lead to new drug targets that will improve the efficacy of chemotherapy. Because taxanes are most often administered in combination regimens with other cytotoxics, MDR resistance to the combined regimen is further complicated by the resistance profile of each cytotoxic in the combination. Finally, the pharmacokinetics of the taxanes is seriously affected by their solubilizing vehicle, Cremophor EL.

More specifically with the taxanes, resistance may also arise from the relative expression and composition of tubulin isoforms, the binding targets for spindle poisons that may differ in resistant cell lines, altering drug sensitivity. Preliminary data in paclitaxel-resistant variants reveal changes in β-tubulin expression in some of these cells, and mutations in the predominant isoform (class I, M40) that were detected in a human ovarian cell line, A2780/1A9 (Giannakakou P, etal, J Biol Chem 1997; 272(27):17118-17125). Investigators at Stanford University (Stanford, CA) are studying laboratory data from patients with breast and ovarian cancer or lymphomas, undergoing protocol therapies with taxanes, to establish any relevance of altered tubulin gene expression in resistant tumors. Also, these investigators are evaluating novel mechanisms of resistance to taxanes by the genomic profiling of taxane-resistant human ovarian and breast cancer variants using microarray technology.

Under an NCI 10-year grant, investigators at the University of California at Santa Barbara are also working to determine the mechanistic relationship between suppression of spindle microtubule dynamics by paclitaxel, and inhibition of cell-cycle progression from metaphase to anaphase; examine the effects of paclitaxel on the biochemical and ultrastructural interactions of microtubules with key spindle components, including quantitation of the number of microtubules attached to kinetochores; and determine how the tubulin isotype composition of tumor cells contributes to the differential sensitivity of the cells to paclitaxel. Effects of altering levels of tubulin isotype expression on the sensitivity or resistance to paclitaxel are being tested by stably transfecting human tumor cells with cDNAs for selected β-tubulin isotypes.

To investigate whether β-tubulin mutations were factors in drug resistance, constitutional genomic DNA and paired tumor DNA were isolated from 49 biopsies from 43 Spanish and 6 American patients with Stage IIIb/IV nsclc who had been treated with a 3-hour paclitaxel (210 mg/m^2) infusion, or a 24-hour paclitaxel (200 mg/m^2) infusion, respectively. Oligonucleotides specific to β-tubulin were designed for PCR amplification and sequencing of GTP- and paclitaxel-binding β-tubulin domains. Of 49 patients, 16 (33%) had β-tubulin mutations in exons 1 (=1) or 4 (n=15). None of the patients with β-tubulin mutations responded, whereas 13/33 (39.4%) patients without such mutations experienced CR or PR. MST was 3 months for the 16 patients with β-tubulin mutations and 10 months for the 33 patients without such mutations. Therefore, it appears that β-tubulin gene mutations are a strong predictor

of response to paclitaxel, and may represent a novel mechanism of resistance in nsclc (Monzo M, etal, J Clin Oncol, Jun 1999;17(6):1786-93).

Based on these assumptions, presence of β-tubulin mutations has been proposed as the basis for chemotherapeutic drug selection in the management of patients with advanced nsclc. However, investigators at Duke University (Durham, NC) did not find that the presence of β-tubulin mutation in nsclc tumor samples to be more frequent than in cell lines. Frequency of genetic alterations of other genes in nsclc is generally greater in cell lines than in tumor samples. To better study the association of β-tubulin mutation with tumor-cell growth and taxane resistance, β-tubulin was analyzed in 25 nsclc cell lines. Only two sequence variants, both heterozygous single nucleotide variants in the third position of codons 187 and 217, were identified in the coding region and adjacent splice sites, that did not change the predicted amino acid. Each variant was present in one cell line and likely represents a polymorphism. Thus, mutations of β-tubulin do not appear to be common in nsclc cell lines. It may be that previously reported β-tubulin mutations in nsclc were attributable to an artifact of coamplification of pseudogenes (Kelley MJ, etal, ASCO01, Abs. 1330:333a). Nevertheless, tubulin mutations that result in a compromised paclitaxel-tubulin interaction and paclitaxel resistance, have been shown to indirectly inhibit downstream events that lead to cell death, and this, in turn, may contribute to the drug-resistance phenotype (Poruchynsky MS, etal, Biochem Pharmacol, 1 Dec 2001;62(11):1469-80).

Gene mutations and promoter methylation are found in serum DNA of several malignancies. When the presence of genetic abnormalities (methylation status of RASSF1A and TMS1, K-ras codon 12 mutations, and β-tubulin mutations) in primary tumor and paired serum DNA and their impact on survival was examined in 53 patients with resected nsclc, overall, 69% had at least one genetic alteration in tumor and 74% had at least one in serum. RASSF1A was methylated in 23% of cases in both tumor and serum, 7% only in tumor, and 10% only in serum. TMS1 was methylated in 28% in both tumor and serum, 13% only in tumor, and 10% only in serum, 6% had K-ras mutations in both tumor and serum, 14% only in tumor, and 16% only in serum, and 6% had β-tubulin mutations in both tumor and serum, 2% only in tumor, and 9% only in serum; β-tubulin mutations were found in tumor in 7.5% and in serum in 15% of all patients. Methylation of RASSF1A or TMS1 did not influence survival. Serum K-ras mutations correlated with worse survival and β-tubulin mutations had a strong negative impact on survival. In conclusion, gene abnormalities in serum may indicate a higher degree of relapse. The negative impact of K-ras and β-tubulin mutations reconfirms previous findings (Sarries C, etal, AACR-EORTC-NCI01, Abs. 749).

Emergence of MDR results in administering a toxic treatment to a patient who has no chance of responding to the drug. Therefore, identifying tumors highly resistant to certain cytotoxic drugs would spare patients unnecessary highly toxic treatment. Oncotech (Tustin, CA) has developed a test, the Extreme Drug Resistance (EDR) assay, that identifies resistant tumors with a 99% accuracy. The company has been evaluating this assay in a multicenter, open-label, single-arm, blinded, phase II clinical trial (protocol ID: ONCOTECH-OTBR01; NCI-V98-1391; UCIRVINE-97-02) that was initiated in July 1997. The trial is designed to determine the reliability the EDR assay in measuring drug resistance to paclitaxel in patients with metastatic (Stage IV) or recurrent breast cancer, including male breast cancer. Objectives of the trial are to evaluate the proportion of patients with extreme, intermediate, and low drug resistance to paclitaxel using the EDR assay. The trial has been designed to assess response to paclitaxel therapy in approximately 100 patients with previously treated metastatic breast cancer who have undergone a pretreatment EDR assay; establish time-to-tumor progression during paclitaxel therapy in these patients; and determine prospectively the predictive value of the EDR assay relative to clinical outcome by correlating assay results with clinical tumor response and time-to-tumor progression during paclitaxel therapy. According to the protocol, patients' tumor tissue samples are collected by excisional biopsy, core biopsy, or malignant fluid aspiration, and then tested by the EDR assay to determine probability of drug resistance to paclitaxel. After successful completion of evaluation of the EDR assay (approximately 7 days), patients are treated with paclitaxel by IV infusion over 1-3 hours, repeated every 3 weeks. Treatment continues until there is documented evidence of tumor progression or unacceptable toxicity. Patients' clinical response to paclitaxel therapy is compared with the response predicted by the EDR assay.

Various approaches have been developed to overcome MDR in a broad range of chemotherapeutics, including the taxanes:

- P-gp inhibitors such as cyclosporin A (CsA), PSC833, GF120918, and R101933 that may directly affect MDR
- combination trials with various inhibitors of oncogenes/pathways that may indirectly lower resistance by inactivating endogenous contributors to MDR (Exhibit 4)

To date, inhibitors of P-gp activity have had limited clinical success mostly attributed to pharmacokinetic interactions resulting in unacceptable increases in severity and frequency of side effects of the coadministered anticancer drug, attributable to competition at the level of cytochrome-P450 3A isozymes, the major metabolic route of many drugs.

Cyclosporin A (CsA) and its analogs/derivatives represent a family of non-specific P-gp reversal agents that have generally failed to modulate MDR in the clinic. Clinical efficacy of these agents has been limited because of unacceptable side effects at doses that were suboptimal

Exhibit 3
Estimated Quarterly USA Sales of Taxanes in 2001

	USA Sales in 1Q01 ($ mil.)	USA Sales in 2Q01 ($ mil.)	USA Sales in 3Q01 ($ mil.)	USA Sales in 4Q01 ($ mil.)	USA Sales in 2001 ($ mil.)	Change (%)	ROW Sales 2001 ($ mil.)	Change (%)
Taxol	179.0	160.0	120.0	86.0	545.0	(45.0)	625.0	8.0[1]
Taxotere[2]	98.8	115.6	130.1	133.7	478.2	41.1	408.5	(13.1)
Onxol	50.0	77.0	45.0	45.0	217.0	520.0	NA	NA
Total	327.8	352.6	295.1	264.7	1,240.2	(8.8)	1,033.5	1.8

[1] ROW sales increased 15% excluding foreign exchange factors, led by strong sales growth in Japan.
[2] Estimated sales are based on prevailing euro rates at the time of the financial reports.
Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), February 2002

for maximum P-gp inhibition and because they substantially altered the pharmacokinetics of anticancer drugs that are P-gp substrates. Although this class of drugs failed to sufficiently modulate P-gp resistance in clinical trials of various cytotoxics, the finding that paclitaxel, and perhaps docetaxel, have adequate bioavailability after oral administration in humans when P-gp is blocked by cyclosporin A, allowed the pursuit of oral formulations of the taxanes.

Coadministration of oral CsA strongly enhanced the oral bioavailability of docetaxel which is very low at least in part, because of its affinity for intestinal P-gp. This affinity may be further aggravated by metabolism of docetaxel by cytochrome P450 (CYP) 3A4 in gut and liver. In a study to determine if coadministration of CsA would enhance the systemic exposure to oral docetaxel, 14 patients with solid tumors were treated with one course of oral docetaxel (75 mg/m^2) with or without a single oral dose of CsA (15 mg/kg) which preceded oral docetaxel by 30 minutes. During subsequent courses, patients were treated with IV docetaxel (100 mg/m^2). The absolute bioavailability of oral docetaxel was 8% ± 6% without and 90% ± 44% with CsA. Interpatient variability in the systemic exposure after oral drug administration was of the same order as after IV administration. Furthermore, the oral combination regimen was well tolerated (Malingre MM, etal, J Clin Oncol 2001 Feb 15;19(4):1160-6).

Cyclosporin is currently in two phase I clinical trials, in combination with paclitaxel and a radioimmunoconjugate, both initiated in March 2001, at the University of California Davis. One trial (protocol IDs: UCD-991869; NCI-V00-1641), being conducted by Dr. Robert T. O'Donnell, is a dose-escalation study of oral CsA, in combination with IV paclitaxel and IV Lym-1 monoclonal antibody (MAb) labeled with yttrium 90, in recurrent or refractory non-Hodgkin's lymphoma (NHL). Another dose-escalation clinical trial (protocol IDs: UCD-992080; NCI-V00-1640), being conducted by Dr. Carol M. Richman, is investigating yttrium 90-labeled m170, a panadenocarcinoma MAb, administered in combination with CsA and paclitaxel, in patients with recurrent or refractory metastatic breast cancer who may also undergo autologous peripheral blood stem cell transplantation, if needed.

One derivative of cyclosporin that lacked its immunosuppressive attributes, PSC833 or valspodar (Amdray; Novartis), demonstrated significant potency in reversing MDR *in vitro* and *in vivo*, to enhance toxicity of cytotoxic drugs. Although in early clinical trials in ovarian cancer, PSC833 demonstrated some activity when combined with doxorubicin, cisplatin, etoposide, and paclitaxel, response statistics were not overwhelming. Recently, Novartis terminated clinical development of this drug which had been and was being evaluated in numerous clinical trials including a phase III clinical trial (protocol ID: PSC B351) in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone, in Stage IV or suboptimally debulked Stage III epithelial ovarian cancer, or primary cancer of the peritoneum.

In a phase II clinical trial, conducted by the Gynecologic Oncology Group (GOG), the combination of paclitaxel and valspodar demonstrated limited activity in patients with paclitaxel-resistant ovarian cancer. According to the protocol, patients were treated with valspodar (5 mg/kg), orally, *qid* x 12 doses, and with paclitaxel (70 mg/m^2) IV for 3 hours on day 2, 2 hours after the fifth or sixth dose of valspodar; treatment was repeated every 21 days. Among 60 enrolled patients, 58 were assessable for response. There were 5 (8.6%) PR with a median duration of response of 5.0 months (range=1.9-10.5 months). Median progression-free survival was 1.5 months. Grade 3 or 4 toxicities observed were neutropenia, anemia, nausea and vomiting, peripheral neuropathy, and cerebellar ataxia. Immunohistochemical staining for P-gp was positive for one of two responding patients (Fracasso PM, etal, J Clin Oncol, 15 Jun 2001;19(12):2975-82).

GF120918, under development by GlaxoSmithKline, is a potent inhibitor of P-gp and breast cancer resistance protein (BCRP). GF120918 is currently being evaluated as a means of enhancing the oral bioavailability of topotecan (Schellens JHM, etal, ASCO01, Abs. 292:75a).

ONT-093 (formerly OC144-093), under development by Ontogen (Carlsbad, CA), is an imidazole derivative P-gp inhibitor that reverses the effects of MDR. ONT-093 was created through solid-phase combinatorial chemistry based on Ontogen's proprietary OntoBLOCK system. A phase I clinical trial of oral ONT-093 in combination with IV paclitaxel in solid tumors, was initiated in May 2001, at British Columbia Cancer Agency in Canada, following approval of a Canadian IND. In this six-cohort trial, each patient is initially treated with Taxol alone followed by escalating doses of both Taxol and oral ONT-093. Ontogen is also evaluating ONT-093 in phase I clinical testing as a means of enhancing the oral bioavailability of cytotoxic drugs that are P-gp substrates recessitating either high dosage forms of the drug or IV administration.

A phase I study of the safety, tolerability and pharmacokinetics of ONT-093, following IV infusion in healthy volunteers, was completed in January 1999. A second phase I study of the compound via oral administration in healthy male volunteers was completed in July 2000. These studies indicated that the drug is safe and well tolerated when administered orally in doses of up to 500 mg twice daily. In a randomized crossover phase I clinical study, ONT-093 was administered with and without a fatty meal. Following single 400 mg oral doses, plasma concentration of ONT-093 was significantly higher than that required for full reversal of P-gp-mediated MDR in preclinical models. There were no adverse events or evidence of CNS effects. The study also found a significant increase in the oral bioavailability of ONT-093 when administered with a fatty meal compared to when fasting. Based on previous IV data, the oral bioavailability was estimated to be greater than 60% with food, and its terminal half-life about 22 hours, suggesting that once- or twice-a-day oral dosing may be sufficient to maintain therapeutic levels.

R101933, in development by Janssen-Cilag (Berchem, Belgium), is a potent second-generation inhibitor of P-gp activity. R101933 differs from other P-gp inhibitors in that its major metabolic pathway is independent of cytochrome-P450 3A4. The drug has been evaluated in clinical trials both via oral and parenteral routes. In a phase I clinical trial, 15 patients were treated with oral R101933 monotherapy at a dose escalated from 200 mg to 300 mg, twice daily (cycle 0); an escalating IV dose of docetaxel (60 mg/m^2, 75 mg/m^2, and 100 mg/m^2) as a 1-hour infusion (cycle 1); and combination of both (cycle 2 and further). DLT consisting of mucositis and neutropenic fever was reached at the docetaxel dose of 100 mg/m^2 combined with R101933 300 mg *bid*, and MTD was set at docetaxel 100 mg/m^2 with R101933 at 200 mg *bid*. Plasma concentrations of R101933 achieved in patients were in the same range as those required in preclinical rodent models to overcome paclitaxel resistance. The plasma pharmacokinetics of docetaxel were not influenced by the R101933 cotreatment at any dose level tested, allowing further clinical development of this agent (van Zuylen L, etal, Clin Cancer Res, Apr 2000;6(4):1365-71).

However, results from docetaxel-based in combinations with the orally administered R101933 indicated that a further increase of the level of P-gp inhibition could not be reached by oral administration because of low oral bioavailability of R101933. In addition, in a phase I clinical trial investigating the combination of R101933 and epirubicin, all patients developed a strong aversion to the taste of R101933.

Therefore, further clinical trials were initiated to assess the feasibility of combining docetaxel with IV R101933. In a multicenter, multinational, phase II clinical trial (protocol ID: EORTC-16004), sponsored by the NCI and the EORTC, and being conducted by the EORTC Breast Cancer Cooperative Group, the activity of R101933 is being evaluated in combination with paclitaxel or docetaxel in terms of response to treatment and level of clinical benefit in patients with taxane-refractory metastatic breast cancer. The trial is also designed to determine the safety of this regimen and its acute side effects. According to the protocol, patients are treated with R101933 IV over 1 hour immediately followed by IV paclitaxel over 3 hours or IV docetaxel over 1 hour on day 1. Treatment repeats every 21 days for 7 courses in the absence of disease progression or unacceptable toxicity. Patients with stable disease after 7 courses may continue with treatment at the investigator's discretion. Patients are followed every 6 weeks until disease progression. A total of 12-35 patients will be accrued for this study initiated in September 2001.

tRA96023

Researchers at the State University of New York (SUNY) Stony Brook and at Roswell Park Cancer Institute (Buffalo, NY), have synthesized tRA96023, a novel, nontoxic taxoid that blocks P-gp function and reverses MDR *in vitro* and *in vivo*. This agent is one among a large number of synthesized, taxane-based, nontoxic MDR-reversal agents that, when used in combination with various cancer chemotherapeutics, often are able to completely sensitize cancer cells. When administered with paclitaxel *in vitro*, tRA96023 (1 μM) reduced the IC^{50} of paclitaxel in several P-gp-positive, paclitaxel-resistant tumor cell lines by up to 99%. In SCID mice implanted subcutaneously with the P-gp expressing human colon tumor DLD-1, a cumulative dose of 80 mg/kg/po of tRA96023, formulated in Tween-80, significantly increased the efficacy of oral IDN5109 (480 mg/kg).

This combination yielded tumor-growth delay of 86 days, with 2 of 6 animals being cured (no palpable tumor), compared to 52 days and no cures with IDN5109 alone. Paclitaxel (200 mg/kg cumulative dose), administered orally, had no effect on the A121 human ovarian tumor implanted subcutaneously in SCID mice, most likely because of intestinal P-gp expression. However, when administered together with a cumulative dose of 80 mg/kg/po of tRA96023, paclitaxel inhibited tumor growth, resulting in a significant tumor growth delay, as compared to control, of 14 days (Vredenburg, etal, AACR-NCI-EORTC01, Abs 416).

VX-710 (Incel), in development by Vertex (Cambridge, MA), blocks both P-gp and MRP. Incel, an IV compound, and VX-853 (timcodar dimesylate), its oral counterpart, are administered in combination with cancer chemotherapy agents. Vertex's research shows that Incel enhances accumulation of chemotherapy agents in tumor cells, thereby restoring the sensitivity of tumor cells to treatment with cytotoxic drugs. Incel has been evaluated in a broad phase II program involving six clinical trials. VX-853, an oral MDR-1 and MRP inhibitor, is in phase I clinical trials in combination with doxorubicin.

VX-710 is being developed in collaboration with Shire BioChem (Laval, Quebec) that initiated a Canadian phase II trial of VX-710, in combination with paclitaxel, for treatment of advanced ovarian cancer refractory to paclitaxel, in August 1997. Patients are treated by a continuous 24-hour infusion of VX-710 (120 mg/m^2/hour) administered via a central venous catheter. The trial, being conducted at McGill University (Montreal, Canada), has enrolled about 50 patients being treated with the combination of a 24-hour infusion of VX-710 and paclitaxel, administered as a 3-hour infusion 4 hours after initiation of the VX-710 infusion. The most common toxicities observed were asthenia, tachycardia, anorexia, nausea, vomiting and vasodilatation. When VX-710 was administered peripherally, there were 3 cases of Grade 4 neutropenia, 1 episode of neutropenia with sepsis, 1 of elevated liver enzymes, and 1 of chemical phlebitis. Pharmacokinetic data showed that there was a significant reduction in paclitaxel clearance when administered with a 24-hour infusion of VX-710 (120 mg/m^2/hour), in combination with paclitaxel doses at 60 and 80 mg/m^2. This regimen resulted in an AUC similar to that reported when paclitaxel is administered alone at doses of 135 mg/m^2 or 175 mg/m^2 respectively.

XR9576 (tariquidar), under development by Xenova (Slough, Berkshire, UK), is a specific P-gp inhibitor that blocks P-gp function for up to 24 hours after a single dose without significant toxicity. In preclinical studies, XR9576 proved effective in restoring the drug sensitivity of a broad range of human cancers exhibiting MDR, with long duration of action and good tumor distribution. Tariquidar, in combination with doxorubicin, paclitaxel, or vinorelbine, is well tolerated, with only minor alterations in the clearance and drug exposure of the anticancer drugs observed. XR9576 is being evaluated in both IV and oral routes of administration.

In a phase IIa clinical trial, involving the combination of IV XR9576 and paclitaxel, it was shown that paclitaxel can be administered at the full normal dose in combination with a single administration of XR9576. The study was carried out at the Royal Surrey County Hospital (Guildford, UK), in 12 patients with ovarian cancer recurring more than 6 months after previous treatment, who had previously been treated with a variety of cytotoxic drugs, including paclitaxel and platinum agents. Patients were administered IV paclitaxel (175 mg/m^2) with a single IV dose of XR9576 (150 mg/m^2) prior to administration of paclitaxel. Results of this trial indicate that XR9576 is well tolerated when administered with paclitaxel, causing no significant drug interactions. Initial indications of response obtained from this study will be used to design a pivotal phase III clinical trial of XR9576 in combination with paclitaxel. Phase IIb/III clinical trials with oral tariquidar are scheduled to begin in mid-2002.

In August 2001, QLT (Vancouver, Canada) entered into an exclusive development and license agreement for XR9576 with Xenova, under which QLT obtained marketing rights for North America. Xenova retained marketing rights in Europe and the rest of the world. Under terms of the agreement, QLT paid Xenova an initial licensing fee of $10 million, and will provide up to $45 million in funding to develop XR 9576. QLT will also make milestone payments up to a maximum of $50 million. Upon commercialization, QLT will pay a royalty to Xenova in the range of 15% to 22%, depending on the level of North American sales.

Chemosensitization

Combination of taxanes with various other agents as well as radiation therapy, has been shown to enhance their effectiveness. However, so far most combinations with other cytotoxics have compounded the toxicity of such regimens while providing only marginal effectiveness. More promising are combinations with regulatory agents that are intrinsically less toxic. Therefore, the search continues for regulatory agents acting on underlying mechanisms that enhance the activity of cytotoxics such as the taxanes without further compromising their safety profile.

AVI-4557, part of the NeuGene technology platform of AVI Biopharma (Portland, OR), is an antisense phosphorodiamidate morpholino oligonucleotide (PMO) targeting the liver enzyme cytochrome P450 3A2 (CYP3A4) mRNA. AVI Biopharma has completed preclinical studies using its NeuGene antisense technology targeting liver cytochrome P450 enzymes that control metabolism of most drugs. By downregulating liver cytochrome enzymes, AVI plans to improve pharmacokinetics of existing FDA-approved drugs. In preclinical trials, antisense inhibition of CYP3A4 appeared to enhance the cytocidal activity of paclitaxel by preventing degradation to inactive products.

In November 2001, AVI-4557 completed phase I clinical trials in healthy volunteers. According to the protocol, 48 healthy volunteers divided into 6 groups, were treated with a 10 mg, 30 mg or 90 mg dose of AVI-4557, either by IV or subcutaneous injection. In the second part of this phase I clinical trial, AVI-4557 will be evaluated in an additional 48 volunteers, to see whether it can improve the pharmacokinetic profile of a test drug (midazolam). This study will also use the same three doses of AVI-4557, delivered either IV or subcutaneously.

Exhibit 4
Selected Regulatory Agents Being Clinically[1] Evaluated in Combination with Commercially Available Taxanes

Developer ❑ Affiliates	Regulatory Agent[2]	Description of Regulatory Agent ❑ Administration Route	Status ❑ Indications	References[3]
Abgenix ❑ Japan Tobacco, Immunex	ABX-EGF (formerly clone E7.6.3)	Fully human anti-epidermal growth factor receptor (EGFr) monoclonal antibody (MAb) ❑ IV	Phase III (ongoing 2/02) ➢USA ❑ advanced or metastatic nsclc, first-line	
Allos Therapeutics ❑ National Cancer Institute (NCI)	Efaproxiral sodium ❑ RSR13	Synthetic allosteric hemoglobin modifier that increases the release of oxygen from hemoglobin ❑ continuous IV, central venous access	Phase II (begin 10/98, completed 8/00)➢USA, Canada ❑ locally advanced, inoperable Stage IIIa or IIIb nsclc	Choy H, etal, ASCO01, Abs. 1248:313a
AstraZeneca	ZD1839 ❑ Iressa	A quinazoline derivative that selectively inhibits EGFr tyrosine kinase (EGFr-TK)-mediated intracellular signaling pathways ❑ PO	Phase III (begin 5/00, completed 5/01)➢USA, Canada, Europe ❑ first-line treatment of advanced or metastatic (Stage IIIb or Stage IV) nsclc	Miller VA, etal, ASCO01, Abs. 1301: 326a; Gatzemeier U, etal, ASCO01, Abs. 2775:256b
Aventis Pharma ❑ National Cancer Institute (NCI)	Flavopiridol ❑ NSC-649890, L86-8275, HMR-1275	Semisynthetic analog of rohitukine, isolated from the bark of the Indian tree *Dysoxylum binectariferum*, that is a potent CDK1 inhibitor; arrests cell cycle progression in either G1 or G2 ❑ continuous IV	Phase II (begin 7/00, ongoing 2/02)➢USA ❑ refractory advanced or metastatic, esophageal cancer	
BioNumerik Pharmaceuticals ❑ Grelan Pharmaceutical, Baxter Oncology	Dimesna ❑ BNP7787	Water-soluble, reducible disulfide having activity as a thiolmodulating chemoprotectant for cytotoxic chemotherapy, including taxanes and platinum-based anticancer drugs ❑ PO, IV	Phase III (ongoing 1/02) ➢USA, Europe; phase I (begin 1Q00) Japan ❑ cisplatin- or paclitaxel-related toxicity	See text
Bristol-Myers Squibb	BMS-214662	Blocks Ras processing by inhibiting farnesyltransferase enzyme activity ❑ IV	Phase I (temporarily closed 1/02)➢USA ❑ advanced solid tumors	
Bristol-Myers Squibb ❑ Celltech Group	BMS-275291, D-2163	Matrix metaloproteinase inhibitor (MMPI) that acts selectively against specific MMP enzymes without affecting TNF or IL-1 release believed to play a key role in the inflammation process and may lead to side effects ❑ PO	Phase II/III (begin 6/01, ongoing 2/02)➢Europe (UK), USA ❑ advanced or metastatic nsclc	
Bristol-Myers Squibb ❑ National Cancer Institute (NCI), CRC Technology	Bryostatin-1 (BRYO) ❑ NSC-339555	Natural macrocyclic lactone derived from the marine bryozoan *Bugula neritina* that is a ligand and inhibitor of protein kinase C (PKC); a novel agent that has antineoplastic, hematopoietic and immunomodulatory activity in a variety of *n vitro* and *in vivo* systems ❑ IV	Phase II (begin 2/01, ongoing 2/02)➢USA ❑ locally advanced or metastatic esophageal or stomach cancer; phase II (completed 10/01)➢USA hormone-refractory prostate cancer	Kaubisch A, etal. ASCO99, Abs. 639:166a
Canji ❑ Transgene, Genzyme Molecular Oncology, ML Laboratories	rAd/p53 ❑ SCH58 500 (formerly ACN53)	Recombinant adenovirus encoding wild-type p53 ❑ intratumoral, intraperitoneal, intrahepatic, intravesical, bronchial lavage, bronchoscopic intratumoral	Phase II/III (began 2/99, completed 7/01)➢USA; phase II/III (begin 10/00, ongoing 2/02)➢Europe ❑ Stage III, newly diagnosed, ovarian cancer	Schuler M, etal, J Clin Oncol, 2001 Mar 15;19(6):1750-8

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Celgene ❑ EntreMed, Children's Hospital at Harvard Medical School, Pharmion, Bristol-Myers Squibb, Royalty Pharma	Thalidomide ❑ Thalidomid, Thalomid	Antiangiogenic compound; may block certain growth factors such as bFGF and vascular endothelial growth factor (VEGF) ❑ PO	Phase III (begin 1/01, ongoing 7/01)➢USA ❑ advanced (Stage IIIa/IIIb) nsclc; adenosquamous, squamous or bronchoalveolar cell lung cancer; adenocarcinoma of the lung; large-cell lung cancer	
Cell Pathways ❑ Paladin Labs, Aventis Pharma, Roche Laboratories, Eli Lilly, GlaxoSmithKline	Exisulind, sulindac sulfone ❑ FGN-1 ❑ Aptosyn (formely Prevatac)	Sulfone metabolite of the nonsteroidal anti-inflammatory drug (NSAID) sulindac; member of the class of proapoptoticdrugs termed selective apoptotic antineoplastic drugs (SAAND) ❑ PO	Phase III (begin 3/01, suspended 10/01)➢USA ❑ refractory nsclc; phase I/II (begin 5/01, ongoing 10/01) ➢USA ❑ first-line treatment of advanced nsclc; phase I/II (ongoing 4/01) ➢USA ❑ metastatic, hormone-refractory prostate cancer	
Cytran ❑ Alza, AIDS Malignancy Consortium	IM-862	Naturally occurring thymic dipeptide consisting of tryptophan and glutamic acid; inhibits angiogenesis growth factors,VEGF and bFGF and increases production of IL-12 ❑ intranasal	Phase II (begin 5/01) ➢USA ❑ advanced or metastatic ovarian cancer	
EntreMed ❑ Bristol-Myers Squibb, Children's Hospital at Harvard Medical School, National Cancer Institute (NCI), Tetrionics, U Iowa, Aventis Pharma	2-methoxyestradiol (2-ME2) ❑ Panzem	Non-estrogenic endogenous metabolite of estradiol ❑ PO	Phase I (ongoing 9/01) ➢USA ❑ advanced breast cancer	
Genaera	Squalamine ❑ MSI-1256F	Synthetic version of an aminosterol originally obtained form the dogfish shark *Squalus acanthias*; cationic steroid characterized by a condensationof an anionic bile salt intermediate with the polyamine, spermidine; angiogenesis inhibitor ❑ IV	Phase II (begin 7/99, completed 6/01)➢USA; phase IIb (begin11/01) ➢USA ❑ advanced or metastatic (Stage IIIb or Stage IV) nsclc	Schiller JH, etal ASCO01, Abs. 1353:339a
Genentech ❑ Hoffmann-La Roche, Bristol-Myers Squibb, Protein Design Labs (PDL), ImmunoGen	Trastuzumab ❑ Herceptin	Recombinant DNA-derived humanized MAb targeting the HER2 protein on tumor cells; lgG1 κ immunoglobulin ❑ infusion	Phase III (begin 2/00 and 10/00)➢USA, Canada ❑ locally advanced breast cancer; phase III (begin 8/99, ongoing 10/01) ➢USA, Europe ❑ metastatic breast cancer; phase II (begin 12/00, ongoing 2/01) ➢USA ❑ locally advanced or metastatic bladder cancer	Norton L, etal, ASCO99, Abs 483:127a

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Genentech ❑ ImmunoGen	Bevacizumab ❑ rhuMAb-VEGF ❑ Avastin	MAb antagonist of VEGF angiogenesis inhibitor ❑ IV	Phase II/III (begin 7/01, ongoing 12/01)➢USA advanced (Stage IIIb or Stage IV), or recurrent nsclc; phase III (begin 12/01)➢USA ❑ locally recurrent or metastatic breast cancer; phase II (begin 5/01)➢USA ❑ Stage IIIb or IV inflammatory breast cancer; phase II (begin 11/01) ➢USA ❑ locally advanced breast cancer	DeVore RF, etal, ASCO 2000, Abs. 1896:485a
Genta ❑ Molecular Biosystems, National Cancer Institute (NCI), U Pennsylvania, Avecia	Oblimersen (formerly augmerosen) ❑ G3139 ❑ Genasense	18-mer fully phosphorothioated antisense oligonucleotide targeting the bcl-2 gene; the lead compound of the Anticode (antisense) technology platform ❑ subcutaneous, IV	Phase I/II (begin 7/00, ongoing 12/01)➢USA ❑ androgen-independent prostate cancer; phase II/III (begin 10/01)➢USA ❑ refractory nsclc	Scher HI, etal, ASCO00, Abs. 774:199a; De Bono JS, etal, ASCO01, Abs. 474:119a
Hybridon	GEM 231 (formerly HYB 165)	End-modified, antisense 18-mer, mixed-backbone RNA/DNA oligonucleotide targeting the RIa cAMP-binding regulatory subunit of protein kinase A type I (PKAI) ❑ IV, intraperitoneal, PO	Phase I (begin 7/99, closed 01)➢USA; phase II (ongoing 2/02)➢USA ❑ refractory solid tumors	Mani S, etal, NCI-EORTC-AACR00, Abs. 534 and 535
ImClone Systems ❑ U California, San Diego, Aventis Pharma, Merck KGgA, Bristol-Myers Squibb	IMC-C225 ❑ Erbitux (formerly Cetuximab)	Chimerized MAb directed against EGFr ❑ IV	Phase II (begin 11/99, closed 12/01)➢USA, Europe ❑ advanced, refractory head and neck cancer; phase I (completed 1/00)➢USA ❑ metastatic breast cancer	Hong WK, etal, ASCO01, Abs. 895:224a
Isis Pharmaceuticals ❑ Eli Lilly	ISIS 3521, ISI641A, CGP64128A	20-mer antisense phosphorothioate antisense oligonucleotide inhibitor of protein kinase C (PKC)-α isoform ❑ IV	Phase III (begin 9/00, completed 1/02)➢USA, Europe ❑ advanced nsclc	Sikic BI, etal, ASCO99, Abs. 1718:445a; Yuen A, etal, AACR-NCI-EORTC99, Abs. 580:118; Yuen A, etal, ASCO00, Abs. 1802:459a; Yuen A, etal, AACR-NCI-EORTC01, Abs. 140
Janssen Pharmaceutica ❑ Kyowa Hakko Kogyo	R115777 ❑ Zarnestra	Farnesyl protein transferase inhibitor; imidazole; inhibits activated p21 ras ❑ PO	Phase I (begin 8/01, ongoing 2/02)➢USA ❑ Stage IIIa/IIIb nsclc	Awada A, etal, AACR-NCI-EORTC01, Abs. 602
Janssen-Cilag	R101933	Novel agent with highly specific inhibition of GP-160–associated multidrug resistance (MDR) ❑ PO, IV	Phase II (begin 9/01) ➢Europe ❑ metastatic or recurrent breast cancer	van Zuylen L, etal, Clin Cancer Res, Apr 2000;6(4):1365-71
National Cancer Institute (NCI)	Carboxyamidotriazole (CAI) ❑ NSC-609974	Synthetic inhibitor of non-voltage-gated calcium influx-regulated (non-excitable) signal pathways; metastasis inhibitor that targets a pertussin toxin-sensitive G protein; reversibly inhibits angiogenesis, tumor cell proliferation, and metastatic potential ❑ PO	Phase I (begin 10/84, ongoing 8/01)➢USA ❑ refractory solid tumors or lymphoma	

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Ontogen	ONT-093 (OC144-093)	P-glycoprotien inhibitor; reverses the effects of multidrug resistance associated with cytotoxic chemotherapy ❑ IV, PO	Phase I (begin 5/01) ➢Canada ❑ solid tumor	See text
ONYX Pharmaceuticals ❑ Pfizer, PolyMASC Pharmaceuticals, Xoma	CI-1042, ONYX-015, dl1520	Genetically engineered E1B-55kD gene-deleted group C adenovirus that replicates in and lyses cells lacking p53 activity ❑ intralesional, intratumoral, intraoperative, mouthwash, intra-arterial, IV	Phase I (completed 3/00) ➢USA ❑ refractory, solid tumors, metastasized to the lung	Nemunaitis J, etal, 9nth International Conference on Gene Therapy of Cancer (ICGTC00), San Diego, CA, December 7-9, 2000, Abs. O-27:S80
OSI Pharmaceuticals ❑ Pfizer, Genentech, Hoffmann-La Roche	Erlotinib ❑ CP-358,774, OSI-774 ❑ Tarceva	Small molecule that directly inhibits EGFr tyrosine kinase (EGFr-TK) ❑ PO, IV	Phase Ib (begin 3/01) ➢USA ❑ advanced solid tumors; phase III (begin 7/21)➢USA ❑ advanced, metastatic (Stage IV/IIIb), or recurrent nsclc	
Parke-Davis ❑ U Texas M. D. Anderson Cancer Center, National Institutes of Health (NIH)	Suramin ❑ NSC-34936, CI-1003 ❑ Metaret	Polysulfonated naphthathylamine derivative; inhibits angiogenesis and enhances apoptosis; antiparasitic agent ❑ bolus, IV	Phase I/II (begin 9/00, ongoing 3/01)➢USA ❑ advanced (Stage IIIb/IV) or recurrent nsclc	
Pfizer Global Research and Development	AG3340 ❑ Prinomastat	Synthetic selective inhibitor of certain matrix metalloprotease (MMP) enzymes such as gelatinase A and B, stromelysin-1 and collagenase-3; angiogenesis inhibitor ❑ PO	Phase III (ongoing 8/00) ➢USA ❑ advanced (Stage IIIb) nsclc	Smylie M, etal, ASCO01, Abs. 1226:307a; Collier M, etal, ASCO99, Abs. 1861:482a
Pharmacyclics ❑ NCI, U Texas, Hoechst Celanese, Abbott Laboratories	Motexafin gadolinium ❑ Xcytrin	Gadolinium texaphyrin (Gd-Tex) that selectively accumulates in cancer cells sensitizing them to radiation ❑ IV	Phase I (begin 1/00, ongoing 4/00)➢USA ❑ Stage IIIa nsclc	
Ribozyme Pharmaceuticals (RPI) ❑ Chiron, U Colorado, Competitve Technologies	RPI.4610 ❑ Angiozyme	Nuclease-stabilized synthetic hairpin ribozyme targeting mRNA of the Flt-1 (VEGFr1) receptor subtype ❑ IV, subcutaneous (SC), intraperitoneal (IP)	Phase II (begin 9/01) ➢USA ❑ advanced solid tumors	
Schering-Plough	SCH 66336	Orally bioavailable nonpeptide tricyclic farnesyltransferase (FTase) inhibitor (FTI) in the pyridobenzocycloheptene class ❑ PO	Phase I/II (ongoing 5/01) ➢USA ❑ metastatic solid tumors	Khuri FR, etal, ASCO00, Abs. 799:205a; Kim ES, etal, AACR01, Abs. 2629:488
TAP Pharmaceutical Products	Carbamic acid ❑ TNP-470 (formerly AGM-1470)	Antiangiogenic analog of fumagillin ❑ IV, subcutaneous	Phase I (ongoing 5/01) ➢USA ❑ metastatic solid tumors	Herbst RS, etal, ASCO00, Abs. 707:182a; Hai TT, etal, ASCO01, Abs. 394:99a; Baidas S, etal, ASCO00, Abs. 800:205a
Targeted Genetics ❑ Laboratories Fournier U Pittsburgh, Arizona Cancer Center, U Texas M. D. Anderson Cancer Center	tg-DCC-E1A, RGG-0853, LF-16-0519	*In vivo* nonviral delivery of E1A adenovirus gene that acts as a tumor suppressor gene, complexed with DC-cholesterol; transcriptionally downregulates HER2/neu expression; prevents metastases ❑ intraperitoneal, intratumoral	Phase I (begin 11/99, ongoing 12/01)➢USA ❑ resected ovarian cancer	

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Vertex Pharmaceuticals ❑ Shire BioChem	Biricodar dicitrate ❑ VX-710 ❑ Incel	Blocks activity of the MDR-1 protein pump to combat multidrug resistance; resensitizes cancer cells to chemotherapy ❑ IV	Phase II (ongoing 2/02) ➢Canada ❑ advanced, refractory ovarian cancer	See text
Vion Pharmaceuticals ❑ Yale University	3-AP, OCX-191 ❑ Triapine	Ribonucleotide reductase inhibitor ❑ parenteral, IV	Phase I (begin 12/00, ongoing 7/01)➢USA ❑ advanced or metastatic, refractory solid tumors	
Xenova Group ❑ QLT	Tariquidar ❑ XR9576	Tariquidar is a selective potent inhibitor of the action of the P-gp pump; may prevent chemotherapy failure attributed to drug resistance ❑ IV, PO	Phase IIa (completed 3/00) ➢Europe (UK) ❑ refractory ovarian cancer	

[1] Only agents in clinical trials are listed. Many others have shown synergism with the taxanes in preclinical evaluations.

[2] For details about these agents, subscribers should interrogate NEW MEDICINE's Oncology KnowledgeBASE (nm/OK) residing at www.oncologyknowledgebase.com.

[3] Only references involving results from clinical trials using taxane-based combination therapies are cited.

*Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|**OK**), February 2002*

Toxicity

Side effects associated with taxane-based chemotherapy are profound, including hematologic toxicity such as severe neutropenia, and neurosensory effects, asthenia, mucositis and nail toxicity. Arthralgias and myathralgias are dose-limiting in paclitaxel therapy. Also, because taxanes are most commonly part of combination therapies, their toxicities are further accentuated by those of the other agents constituting a specific regimen. For instance, peripheral neuropathy is a common and serious dose-limiting toxicity (DLT) in taxane- and platinum-based chemotherapy. Neurotoxic effects may arise from direct taxane and platinum interactions with tubulin.

Docetaxel-induced adverse events have been shown to occur most frequently in patients with impaired liver function, and a reduction in dosage in those with raised levels of transaminases and alkaline phosphatase is recommended to improve the tolerability of the drug. The incidence and severity of problematic adverse effects such as hypersensitivity, skin reactions, and a cumulative fluid retention syndrome are minimized with the routine administration of a 3- to 5-day corticosteroid-based premedication regimen with each docetaxel infusion.

Treatment with nonsteroidal anti-inflammatory drugs, narcotic analgesics, or steroids is unsatisfactory for symptom relief in many patients. Therefore, developers are pursuing various approaches to mitigate the toxic effects of taxane-based regimens.

Long-term toxicity of taxanes is also relevant because in some cases, as in ovarian cancer, patients are administered paclitaxel-based regimens that may last over a year. However, generally, toxicities associated with these regimens do not preclude long-term administration. When records of patients (n=13) treated with paclitaxel therapy for at least 12 months with intervening periods without therapy shorter than 8 weeks at the Mayo Clinic (Jacksonville, FL) between June 1, 1992 and June 1, 2000, were reviewed for toxicity assessment, chronic (1 year) therapy with paclitaxel was not usually associated with significant worsening of peripheral neuropathy, long term marrow toxicity, or other long-term side effects. Side effects were evaluated for their severity after each cycle of treatment, at 12 months of therapy, and at a follow-up date after discontinuation of treatment. Among the 13 patients evaluated, 5 had ovarian cancer, 5 breast cancer, 2 lung cancer, and 1 nasopharyngeal cancer. Paclitaxel was administered as a single agent in 5/13 patients, and in combination with carboplatin (for some cycles) in 7/13 patients and with VP-16 in 1/13 patients. No significant differences in occurrence and severity of peripheral neuropathy, cytopenias gastrointestinal upset, or dermatologic side effects were noted in these patients after 2 cycles as compared with after 12 months of treatment. Data on peripheral neuropathy status following discontinuation of chronic paclitaxel therapy showed that it improved in 2/4 patients and remained stable in the other 2. In all patients, continuing paclitaxel therapy did not lead to peripheral neuropathy beyond Grade 1 (Andrews T and Colon-Otero G, ASCO01, Abs. 2472:180b).

BNP7787 (Dimesna), under development by BioNumerik Pharmaceuticals (San Antonio, TX) is a water-soluble, reducible disulfide having activity as a thiol-modulating chemoprotectant for cytotoxic chemotherapy, including taxanes and platinum-based regimens. The drug is aimed at mitigating common toxicities, including myelosuppression, emesis, renal toxicity and neurotoxicity associated with cytotoxic chemotherapy. BNP7787 was granted fast track designation in March 2000, to prevent or decrease nerve damage associated with paclitaxel.

A common feature of many first-generation platinum-protecting agents is the presence of reactive sulfur-containing chemical groups that can interact with platinum drugs in the blood plasma to cause toxicity. BNP7787 is a second-generation platinum-protecting compound that is not highly reactive in the plasma, yet can undergo conversion inside normal cells to form a highly reactive metabolite, mesna (2-mercaptoethane sulfonic acid), that can selectively detoxify cisplatin and oxaliplatin tubulin adducts. In addition, BNP7787 prevents and mitigates the dose limiting neurotoxicities associated with taxane interactions with tubulin. In preclinical evaluations, BNP7787, administered orally or IV prior to each dose of paclitaxel, completely protected against neurotoxicity in this model. Additionally, BNP7787 pretreatment did not interfere with taxane antitumor activity when tested against a panel of human tumor cell lines, including breast, ovarian, and lung cancer (Cavalletti E, etal. AACR99, Abs. 2632:398). Increasing concentrations of BNP7787 are associated with increasing levels of tubulin protection, and *in vitro* studies have shown that BNP7787 does not interfere with the cytotoxic activity of taxane and platinum compounds (Hausheer FH, etal, AACR01, Abs. 1990:370).

According to BioNumerik, preclinical studies indicate BNP7787 can also significantly reduce and protect against cisplatin-related kidney toxicity, thereby enhancing cisplatin's antitumor activity. Moreover, the company has stated that BNP7787 may protect against common toxicities of radiation therapy.

A multicenter phase III clinical trial (protocol ID: DMS30203R) of BNP7787 versus placebo is currently ongoing in various centers in metastatic breast cancer treated with paclitaxel-based combinations. The study chair is Andrew Seidman from Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY).

In phase I clinical trials BNP7787 demonstrated a good safety profile at dose levels up to 23 g/m^2, without interfering with chemotherapeutic agent pharmacokinetics (Hausheer F, etal, AACR98, Abs. 1077:158, Boven E, etal. ASCO99, Abs. 646:169a, and Hausheer F, etal, AACR99, Abs. 2633:398). A multicenter phase I clinical trial (protocol IDs: RPCI-DS-9739; NCI-G98-1478; BIONUM-BNP7787IV101) was initiated in March 1998 in patients undergoing treatment with cisplatin and paclitaxel for histologically or cytologically confirmed solid tumors such as non-small cell lung cancer (nsclc), ovarian carcinoma, and squamous cell carcinoma of the head and neck, for which no standard treatment exists or which failed standard therapy. According to the protocol, patients were administered BNP7787 IV alone at doses ranging from 4.1 to 12.3 g/m^2 over 15 minutes; one week later paclitaxel (175 g/m^2) was administered over 3 hours, followed by BNP7787 and cisplatin (75 mg/m^2), with treatment repeated every 21 days. Five patients demonstrated significant, reversible depletion of plasma thiols following administration of BNP7787 at a dose level of 8.2 g/m^2, an effect that may reduce the elimination of intact cisplatin, thereby providing for better therapeutic efficacy by increasing the plasma concentration of active drug (Pendyala L, etal, AACR99, Abs. 562:84). No BNP7787-associated DLT was observed, although mild, transient leukopenia was noted following BNP7787 administration in some patients. No Grade 3 or 4 neurotoxicity or emesis was observed in patients treated with >8 cycles of paclitaxel/cisplatin and BNP7787 at doses >8.2 g/m^2; this is in comparison to a reported 70% incidence of clinically significant neurotoxicity in patients administered 6 cycles of paclitaxel/cisplatin alone. There were 2 major objective tumor responses (Schilsky R, etal, ASCO99, Abs. 647:169a).

In February 2001, BioNumerik entered into a strategic alliance agreement with Asta Medica Oncology (Frankfurt, Germany), now Baxter Oncology (Deerfield, IL), for the development and commercialization of BNP7787. Under terms of the agreement, the partners were pursuing clinical development and registration of BNP7787 in the European Union and major territories outside the USA, Canada and Japan, with Asta Medica having exclusive marketing and sales rights to BNP7787 in those territories. As part of the alliance, BioNumerik received an upfront payment from Asta Medica and will receive a royalty on product sales. BioNumerik also has an alliance, established in May 1996, with Tokyo-based Grelan Pharmaceutical (Tokyo, Japan), a member of the Takeda Group (Tokyo, Japan), for the development and commercialization of BNP7787 in Japan. Developments with Grelan are handled through KI Pharma, a joint venture formed by BioNumerik and Grelan Pharmaceutical.

Prosaptide [formerly Prosaptide TX14(A)] is a pharmacologically active peptide sequence (14 mer) within a growth factor or cytokine that binds to a receptor to elicit a therapeutic effect. In laboratory animals, prosaptide induced neuronal regeneration, prevented neuronal death, alleviated peripheral neuropathy, and relieved neuropathic pain. Prosaptide is under development by BioTechnology General (Iselin, NJ) that acquired, in March 2001, Myelos (San Diego, CA), the originator of this agent. In a phase II clinical trial, prosaptide was shown to effectively decrease pain associated with diabetic peripheral neuropathy without deleterious side effects. The drug was also evaluated in preclinical trials as a treatment for paclitaxel-induced neurotoxicity (Campana WM, etal, Neurotoxicology 1998 Apr;19(2):237-44).

APPROVED AND/OR COMMERCIALLY AVAILABLE TAXANES

Spindle poisons have been in use in the treatment of cancer before the advent of taxanes. Two such spindle poisons, vincristine and vinorelbine, are widely used generic anticancers with cytotoxic activity similar to paclitaxel and docetaxel. A common mechanism, i.e., suppression of microtubule dynamics, underlies the actions of many of these antimitotic drugs.

Paclitaxel

Paclitaxel is α tubulin-disrupting agent that binds preferentially to β-tubulin. Paclitaxel promotes the polymerization of microtubules, inhibits microtubule disassembly, arrests eukaryotic cell division, and causes DNA fragmentation, subsequently inducing apoptosis signaling to initiate destruction of proliferating tumor cells. Numerous clinical trials have been carried out or are ongoing with paclitaxel as monotherapy, and in combination with other cytotoxics as well as regulatory agents, for treatment of numerous cancer types. However, the market for paclitaxel (Taxol), a blockbuster drug for Bristol-Myers Squibb, has been rapidly eroding because of aggressive generic competition both here and abroad. Although revenues in this market are declining rapidly in the USA, demand for the drug is at an all-time high making development of novel formulations/analogs of paclitaxel a high priority among many companies.

Taxol, marketed by Bristol-Myers Squibb, is a semisynthetic paclitaxel formulated in Cremaphor EL, a polyethoxylated castor oil and ethanol vehicle. In 2000, global sales of Taxol were $1,592 million, up 7.5% from 1999 levels, representing a cumulative average growth rate (CAGR) of 19.2 % from 1997 levels. However, 2000 was the last growth year for Taxol. Global sales fell by 24.8% to $1,197 million in 2001, as USA sales declined by 45% because of generic competition (Exhibits 1, 2 and 3).

Currently, Taxol is produced semisynthetically from an intermediate harvested from the leaves of yew trees. This intermediate is then chemically modified to produce active paclitaxel.

Paxene, as well as the generic Onxol, are natural paclitaxels derived from the needles of the yew tree, being marketed by Ivax (Miami, FL). Ivax had received a tentative FDA approval for Paxene in December 1997, as a treatment for Kaposi's sarcoma (KS) after failure of first-line, or subsequent systemic chemotherapy. However, in view of Taxol's orphan drug exclusivity for this indication, the application could not be finally approved for marketing in the USA until August 4, 2004. However, since then, Ivax obtained FDA clearance to market Onxol, its generic version of paclitaxel, and the Paxene introduction issue became moot.

Ivax' paclitaxel is the only brand-equivalent product to have undergone extensive preclinical, pharmacologic and clinical studies at over 100 sites in North America, Europe and Australia, involving more than 700 patients with non-small cell lung, breast and ovarian cancer, and AIDS-related KS. Ivax filed an application for regulatory approval of Paxene to treat AIDS-related KS in the European Union in 1997, and the European Committee for Proprietary Medical Products approved this application in July 1999. In April 2000, Paxene was approved for the same indication in Canada by the Health Protection Branch. Paxene has been on the market in certain European countries since mid-1999, supplied by Galena (Opava, Czech Republic), a wholly owned subsidiary of Ivax (see FO, pp 1031).

Docetaxel

Docetaxel works via a different mechanism than that of paclitaxel, disrupting the microtubular network in cells that is essential for mitosis to occur, as well as effecting normal microtubule-regulated cellular activities. Docetaxel inhibits cancer cell division by essentially "freezing" the cell's internal skeleton comprised of microtubules. Taxotere promotes microtubule assembly and blocks disassembly, thereby preventing cancer cells from dividing, resulting in cancer cell death. Taxotere synthesis from the 10-deacetylbaccatin III precursor, found in the needles of the European yew tree (*taxus baccata*), is less complex than the synthesis of paclitaxel.

Taxotere, marketed by Aventis, is the only commercially available docetaxel. The global market for Taxotere was $688.8 million in 2000, up 21.2% from 1999 levels, representing a CAGR of 40.6% from 1997 levels (Exhibits 1, 2 and 3). Worldwide sales of Taxotere were $886.7 million in 2001, up 28.7% from 2000 levels. Sales in the USA increased by 41.1% in 2001 while non-USA sales remained pretty much flat. A codevelopment and marketing arrangement with Chugai (Tokyo, Japan) for the Japanese market was terminated at the end of March 2001. Chugai received an early cancellation fee of 8.4 billion yen. Aventis anticipates global sales of docetaxel to reach the $1 billion mark in 2002.

Aventis is also developing, LIT976, a lyophilized formulation of docetaxel, currently in phase II clinical trials.

TAXANE SOURCES, PRODUCTION PROCESSES, AND GENERIC PACLITAXEL

Several sources of paclitaxel, mostly based on various proprietary extraction and purification methods, are being offered by a variety of USA and foreign companies. Currently, alternative approaches to obtain taxanes include extraction from natural sources, chemical synthesis or semisynthesis, cellular culture production, and genetic engineering. Although after decades of effort (because of their molecular complexity), taxanes were finally synthesized in 1994, it is unlikely that synthetic paclitaxel, requiring several complex steps to produce will be needed to fill demand. However, its synthesis has allowed scientists to modify the molecule in hopes of improving its cytotoxic effects and altering its toxicity profile.

Because semisynthesis of taxanes requires an intermediate derived from yew species that only grow in certain locales, both academic and industrial scientists are seeking to develop approaches to culture Taxus cells and induce them to produce this compound *in vitro*. Production of paclitaxel in culture would obviate the need for harvesting large quantities of yew byproducts.

Exhibit 5
Novel Taxane Analogs and Formulations

Developer ❑ Affiliate(s)	Generic Name ❑ Number ❑ Brand Name	Description ❑ Administration Route	Status ❑ Indication(s)
American BioScience (ABI)	Paclitaxel ❑ ABI-007	Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel ❑ IV, intra-arterial	Phase I (completed 3/01)➢USA ❑ advanced, refractory solid tumors; phase III (ongoing 2/02)➢USA, Europe ❑ metastatic (Stage IV) breast cancer; phase I (completed 00) ➢Europe (Italy) ❑ metastatic, refractory head and neck and anal canal cancer
Aphios ❑ Harvard Medical School, Abbott Laboratories	Paclitaxel ❑ Taxosomes	Liposomal paclitaxel based on a nanosomal phospholipid formulation ❑ IV	Preclin (ongoing 12/01)➢USA ❑ solid tumors
Aphios	Paclitaxel ❑ Dermos	Topical formulation of paclitaxel	Preclin (ongoing 12/01)➢USA ❑ Kaposi's sarcoma (KS)
Aventis Pharmaceuticals	LIT976	Lyophilized formulation of docetaxel ❑ IV	Phase II (ongoing 1/02)➢USA, Canada, Europe ❑ advanced solid tumors
Aventis Pharmaceuticals	RPR-109881A, RPR109881	High-potency third generation taxane; holds promise for treatment of brain metastases and taxane-resistant tumors ❑ IV	Phase II (ongoing 2/02)➢USA, Europe, Canada ❑ advanced solid tumors
Aventis Pharmaceuticals	RPR116258A	Semisynthetic third-generation, potent taxane derivative; weak substrate for P-glycoprotein and able to cross the blood brain barrier ❑ IV	Phase I (completed 01) ➢USA ❑ advanced solid tumors
Aventis Pharmaceuticals	TXD-258, TAX 258	Orally biovailable taxane that crosses the blood brain barrier ❑ IV, PO	Phase I (ongoing 5/01)➢USA ❑ solid tumor
Bayer ❑ Indena, Roswell Park Cancer Center, U New York (SUNY) at Stony Brook	IDN5109, SB-T-101131, Bay 59-8862 ❑ Orataxel	Semisynthetic, orally bioavailable taxane active against P-gp-expressing tumor cells ❑ PO, IV	Phase I (ongoing 5/01)➢USA ❑ solid tumors
Bristol-Myers Squibb (BMS)	Paclitaxel analog ❑ BMS-184476	7-methylthiomethyl ether derivative of paclitaxel; exhibits greater solubility than paclitaxel ❑ infusion	Phase IIb (ongoing 1/02)➢USA ❑ lung cancer; phase IIb (begin 4/01)➢USA, Canada ❑ refractory, metastatic breast cancer
Bristol Myers Squibb (BMS)	Paclitaxel ❑ BMS-188797	Paclitaxel analog ❑ infusion	Phase I (completed 5/01)➢USA ❑ solid tumor
Bristol Myers Squibb (BMS)	BMS-275183	Novel, orally bioavailable taxane ❑ PO	Phase I (ongoing 12/01)➢USA, Europe ❑ solid tumors
Cell Therapeutics (CTI) ❑ U Texas M. D. Anderson Cancer Center, US Oncology	Paclitaxel ❑ CT-2103 ❑ PG-TXL	Poly(L-glutamic acid)-paclitaxel conjugate with enhanced water solubility compared to unconjugated paclitaxel ❑ IV	Phase I (begin 1/00, ongoing 5/01) ➢Europe (UK) ❑ advanced, refractory solid tumors; phase I (ongoing 1/02) ➢USA (combination) ❑ advanced, refractory solid tumors; phase I/II (begin 2/01, ongoing 1/02)➢USA ❑ recurrent ovarian cancer and primary peritoneal cancer; phase II (ongoing 1/02)➢USA ❑ nsclc; phase II (ongoing 1/02)➢USA ❑ refractory colorectal cancer; phase II (planned as of 2/02) ➢USA ❑ refractory breast cancer
Daiichi Pharmaceutical	DJ-927	Novel oral taxane ❑ PO	Phase I (ongoing 12/01)➢Japan ❑ solid tumors

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Enzon	Paclitaxel ❑ PEG-paclitaxel	PEG-modified version of paclitaxel ❑ IV	Phase I (begin 5/01)➢USA ❑ advanced solid tumors or lymphoma
eXegenics ❑ Bristol-Myers Squibb		Gene coding for taxadiene synthase, a key enzyme involved in paclitaxel synthesis; may enable genetically engineered paclitaxel	Research (ongoing 2/02)➢USA ❑ cancer
Genovate Biotechnology	Paclitaxel ❑ Genetaxyl	New formulation of paclitaxel ❑ IV	Phase II (ongoing 1/02)➢Taiwan ❑ breast cancer, refractory nasopharyngeal carcinoma (NPC), nsclc
Guilford Pharmaceuticals ❑ Johns Hopkins U, Massachusetts Institute of Technology (MIT)	Paclitaxel ❑ Paclimer Microspheres	Paclitaxel in PPE (polyphosphoester) microspheres ❑ injection	Phase I (begin 4/00, ongoing 2/02) ➢USA ❑ advanced ovarian cancer
Indena	IDN5390	Novel C-seco taxane derivative characterized by antiangiogenic and antimetastatic activity ❑ injection	Preclin (ongoing 2/02)➢Europe (Italy)
ImmunoGen ❑ State U New York (SUNY) at Stony Brook		Novel taxane compounds used as new effector molecules linked to EGFr MAb using Tumor-Activated Prodrug (TAP) technology ❑ injection	Research (begin 2/00)➢USA ❑ solid tumors
Ivax Laboratories	Paclitaxel ❑ Paxoral	Oral formulation of paclitaxel ❑ PO	Phase I (ongoing 8/99)➢USA, Europe ❑ solid tumors; phase II (ongoing 8/01)➢USA ❑ advanced nsclc, breast cancer and stomach cancer
Nobex	Paclitaxel	Improved, less toxic oral and injectable formulations of paclitaxel ❑ injection, PO	Preclin (ongoing 2/02)➢USA ❑ solid tumors
Pharmacia ❑ NeoPharm, Georgetown U Medical Center	Paclitaxel ❑ PNU-93914 ❑ LEP	Liposome-encapsulated paclitaxel (LEP) based on cardiolipin, a lipid found in cardiac tissue ❑ IV	Phase II/III (ongoing 5/02)➢USA, Europe ❑ refractory solid tumors
Phytogen Life Sciences ❑ State U New York (SUNY)	Paclitaxel	Liposomal formulation of paclitaxel	Research (ongoing 1/02)➢USA ❑ solid tumors
Protarga ❑ Abbott Laboratories, Bryn Mawr College, Martek Biosciences	DHA-paclitaxel ❑ Taxoprexin	Docosahexaenoic acid (DHA)-linked paclitaxel conjugate ❑ PO	Phase I (begin 3/99, completed 00)➢USA, (ongoing 7/01)➢Europe (UK) (combination) ❑ refractory solid tumors; phase II (begin 3/01) ➢Europe (UK) ❑ nsclc; phase II (begin 6/01)➢USA ❑ advanced renal cell carcinoma; phase II (begin 10/01) ➢USA ❑ hormone-refractory, prostate cancer, first-line; phase II (begin 10/01)➢Europe (UK) ❑ advanced breast cancer, first-line; phase II (begin 6/01)➢USA (combination) ❑ metastatic pancreatic or colorectal cancer
Samyang Genex ❑ MacroMed	Paclitaxel ❑ Genexol; OncoGel	Paclitaxel produced in cell culture formulated in hydrogel ❑ intratumoral, intaoperative	Phase I (begin 11/00)➢USA, (ongoing 2/01)➢Europe (Germany) ❑ advanced solid tumors
Sonus Pharmaceuticals ❑ Indena	Paclitaxel formulation ❑ S-8184 (formerly QW8184)	Formulation of paclitaxel in a liquid-in-liquid emulsion ❑ bolus IV	Phase I (begin 2/01, ongoing 2/02)➢USA ❑ advanced, refractory solid tumors
STS Particles	Paclitaxel formulation	Cremophor-free formulation of paclitaxel as a nanoparticle suspension using the Medisperse technology ❑ IV	Research (ongoing 2/02)➢USA ❑ solid tumors

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SuperGen ❑ Janssen Biotech	Paclitaxel formulation ❑ PacoExtra, Paxo Extra	Reformulation of paclitaxel that increases solubility and decreases hypersensitivity and other reactions seen with current formulations ❑ injection	Preclin (ongoing 2/02)➢USA ❑ solid tumors
SuperGen	Paclitaxel	Oral formulation of paclitaxel using pharmaceutically-acceptable, water miscible solubilizers other than Cremophor ❑ IV	Research (ongoing 2/02)➢USA ❑ solid tumors
Supratek Pharma	Paclitaxel formulation ❑ SP1010C	Water-soluble paclitaxel formulation using Supratek's Biotransport carrier technology ❑ IV	Preclin (ongoing 2/02)➢Canada ❑ solid tumors
Supratek Pharma	SP5.210C	Targeted formulation of SP1010C combined with SP5.2, a ligand that targets VEGF receptor 1 (Flt-1) sites, leading to higher accumulation of the drug in the tumor; also produces an antiangiogenic effect in the tumor which is synergistic to the anticancer effect of paclitaxel ❑ IV	Preclin (ongoing 2/02)➢Canada ❑ solid tumors
Taxolog	TL-00139, TL-00050, TL-00068 and TL-00070	Taxol analogs; tested 500 semi-synthetic drugs similar to paclitaxel	Preclin (ongoing 2/02)➢USA ❑ solid tumors
Wyeth-Ayerst Pharmaceuticals ❑ Taxolog	TL-139	Paclitaxel analog ❑ IV	Phase I (begin 7/01)➢USA ❑ solid tumors
Xechem International ❑ U Texas M. D. Anderson Cancer Center, Nordic Drugs, Lachema	Paclitaxel ❑ Paxetol	New formulation of paclitaxel that does not incorporate solubilizing agents such as Cremophor or ethanol but instead uses the excipient, N, N-dimethylacetamide (DMA) as a carrier ❑ IV	Preclin (ongoing 4/01)➢USA ❑ solid tumors

Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), February 2002

Although revenues of paclitaxel are falling precipitously because of generic competition, demand for the drug is rising as it is being shown to be active in a broad variety of tumor types, as monotherapy, or in combination with other agents, either cytotoxic or regulatory. Therefore, despite lower revenues, demand is expected to remain strong. Also, the final settlement regarding the introduction of generic paclitaxel in early 2002, has further increased demand for paclitaxel sources.

The most serious challenge to the taxane market dominance is generic competition. Although generics may only be developed for paclitaxel, availability of lower-priced taxanes will negatively impact the whole market. In January 2002, after protracted litigation, Ivax and Bristol-Myers Squibb agreed to settle all pending Taxol-related litigation between the two companies after the FDA renewed the ANDA for Onxol on January 25, 2002, following the delisting by BMS, on January 17, 2002, of the American BioScience (ABI; Santa Monica, CA) paclitaxel patent from the FDA's Orange Book. The agreement with BMS gives Ivax a royalty-free license to certain of BMS Taxol-related patents. Also, Ivax agreed to dismiss its counterclaims against BMS pending in the United States District Court in New Jersey and in the State Court of Florida. Separately, Ivax is continuing to pursue its counterclaims against ABI in the U.S. District Court in Los Angeles, seeking damages for antitrust violations and anticompetitive conduct arising out of the improper listing of its patent in the FDA's Orange Book and ABI's attempt to enforce the patent against Ivax.

The BMS-Ivax settlement comes amid the most contentious climate in the USA regarding introduction of generic formulations of some of the most popular drugs on the market. The Taxol litigation has been ongoing for a number of years. BMS used every possible loophole in the law to delay the introduction of generics thus saving billions in revenues. However, such tactics caused legislators to review current laws. In May 2001, Senators John McCain (R-AZ), and Charles Schumer (D-NY) introduced the Greater Access to Affordable Pharmaceuticals Act (GAAP) (S. 812), a bipartisan legislation designed to improve access to generic drugs and clean up abuses under the 1984 Hatch-Waxman Act which has been seriously undermined by patent law loopholes that have allowed brand-

name drugmakers to use a variety of tactics, including collusion with generic drug manufacturers, to delay the approval of lower-cost alternatives by several years.

Numerous companies supply paclitaxel and/or intermediates to generic manufacturers both in the USA and abroad. The following list of companies participating in this sector is by no means inclusive but gives an indication of the competitive nature of the paclitaxel marketplace.

Abbott Laboratories

In July 1999, Abbott Laboratories (Abbott Park, IL) and NaPro BioTherapeutics (Boulder, CO) signed an exclusive long-term collaborative agreement to develop and commercialize one or more formulations of paclitaxel for the treatment of a variety of cancer indications in the USA and Canada (see FO p 1032).

Aphios

Aphios (Woburn, MA) uses its proprietary and patented SuperFluids CXP technology to manufacture an all natural paclitaxel from the renewable needles of the ornamental yew tree in a cost-competitive and environmentally friendly manner (see FO, p 1029). The company is seeking a marketing partner for LoTax, its generic version of paclitaxel.

Biolyse Pharma

Biolyse Pharma (St. Catharines, Ontario, Canada) has approval to market generic paclitaxel, in a dose of 6 mg/ml IV injection, in Canada.

Dabur India

Dabur India (Delhi, India), a herbal products company, produces semisynthetic, pharmaceutical-grade, final-dose form paclitaxel, starting from such raw material as leaves and needles of the Himalayan yew tree. Dabur markets paclitaxel in India, and has rights to market the product in China, and certain other markets.

eXegenics

eXegenics (Dallas, TX), formerly known as Cytoclonal Pharmaceutics, is pursuing its paclitaxel-related fermentation production system and genes, in collaboration with Bristol-Myers Squibb (see FO pp 638 and 1029).

Faulding

In January 1995, Faulding (Parkside, SA, Australia), a part of the Mayne Group (formerly Mayne Nickless), obtained marketing approval for paclitaxel (Anzatax) in Australia, New Zealand, and eight other countries in southeast Asia, and certain Middle East markets, for treatment of ovarian cancer and advanced refractory breast cancer (see FO, p 1030). In September 2000, NaPro Biotherapeutics expanded its development and marketing relationship with Faulding to include all of Central America, South America and Mexico, as well as South Africa and certain additional territories in Southeast Asia and the Middle East.

In March 2001, Faulding, entered into a long-term agreement with NaPro Biotherapeutics relating to the European marketing rights of paclitaxel. Under the agreement, NaPro will supply paclitaxel raw material exclusively to Faulding to formulate and finish the product at its facility located in Mulgrave, Victoria. The final proprietary paclitaxel formulation will then be marketed and sold by Faulding in Europe. Under the agreement, Faulding paid an upfront licensing fee to NaPro of $7.5 million and will share equally in the net sales of the product in the new territories. Faulding expects to launch paclitaxel in Europe in 2003, after expiration of exclusivity protection.

Indena

Indena (Milan, Italy) was one of the original suppliers of paclitaxel intermediates. The company supplies 10-deacetylbaccatin III, a precursor of Taxol lacking the C-13 side chain and the C10 acetoxy group, obtained from in the twigs and needles of the European Yew tree (*Taxus baccata*). This intermediate was used for the semisynthetic production of Taxol.

In April 2000, Indena entered into an exclusive, 5-year distribution and supply agreement with Bigmar to develop, manufacture and distribute a generic version of Taxol. Indena will supply the raw material, and Bigmar will manufacture the generic drug.

Ivax

Ivax obtained final approval from the FDA in September 2000, after receiving a tentative approval in August 2000, for its ANDA for paclitaxel 6 mg/ml injection. Ivax had filed an ANDA for generic paclitaxel in December 1997, and in August 1998 purchased Immunex' (Seattle, WA) ANDA for paclitaxel, the first ANDA filed with the FDA for generic paclitaxel. Indicated for the treatment of breast and ovarian cancer, Onxol, Ivax' paclitaxel injection is the generic equivalent of Taxol. However, unlike semisynthetic Taxol, Onxol is extracted directly from the needles of yew trees. Onxol was launched in October 2000 and its 180-days of marketing exclusivity ended in mid-2001. Although, only approved by the FDA for the ovarian and breast cancer indications, it is legal for physicians to use generic paclitaxel off-label for other indications as well. In the USA, sales of Onxol were $35 million in 2000 and are estimated at $217 million in 2001.

Ivax also received approval for various indications in Canada in May 2000, Poland in March 2000, and the 15-member states of the European Union, in July 1999. Ivax' Galena subsidiary received an exception from registration to market Paxene for various indications in Belarus in July 1999, and in the Czech Republic in September 2000. Ivax' paclitaxel is marketed in Poland under the brand name Paxenor. In May 2001, production capacity for Ivax' paclitaxel was enhanced when the FDA approved an additional supplier of the paclitaxel-active ingredient and contract manufacturer of the finished product.

Ivax is one of the most aggressive competitors in the paclitaxel sector, having developed both a generic and a branded (Paxene) version of the drug. Ivax is marketing Onxol in the USA through a direct sales force to oncologists and oncology drugs distributors. In August 2001, Ivax entered into a multiyear agreement to supply Onxol to Novation (Irving, TX), a hospital supply chain management company. Also in 2001, Immunex began recognizing royalty revenue from Ivax on sales of Onxol, based on an agreement dated from 1997 (see FO, pp 1031-32).

Mylan Pharmaceuticals

In September 1996, Phytogen Life Sciences gave Mylan (Pittsburgh, PA) an exclusive license to market generic paclitaxel in the USA, Canada and Mexico. Under the agreement, Mylan will purchase bulk product from Phytogen and manufacture the drug using licensed technology.

In September 2000, Mylan received tentative approval from the FDA to manufacture and market paclitaxel injection. Mylan can begin marketing its paclitaxel formulation 6 months after the launch of Ivax' generic version. The approved formulation is 30 mg/5ml (6 mg/ml) of paclitaxel.

NaPro BioTherapeutics

NaPro BioTherapeutics uses a proprietary extraction, isolation and purification (EIP) process to produce paclitaxel from the bark of the Pacific yew tree obtained from private sources. NaPro's paclitaxel has been sold abroad by Faulding as Anzatax since 1995. An agreement to supply Ivax with its paclitaxel requirements was terminated in March 1998. In July 1999, NaPro entered into an agreement with Abbott Laboratories to supply the latter with paclitaxel to be formulated in an unspecified way.

In June 2001, NaPro and JCR Pharmaceuticals (Ashiya, Japan) entered into a mutually exclusive development, supply and distribution agreement for NaPro paclitaxel in Japan. NaPro will manufacture paclitaxel for JCR and the companies will jointly pursue a pharmaceutical filing for NaPro paclitaxel. In addition, JCR will fund the clinical and regulatory program necessary for seeking approval to market NaPro paclitaxel in Japan.

NaPro entered into an exclusive supply and distribution agreement with Tzamal Pharma (Petach-Tikva, Israel) for the development and distribution of its paclitaxel, Biotax, in Israel. Biotax was approved in Israel in January 2001.

Natural Pharmaceuticals

Natural Pharmaceuticals (NPI; Beverly, MA) is focused on the extraction and purification of cGMP bulk active pharmaceuticals from natural sources such as plants, marine organisms and fermentation broths. The first product of NPI is cGMP paclitaxel. NPI owns the rights to large numbers of cultivated yew trees in USA nurseries and uses a proprietary technology that allows efficient production of paclitaxel. In October 2001, NPI entered into a multi-year supply agreement with Cell Therapeutics (CTI; Seattle, WA) to supply CTI with paclitaxel to be used in the production of PG-TXL.

Phytogen Life Sciences

Phytogen Life Sciences (Delta, BC, Canada) is a primary manufacturer and supplier of active pharmaceutical ingredients (API) to the traditional pharmaceutical and phytopharmaceutical industries. The company has expertise in the extraction, isolation, purification and production of API derived from plants and other natural sources that can then be incorporated into regulated, finished prescription products to be sold by others. Phytogen has two principal Canadian investors, Canadian Medical Discoveries Fund, managed by MDS Capital (Toronto, Canada), and Drug Royalty (Toronto, Canada) which invested $2.4 million in return for preferred shares and warrants and an undisclosed percent of revenues for 15 years.

Phytogen has established two paclitaxel API strategic alliances, one with Mylan Pharmaceuticals, and the other with Sinphar Pharmaceutical (Taipei, Taiwan). In October 2000, the US Patent and Trademark Office (USPTO) issued Phytogen patent # 6,136,989, entitled "Method for high yield and large scale extraction of paclitaxel from paclitaxel-containing material", that covers certain aspects of Phytogen's paclitaxel production processes and product composition.

Phytogen also has an exclusive license from the Research Foundation of the State University of New York (SUNY) at Buffalo, to manufacture and sell a liposome-encapsulated formulation of paclitaxel and other taxanes suitable for treating cancer and other diseases.

Phyton

Phyton (was Phyton Catalytic; Ithaca, NY) focuses on the development, production and commercialization of phytotherapeutics based on technology developed at Cornell University (Ithaca, NY). In June 1998, BMS signed an agreement to commercialize proprietary plant cell fermentation (PCF) technology to produce Taxol and related products under a multiyear, multimillion agreement (see FO p 1030). Phyton produces paclitaxel at its German subsidiary in Ahrensburg. In mid-2000, BMS filed an NDA with the FDA for PCF.

A multicenter phase II clinical trial of PCF Taxol is ongoing in Europe, in patients with advanced, refractory breast cancer. Patients having been previously treated with a taxane (paclitaxel or docetaxel) are also eligible if they did not progress within 12 months after taxane therapy. According to the protocol, PCF Taxol (175 mg/m^2) is administered as a 3-hour infusion for a maximum of 10 cycles. The primary endpoint is response rate. Secondary endpoints include safety, time-to-progression, survival and duration of response.

Samyang Genex

Samyang Genex (Seoul, South Korea) manufactures by plant cell culture technology a version of paclitaxel, Genexol. The company, in collaboration with MacroMed (Salt Lake City, Utah), is developing paclitaxel produced in cell culture and formulated in hydrogel (see below). Also see FO, p 39.

Xechem International

Xechem International (New Brunswick, NJ) is a biopharmaceutical company deriving drugs from natural sources. The company is obtaining raw paclitaxel biomass from a Chinese source. In July 2001, Xechem, a subsidiary of Xechem International, obtained notice of regulatory approval from the Indian government to import and sell generic Chinese paclitaxel in India. Xechem is also seeking approval to import and/or sell generic paclitaxel in Indonesia and other Pacific Rim Countries, Africa, Europe, South America and the USA (see FO pp 1030, and 1035-6).

Xechem International is also developing paclitaxel analogs (2",3"-dihalocephalomannine compounds), currently in the research stage. These compounds are more physiologically soluble than paclitaxel. Also, preliminary *in vitro* laboratory data has shown that these compounds may be more effective than paclitaxel or docetaxel in treating certain tumors. In January 1999, Xechem International was awarded patent #5,840,930 by the USPTO containing broad coverage for methods for production of these compounds.

In September 1997, Xechem entered into a licensing agreement with the University of Texas M. D. Anderson Cancer Center (Houston TX) for a new formulation of paclitaxel (Paxetol) that does not incorporate such solubilizing agents as Cremophor or ethanol.

NOVEL FORMULATIONS

At present, paclitaxel is formulated in a nonionic surfactant comprising a mixture of 50:50 Cremophor EL (CrEL) and dehydrated ethanol. This vehicle is not physiologically inert. Although its effects are not fully understood, it is known to have a number of pharmacologic, pharmacokinetic and pharmaceutical effects, among which are serious hypersensitivity reactions. A recently observed phenomenon is the ability of CrEL to form micelles in aqueous solution as well as biological fluids (e.g. plasma) that may greatly influence the pharmacokinetic behavior of the formulated drug. Because of drug entrapment in the micelles, plasma concentrations and clearance of free drug change significantly, leading to alteration in pharmacodynamic characteristics (van Zuylen L, etal, Invest New Drugs, May 2001;19(2):125-41).

To eliminate the need for surfactants, developers are attempting to reformulate taxanes to make them safer, easier to administer, orally available, and improve their dosing and pharmacokinetic profiles. Also, novel formulations will result in proprietary drugs with a huge built-in global market (Exhibit 5).

ABI-007

American BioScience (ABI), formerly VivoRx Pharmaceuticals, is developing ABI-007, a novel protein (albumin)-stabilized, Cremophor-free, nanoparticle formulation of paclitaxel that may be used without premedication, and may allow the administration of paclitaxel safely at doses higher than 175 mg/m^2. In February 2002, at a Goldman Sachs' Oncology Conference held in New York City, ABI reported that since initiation of clinical trials in 1998, over 250 patients had been treated with ABI-007 in phase I /II clinical trials. Two multicenter, phase II clinical trials were undertaken to examine the safety and efficacy profile of ABI-007, administered at the current FDA-approved dose of paclitaxel (175 mg/m^2), and at a much higher dose of 300 mg/m^2 over 30 minutes every 21 days as monotherapy, without steroid pretreatment, in patients with metastatic breast cancer. Data from these phase II clinical trials are expected to be reported at the 2002 meeting of the American Society of Clinical Oncology (ASCO). Also, a multicenter, multinational, randomized, open-label, phase III clinical trial, to directly compare ABI-007 with Taxol, has been initiated in the USA and Europe, and is enrolling patients with metastatic breast cancer. The study's objective is to compare the percentage of patients in the ABI-007 and Taxol arms who achieve CR or PR after a minimum of two cycles of treatment.

In a phase I clinical trial, conducted at M. D. Anderson Cancer Center, 19 patients with advanced solid tumors, 13 with metastatic breast cancer and 6 with melanoma, were treated with ABI-007 without premedication as a 30-minute infusion every 21 days, at the starting dose of 135 mg/m^2; 85 courses were delivered with the median number delivered being 5 (range=1-11). MTD was determined to be 300 mg/m^2. Hematologic toxicity manifested in 1 cycle as neutropenic fever caused by skin infection; otherwise, no Grade 3/4 hematologic toxicity was seen. Cycles with Grade 3/4 nonhematologic toxicity involved nausea/vomiting (n=1), stomatitis (n=2), diarrhea (n=2), constipation (n=1), myalgia (n=1), peripheral neuropathy (n=5), perioral numbness (n=5), fatigue (n=5), skin blisters (n=2), and polyuria/ polydypsia (n=3). Visual toxicities included Grade 3 keratitis (n=3), Grade 2 blurred vision (n=3), and eye flashes (n=1), and Grade I dry-eye syndrome (n=2). No hypersensitivity reactions were seen. DLT was peripheral neuropathy and superficial keratitis (Ibrahim NK, ASCO00, Abs. 609F:155a).

A phase I clinical trial of intra-arterial injection of ABI-007 was completed in 2000, in 28 patients with head and neck (n=18) and anal cancer (n=10), on the premise that increased accumulation of nanoparticles of paclitaxel at the tumor site would increase efficacy, especially in these tumors that are characterized by overexpression of EGF receptors. Among the 18 patients with head and neck can-

cer, 6 had newly diagnosed Stage IV disease, and 12 recurrent disease after surgery, RT, and/or chemotherapy. All of the 10 patients with anal canal cancer had been previously treated with surgery, RT and/or chemotherapy. ABI-007 was injected by percutaneous superselective arterial catheterization every 4 weeks for 3 cycles. MTD was determined at 270 mg/m^2 and treatment dose was 250 mg/m^2. Among the 18 head and neck cancer patients toxicities included Grade I/II alopecia (24%), flu syndrome (22%), and neurological (12%), gastrointestinal (12%), cutaneous (8%), ocular (7%) effects; 15% experienced bone marrow toxicity (Grade I=9, Grade II=3, Grade IV=1). Among 17 evaluable patients, 52% experienced PR, and 12% MR, while disease stabilized in 24%, and progressed in 12%. Among anal canal cancer patients, toxicities included Grade I/II alopecia (29%), flu syndrome (25%), and gastrointestinal side effects (12%), and Grade I neurological (10%) and cutaneous (7%) side effects; 17% experienced bone marrow toxicities (Grade II=2, Grade III=1 and Grade IV=2). Among 10 evaluable patients, there was one pathologic CR, 3 PR, 1 MR, and disease stabilized in 4 and progressed in 1. Carotid catheterization-related complications involved 3 previously treated patients >70 years-of-age who fully recovered (Damascelli B, etal, ASCO00, Abs. 816:209a).

In November 2001, American BioScience filed an IPO of its American Pharmaceutical Partners (APP; Los Angeles, CA) subsidiary. Approximately $45 million, obtained from the IPO, was paid to American BioScience to secure the exclusive North American marketing and manufacturing rights for ABI-007.

CT-2103 (PG-TXL)

Cell Therapeutics (CTI; Seattle, WA), in collaboration with the University of Texas M. D. Anderson Cancer Center, is developing CT-2103 (PG-TXL), a water-soluble macromolecular compound comprised of paclitaxel and poly-L-glutamic (PG) acid with a molecular weight of approximately 80 kD. Paclitaxel is linked to PG through an ester bond between the 2' OH group of paclitaxel and the γ-carboxylic acid residues of PG.

Compared to paclitaxel, CT-2103 has improved biodistribution to tumors, mediated through the enhanced permeability and retention effect of tumor vasculature on macromolecules. CT-2103 shows selective distribution to tissues, such as tumors that possess a leaky vascular endothelial membrane. Tumors contain blood vessels with fenestrations that make these vessels leaky. These abnormal vessels can act like a strainer, trapping large molecules such as the polyglutamate polymers as they circulate in the bloodstream. In contrast, the conjugates do not enter normal tissues because the blood vessels in normal tissues do not contain fenestrations. The polymers are predominately confined to the bloodstream until they are degraded and excreted by the kidneys. If loaded with a chemotherapeutic drug such as paclitaxel, the polyglutamate carrier unloads its cancer-killing agent at the tumor site, delivering a larger dose directly to the tumor while largely sparing normal tissue its toxic side effects. In preclinical trials, the dose of PG-TXL could be escalated by 400% over that of effective paclitaxel dose levels.

CT-2103 is soluble in aqueous solution, and exposes normal organs to the conjugated form of paclitaxel which has been shown to be non-toxic *in vitro*, and this may minimize overall toxicity. When CT-2103 was compared to paclitaxel in Cremophor at their respective MTD in a variety of syngeneic and xenogeneic *in vivo* tumor models (in both single dose and multidose studies) including ovarian tumors, CT-2103 showed enhanced efficacy over paclitaxel. CT-2103 also exhibited a higher MTD and enhanced antitumor activity in a variety of syngeneic and xenograft models compared to paclitaxel. PG-TXL can be administered in a 10-minute IV infusion, and does not require premedication.

CT-2103, because of its probable uptake by pinocytosis and intracellular release of free paclitaxel, is relatively unaffected by membrane pumps such as P-gp. In 3 cell lines (HCT-15, LoVo and Colo-320 DM) expressing high levels of P-gp, and 3 others (HCT-116, HT-29 and LS174t) that did not express P-gp, CT-2103 showed superior antitumor activity compared with free paclitaxel, resulting in tumor regression in the HT-29 and HCT-116, mdr-1-negative models. Free paclitaxel had no antitumor effect on the mdr-1-positive HCT-15 tumor, while CT-2103 at 120 mg/kg and 150 mg/kg paclitaxel equivalent caused a tumor growth delay of 3.6 and 9.6 days, respectively (de Vries P, etal, AACR01, Abs. 462:86).

In preclinical trials, PG-TXL was also a highly potent enhancer of tumor radioresponse *in vivo*. When irradiation was administered at 24 hours after treatment with IV PG-TXL at equivalent paclitaxel doses of 47 mg/kg, 80 mg/kg, and 120 mg/kg, the mean enhancement factors were 0.75, 1.8, and 4.2, respectively. In tumors irradiated at 14 Gy prior to PG-TXL (120 mg/kg), the enhancement factor was 4.3. The radiosensitization effects of PG-TXL were dose dependent. PG-TXL at 120 mg/kg had a superadditive radiosensitization effect, independent of treatment schedule, and may be effectively used before or after radiotherapy (Ke S, etal, AACR99, Abs. 4223:640-1). Effectiveness of PG-TXL in this setting may be attributable to the fact that this drug is delivered at an optimal concentration and is maintained in the tumor for a prolonged period. Possible mechanisms include G2/M arrest, increased tumor blood supply and drug uptake, and sustained paclitaxel release.

When mice with intramuscularly implanted ovarian carcinoma OCa-1 tumors were treated with IV PG-TXL alone or in combination with single doses of local radiation therapy (RT), the enhancement factors at a 24-hour interval, as measured by incremental tumor growth delay, compared with radiation alone, ranged from 2.48 to 4.28. These values varied as a function of radiation dose and also

as a function of the time interval between injection of PG-TXL and tumor irradiation. The enhancement factor increased with decreasing interval, suggesting that radiation may in turn mediate the sensitivity of tumor toward PG-TXL, implying that the mechanism of PG-TXL's radiopotentiation activity is probably multifactorial (Ke S, etal, J Control Release, 6 Jul 2001;74(1-3):237-42).

In a study conducted to assess PG-TXL-RT interaction using clinically relevant treatment conditions and response endpoints and to establish normal tissue (small intestine, skin, and hair) damage, mice bearing 7-mm OCa-I ovarian carcinoma were treated IV with PG-TXL at an equivalent paclitaxel dose of 80 mg/kg, and 24 hours later by local tumor RT with 5 daily doses ranging from 1 Gy to 16 Gy per fraction (total dose 5 Gy to 90 Gy). PG-TXL dramatically enhanced tumor radiocurability after fractionated RT providing an enhancement factor of 8.2 at the TCD50 level. Because normal tissue radioresponse was unaffected, therapeutic ratio was greatly increased. It is believed that such a large increase in therapeutic gain using preclinical tumor and normal tissue models has not been previously reported for any radiomodulating agent (Mason, KA, etal, AACR-NCI-EORTC01, Abs. 769).

In July 1999, Cancer Research Campaign (London, UK) agreed to begin a phase I dose escalation clinical trial of PG-TXL in solid tumors, in the UK. In April 2001, CTI entered into a research services agreement with US Oncology to conduct up to five clinical trials in colorectal and lung cancers with PG-TXL. In October 2000, the FDA approved an IND to commence clinical trials in the USA, which were ongoing as of January 2002. Combination trials with cisplatin are to enroll 12-30 patients and with carboplatin, 18 patients. These trials will be conducted by US Oncology. A phase II clinical trial of PG-TXL as first-line therapy in high-risk nsclc and another phase II clinical trial of PG-TXL as second-line therapy in colorectal cancer were ongoing as of January 2002. A phase II clinical trial in refractory breast cancer was being planned as of January 2002. A combination trial with radiotherapy is also to be initiated in 2002.

In a phase I clinical trial, among 17 patients entered at dose levels ranging from 30 mg/m^2 to 720 mg/m^2, a total of 57 cycles were administered (range=1-18 per patient). Primary tumor sites are colorectal cancer (n=5), nsclc (n=4), renal cell carcinoma (n=2), leiomyosarcoma (n=1), unknown primary (n=2), pleural adenocarcinoma (n=1), cystic adenocarcinoma of carotid (n=1) and mesothelioma (n=1). At 720 mg/m^2 (266 mg/m^2 paclitaxel equivalent), DLT was seen in 2/6 patients (1 neutropenia and 1 motor neuropathy), so a dose of 630 mg/m^2 (233 mg/m^2 paclitaxel equivalent) was being investigated as the possible MTD. Grade 4 neutropenia was observed at the 720 mg/m^2 and 630 mg/m^2 dose levels. Aside from one patient with Grade 3 motor neuropathy (DLT) only Grade 1 sensory neuropathy was observed; 3 patients experienced hypersensitivity reactions to treatment. CT-2103 exhibited a long plasma half-life of up to 162 hours. There was 1 confirmed PR after 2 cycles in a patient with mesothelioma at 480 mg/m^2 (176 mg/m^2 paclitaxel equivalent). This persisted until 2 months following completion of six cycles of treatment (Todd R, etal, EORTC-AACR-NCI01, Abs. 115).

In an open-label, phase I clinical trial, being conducted at M. D. Anderson Cancer Center, escalating doses of CT-2103, administered as a 10-minute IV infusion, were followed by a 3-hour IV infusion of cisplatin every 21 days. Among 4 patients with various solid tumors enrolled in the study, 3 were treated with a paclitaxel-equivalent dose of 175 mg/m^2, and the 4th with two infusions at a paclitaxel-equivalent dose of 210 mg/m^2. There was no DLT. One male patient was withdrawn from the study because of progressive peritoneal adenocarcinoma. The other 3 patients, all women with potentially platinum sensitive tumors, responded to this combination regimen. One patient with recurrent papillary serous ovarian carcinoma, who had been previously treated with cisplatin, paclitaxel and amifostine (Ethyol; MedImmune) followed by paclitaxel consolidation, and then on relapse progressed on topotecan, experienced a PR (80% reduction tumor measurement and normalization of CA-125) after completing 6 cycles of CT-2103/cisplatin. A mild hypersensitivity reaction during the second infusion did not recur with the addition of prophylactic dexamethasone and diphenhydramine. In another patient with advanced recurrent primary peritoneal adenocarcinoma, previously treated with carboplatin and paclitaxel, intraperitoneal IL-12, and carboplatin reinduction, the tumor shrunk on CT scan and CA-125 decreased from 564 to 87, after 5 cycles of CT-2103/cisplatin. In the fourth patient with endometrial cancer which recurred after platinum based therapy, CA-125 dropped from 50 to 24 after the first cycle of CT-2103/cisplatin. This study is ongoing and plasma samples for pharmacokinetic evaluations are being collected from all patients (Kudelka, AP, etal, AACR-NCI-EORTC01, Abs. 287).

An open-label, phase I/II clinical trial (protocol ID: MSKCC-01024; NCI-G01-1947; CTI-1071) was initiated in February 2001 as third-line salvage chemotherapy in disease resistant or refractory to Taxol. The study will determine the response rate and time to treatment failure in patients with recurrent ovarian epithelial, fallopian tube, or primary peritoneal carcinoma, treated with CT-2103 and the tolerability and safety of the previously established dose and schedule of CT-2103 in these patients. According to the protocol, patients are being treated with CT-2103 IV over 10 minutes on day 1; treatment repeats every 3 weeks in the absence of disease progression or unacceptable toxicity. Patients are followed between 1-3 months and then every 3 months thereafter. A total of 20-40 patients will be accrued for each phase of this study being conducted at Memorial Sloan-Kettering Cancer Center with Paul Sabbatini, MD, as the Study Chair.

In the phase I segment of this study, 8 patients with recurrent disease after at least 2 prior systemic therapies,

including paclitaxel-based regimens (ovarian cancer=5 and peritoneal cancer=2), were treated at a paclitaxel-equivalent dose of 175 mg/m^2 for 1 to 3 cycles. There was no DLT, hypersensitivity, neuropathy, or alopecia. Grade 1 increases in liver enzymes were noted in 3 patients, transient Grade 3 leukopenia and neutropenia in 1, and Grade 1 diarrhea, fatigue, nausea, and insomnia in 1. A reduction of >50% was noted from start of treatment in 3 /4 patients with elevated CA-125 at baseline. One patient who completed three cycles experienced a PR, as demonstrated by repeat CT scans. If no DLT is seen in 6 patients, subsequent patients are being treated at a paclitaxel-equivalent dose of 235 mg/m^2 (Sabbatini P, etal, AACR-NCI-EORTC01, Abs. 470). The phase II component of this trial is ongoing at Memorial Sloan-Kettering Cancer Center. As of December 2001, 61 patients had been enrolled out of the 80 planned. According to preliminary results, among 16 evaluable patients of 61 treated to date, there were 8 responses, 4 major. There was no significant nerve damage, hair loss or neutropenia.

In October 2001, CTI Technologies (CTIT), a wholly owned subsidiary of CTI, entered into a licensing agreement with Chugai Pharmaceutical for the development and commercialization of PG-TXL in several Asian markets, including Japan and South Korea. Under terms of the agreement, in exchange for rights to PG-TXL, Chugai committed up to $73 million in license fees, milestone payments, and development expenditures over the course of the licensing agreement. CTIT received a $3 million initial payment upon execution of the agreement. In addition, CTIT will also receive royalties on product sales in the territories covered under the agreement.

In October 2001, CTI entered into a supply agreement with Natural Pharmaceuticals (NPI) to establish a multi-year supply schedule over which NPI will provide significant quantities of paclitaxel to CTI.

Fibrinogen-Coated Emulsion Formulation of Docetaxel

The observation that several types of tumors have high deposits of fibrin indicative of elevated levels of thrombin, has led researchers at the University of Cincinnati Medical Center (Cincinnati, OH) to investigate if fibrinogen-coated particles can be targeted to tumors. Subsequently, a fibrinogen-coated formulation of docetaxel with adequate physicochemical and biologic activity was created that was selectively delivered to tumor tissues in *in vivo* studies. The formulation consists of a docetaxel emulsion prepared in olive oil using F68 as a surfactant. The emulsion particles were coated with fibrinogen by incubating the emulsion with fibrinogen for 30 minutes. The formulation was optimized with regards to its physicochemical stability, fibrinogen functionality and *in vitro* cytotoxicity, was stable at 4° C for a month, and retained the coagulation activity of fibrinogen and the cytotoxicity of docetaxel in all cell lines investigated.

Cytotoxic activity of the formulation was evaluated *in vitro* against several cell lines such as human breast carcinoma MCF-7, mouse leukemia L1210, and mouse melanoma B16F10, and *in vivo* by determining fibrinogen levels and accumulation of ^{125}I- labeled fibrinogen in various tissues of tumor-bearing animals, including athymic nude Balb/C mice implanted with MCF-7 tumors, transgenic MMTV PyVT mice that spontaneously develop mammary tumors, and C57/BL6 mice implanted with B16F10 melanoma tumors. In preliminary *in vivo* experiments to assess fibrin(ogen) deposits in tumors, significantly higher accumulation of FITC-conjugated antibody against fibrinogen was observed in and around tumor tissues. Similarly, ^{125}I- labeled fibrinogen exhibited selective accumulation in tumor tissues. For example, the MCF-7 tumors and B16 melanomas accounted for more than 46% of the total radioactivity in tissues collected. Further studies on the *in vivo* antitumor activity of the formulation and pharmacokinetics of docetaxel are currently in progress (Jakate AS, etal, AACR01, Abs. 747:139). This tumor-targeting approach is available for licensing.

Genetaxyl

Genetaxyl, a proprietary formulation of paclitaxel, is under development by Genovate Biotechnology (Hsinchu, Taiwan), formerly Genelabs Biotechnologies (GBL). GBL was founded in 1995 in an alliance between Genelabs Technologies (Redwood City, CA), the government of Taiwan (35% ownership) and local Taiwanese investors.

Genetaxyl is being evaluated in several phase II clinical trials. One such trial, in breast cancer, is being conducted at Veterans General Hospital-Taipei (VGH-Taipei) and Mackay Memorial Hospital (MMH; Tapei, Taiwan). Preliminary results show that Genetaxyl is efficacious and well tolerated. This study is to be completed in late 2002. Another phase II clinical trial in nsclc is being conducted at Koo Foundation Sun Yat-Sen Cancer Center (Taipei, Taiwan) that is also carrying out a phase II clinical trial in refractory nasopharyngeal carcinoma in combination with 5-fluorouracil and leucovorin. Objectives of this open-label trial are to evaluate the efficacy and safety of Genetaxyl in this setting. Approximate 30 patients with recurrent NPC following radiotherapy and chemotherapy will be recruited. Patients are treated with 5-FU (1000 mg/m^2) and leucovorin (100 mg/m^2), as a 24-hour IV infusion, followed by a 1-hour IV infusion of Genetaxyl (45 mg/m^2), once a week, for 3 weeks with one week rest, for a minimum of 2 and maximum of 6 cycles. All patients are being premedicated with 10 mg of IV dexamethasone 12 hours and 6 hours before the Genetaxyl infusion, and 10 mg dexamethasone, 30 mg diphenhydramine, and 50 mg ranitidine 30 minutes IV before the Genetaxyl infusion.

Liposome-encapsulated Paclitaxel (LEP)

NeoPharm (Lake Forest, IL) is developing liposome-encapsulated paclitaxel (LEP), in collaboration with Pharmacia, under rights obtained from Georgetown

University (Washington, DC). NeoPharm has developed a synthetically derived cardiolipin, which may provide a reliable lipid source for making liposomes. NeoLipid technology, NeoPharm's proprietary, electrostatic liposome encapsulation delivery system, takes advantage of the naturally occurring electrical charge of a drug, combining it with proprietary oppositely charged lipids. The drug and the liposome structure surrounding it are strongly attracted to each other, resulting in a stable product during storage and after reconstitution and IV administration. The construct is also less expensive and easier to manufacture and deliver because there is less waste as a result of the inherently greater stability of the electrostatic liposome structure. Also see FO, p 1034.

LEP was the first liposomal taxane to enter clinical trials. Enrollment in a phase I/II clinical trial involving 31 patients with refractory solid tumors was completed in April 2000. To date, this trial has demonstrated that LEP may be administered at higher doses than standard paclitaxel. Also, 6 patients responded with tumor reduction >35% and disease stabilized in 12 others, with 4 of these remaining stable for >12 months. None of the patients experienced hair loss or nausea. International multicenter phase II/III clinical trials, initiated by Pharmacia in 2000, are ongoing.

In a phase I clinical trial, conducted at the Rotterdam Cancer Institute in the Netherlands, LEP was administered IV, weekly, over 45 minutes, for 6 weeks of an 8-week cycle, in patients with refractory solid tumors. Dose levels tested included 90 mg/m^2/week (dose level I, n=3) and 120 mg/m^2/week (dose level II, n=4). Among 7 patients, one each with oropharynx, gallbladder, pancreatic, stomach and colon cancer, and 2 with miscellaneous tumors, treatment was stopped after one administration of LEP in 1 patient because of early progressive disease. Toxicities involved mild-to-moderate hematologic effects, including Grade 2 WBC (n=1), Grade 2 platelets (n=1), Grade 1 ANC (n=3), and Grade 1 hemoglobin (n=4). Nonhematologic toxicities included Grade 1 nausea (n=3), vomiting (n=1), fatigue (n=2) and taste change (n=1). Regarding pharmacokinetics, the terminal half-life of free paclitaxel was long, and the terminal half-life of both free and total paclitaxel was considerably longer than Taxol. Patient accrual is continuing and, so far, MTD had not been reached (Soepenberg O, etal, AACR-EORTC-NCI01, Abs. 101).

In a phase I clinical trial, conducted at Fox Chase-Temple University Cancer Center (Philadelphia, PA), LEP was administered IV over 45 minutes every 3 weeks using standard IV tubing. No antiemetics were administered. Among 26 patients [Stage IV nsclc=21, sclc=1 breast cancer=2, nasopharyngeal cancer=1, and unknown primary=1; prior chemotherapy=10; prior paclitaxel=3, and 5 chemotherapy-naive treated with prior radiation], treated at escalating dose levels, 3 at 90 mg/m^2, 3 at 135 mg/m^2, 11 at 175 mg/m^2, 6 at 250 mg/m^2, and 3 at 300 mg/m^2, a total of 105 cycles were administered. No neuropathies or myalgias were observed at any dose level, and no alopecia was seen at doses ≥175 mg/m^2. DLT was seen in 2 patients at 300 mg/m^2 (mucositis), 2 at 250 mg/m^2 (neutropenic sepsis, anaphylaxis), and 1 at 175 mg/m^2 (anaphylaxis). Hematologic toxicities included Grade 4 neutropenia and leukopenia and Grade 3 thrombocytopenia and anemia starting at 175 mg/m^2. Nonhematologic toxicities included Grade 3/4 mucositis and Grade 3 diarrhea at doses ≥250 mg/m^2. Routine premedication with diphenhydramine and hydrocortisone mostly eliminated liposome infusion reactions that included transient back pain and flushing in 5 patients and rigors in 1. One patient treated at the 300 mg/m^2 dose level died from complications of severe mucositis, and one at 250 mg/m^2 died from complications of the primary tumor and neutropenic sepsis. There were 2 PR (breast cancer and nsclc) and 3 MR (1 breast cancer and 2 nsclc). Patient accrual continued with dose escalation to 200 mg/m^2 (Treat JA, ASCO00, Abs. 881:225a).

In November 2000, Neopharm was issued patent #6,146,659 by the USPTO that covers novel administration of LEP with an improved side effect profile. In July 1999, Neopharm received a $2 million milestone payment from Pharmacia and also transferred the IND for LEP to Pharmacia as part of the licensing agreement.

OncoGel

OncoGel is an injectable depot formulation of paclitaxel, currently in development by MacroMed, that uses the ReGel drug delivery system (also see FO pp 639 and 1033-34). OncoGel is an intratumoral formulation of paclitaxel and ReGel, a proprietary triblock copolymer of lactic acid, glycolic acid and polyethylene glycol (PEG 1000) that when mixed in water, forms a hydrophobic, biodegradable gel at body temperature. ReGel is a temperature-sensitive (thermally reversible) biodegradable hydrogel. Below room temperature OncoGel is a simple aqueous solution but gels at body temperature. The system cycles through the solution/gel transition repeatedly with no adverse effects. When injected through a small gauge hypodermic needle, the gel provides consistent delivery at the site of injection for approximately 6 weeks, and then degrades into nontoxic products that are metabolized by the liver and kidney. This amphiphilic hydrogel delivery system is particularly well suited for formulation of soluble drugs and proteins without the need of organic solvents.

The ReGel drug delivery system increases the solubility of paclitaxel without the use of Cremaphor, it is biocompatible and biodegradable, is easily administered through a small-gauge needle, and forms a localized depot which keeps the drug at the tumor site for an extended period of time. In preclinical studies, OncoGel has shown greater efficacy in reducing tumor size when compared to systemically delivered controls while significantly reducing the side effects associated with systemically administered paclitaxel. Toxicity testing and animal studies show that ReGel is nontoxic and when formulated with paclitaxel

(Genexol) provides predictable, controlled release of the drug at the site of a solid tumor for over six weeks.

In Europe, the drug is being evaluated in a phase I clinical trial by AE Schindler of the University of Essen in Germany. According to a presentation during the 6th US-Japan Symposium on Drug Delivery Systems, that took place in December 16-21, 2001, in Lahaina, Hawaii, OncoGel, in combination with paclitaxel, was shown to be safe. There was no incidence of either local or systemic toxicity, such as weight loss, neutropenia, neuropathy, nausea or hair loss in any patients during the 9-week, single-dose treatment period nor during the 12-month follow-on period. After a single dose of OncoGel, 35% of the tumors were reduced in size by up to 50%, and tumor growth stopped in 45% of the treated tumors for an overall 80% response rate. Also, when two tumors were treated under humanitarian consideration, one tumor was further reduced and the other was entirely eliminated. An IND to initiate a phase I clinical trials in the USA was obtained in November 2000.

Paclimer Microspheres

Guilford Pharmaceuticals (Baltimore, MD) is evaluating Paclimer Microspheres, a site-specific, controlled-release formulation of paclitaxel that incorporates the drug in a biodegradable polyphosphoester (PPE) polymer matrix (see FO, p 1033). Guilford has licensed exclusive rights to this patent from the Massachusetts Institute of Technology (Cambridge, MA) and Johns Hopkins University (Baltimore, MD).

A multicenter phase I clinical trial (protocol ID: GOG-9904; GP-700-9901) was initiated in April 2000 in patients with recurrent ovarian epithelial cancer or peritoneal cavity cancer, being conducted by the Gynecologic Oncology Group (GOG) with Deborah K. Armstrong, MD, as Study Chair. This dose-escalation clinical trial, to evaluate the drug's safety, tolerability and pharmacokinetics, is expected to enroll approximately 24 women with advanced ovarian cancer. Guilford had filed an IND to commence its clinical program with Paclimer in November 1999. Guilford is also studying the application of Paclimer Microspheres preclinically in the treatment of several types of other solid tumors, including lung cancer.

PacoExtra

SuperGen (Dublin, CA) is formulating paclitaxel with its Extra technology that uses an inert chemical which, when added to a hydrophobic anticancer drug, makes it water soluble and shields the patient's skin from tissue damage at the injection site. The drug is released upon circulation within the bloodstream (also see FO, p 1035).

In December 1999, SuperGen entered into a licensing and research agreement with the Clayton Foundation for Research (Houston, TX) and its technology transfer organization, Research Development Foundation, to acquired worldwide rights to inhaled versions of formulations of a number of taxanes, including paclitaxel. In January and October 2000, SuperGen was issued two patents by the USPTO for a Cremophor-free formulation of paclitaxel. In February 2000, SuperGen was issued patent # 6,017,948 by the USPTO, covering the company's water-miscible formulation of generic paclitaxel.

Paxoral

Paxoral, an oral formulation of paclitaxel, under development by Ivax, is based on the administration of paclitaxel, in combination with oral CsA (either Sandimmune or Neoral). This combination resulted in an 8-fold increase in the systemic exposure of oral paclitaxel (also see FO, pp 1032-33). Treatment with oral drug (60 mg/kg) and cyclosporin A (15 mg/kg) achieved biologically relevant paclitaxel plasma levels in humans (Terwogt JMM, et al, Lancet, 25 Jul 1998;352:285). According to a phase I clinical trial, pharmacokinetic results indicate that coadministration of CsA increases the oral bioavailability of paclitaxel from 4% without CsA to 47 % with CsA. Also, twice-daily dosing of oral paclitaxel in combination with CsA results in better systemic exposure compared with single-dose administration. The drug is currently in phase II clinical trials

Response rate and toxicity of this combination was studied in a phase II clinical trial, conducted in the Netherlands and Germany, in patients with advanced nsclc (Stage IIIb/IV) who were either chemonaive or had been previously treated with a single chemotherapy regimen. Paxoral (90 mg/m^2) was administered twice-daily with at least a 7-hour but not more than a 12-hour dose interval, every week. CsA (10 mg/kg) was administered 30 minutes prior to each dose of oral paclitaxel. Among 26 patients [24 (92%) with advanced disease and 18 (69%) having been previously treated with chemotherapy] treated between August 2000 and November 2000, the median number of administrations was 8 (range=1-23). Most frequently recorded toxicities were Grade 3 neutropenia (n=8 or 31%), Grade 4 neutropenia (n=6 or 23%), Grade 4 febrile neutropenia (n=3 or 12%), Grade 1/2 anemia (n=23 or 88%), Grade 1/2 mucositis (n=7 or 27%), Grade 3 diarrhea (n=2 or 8%), Grade 2 neurotoxicity (n=2 or 8%), Grade 3 neurotoxicity (n=1 or 4%), and Grade 2 nail changes (n=4 or 15%). Three patients went off study prematurely because of febrile neutropenia resulting in 2 deaths, and one case of neurotoxicity. The main reason for treatment delay was neutropenia (79%). Among 23 evaluable patients, there were 6 (26%) PR, and disease stabilized in 8 (35%), and progressed in 9 (39%), for an overall response rate of 26%. After a median follow-up of 5.0 months, median time-to-progression was 3.5 months and MST was >6.7 months (range=0.1-8.4+), with 13/26 patients still alive (Baas P, etal, AACR-NCI-EORTC01, Abs. 444).

In this trial, Paxoral demonstrated a response rate in lung cancer consistent with or higher than that previously reported with single-agent Taxol, with a comparable side effect profile, but without the inconvenience and side effects of prolonged infusions and premedications associ-

ated with Taxol. The incidence of neutropenia in this study was consistent with well-documented and expected side effects associated with paclitaxel. Phase III clinical trials are being planned to compare oral paclitaxel with standard IV chemotherapy as initial treatment of advanced nsclc.

In June 2001, Ivax was issued a notice of allowance in connection with another of its patent applications relating the oral formulation of paclitaxel. This allowance follows the issuance from the USPTO of patent #5,968,972 entitled, "Method for increasing the oral bioactivity of pharmaceutical agents".

PEG-paclitaxel

Enzon (Piscataway, NJ) is developing a PEG-modified version of paclitaxel. Using PEG technology, paclitaxel was modified through the chemical attachment of PEG using a linker designed to deteriorate over time, giving PEG-paclitaxel prodrug attributes. PEG-paclitaxel was designed to be delivered without the need for solubilizing agents or premedications to reduce the potential for serious allergic reactions.

In May 2001, Enzon initiated a multicenter phase I clinical trial for PEG-paclitaxel, designed to determine the safety, tolerability, and pharmacology of this agent in patients with advanced solid tumors and lymphomas. Up to 40 patients will be enrolled in this study. The study is to be completed in May 2002. In December 2000, Enzon had submitted an IND application to the FDA to initiate clinical trials with PEG-paclitaxel.

S-8184

Sonus Pharmaceuticals (Bothell, WA) formulates paclitaxel using its Tocosol emulsion technology. Tocosol features a vitamin-E-based carrier that may reduce toxicity and provide other therapeutic benefits. S-8184 is a Cremophor-free, vitamin E-based paclitaxel emulsion incorporating a P-gp inhibitor and particle size-based tumor targeting. S-8184 has been developed with goals of reducing or eliminating hypersensitivity reactions and premedications, and reducing infusion time, as a result of elimination of Cremophor. The goal of enhancing tumor uptake is addressed via two methods, inclusion of a P-gp inhibitor, alpha-tocopherol polyethylene glycol succinate, and use of emulsion particles in the 60-200 nanometer size range. Tocosol Paclitaxel is a physically and chemically stable submicron oil-in-water emulsion of paclitaxel that can be prepared at high drug loading (8-10 mg/ml) having a mean droplet diameter of <100 nm and 99% cumulative particle size distribution of <200 nm.

Release studies *in vitro* demonstrated low and sustained drug release both in the presence and absence of human serum albumin. Based on single-dose acute toxicity studies, Tocosol Paclitaxel is well tolerated both in mice and rats with about a 3-fold increase in MTD over Taxol. Using the B16 mouse melanoma model, a significant improvement in drug efficacy was observed when compared to Taxol. Tocosol Paclitaxel can be filter-sterilized and administered IV as a 15-minute bolus injection compared to the 3-hour infusion required with Taxol. When compared to Taxol, this emulsion exhibited reduced toxicity and improved efficacy most likely attributable to the composition and physicochemical characteristics of the emulsion (Constantinides PP, etal, Pharm Res, Feb 2000;17(2):175-82). In tests measuring levels of paclitaxel in blood compared with published literature for a 3-hour infusion of Taxol, a bolus injection of S-8184 results in higher peak drug concentrations, longer total drug exposure, and slower clearance times. S-8184 is currently being dosed at 225 mg/m^2 as compared to the standard dosing of Taxol at 175 mg/m^2.

In a phase I clinical trial, S-8184 is being administered every 3 weeks as a 10-minute IV push to patients with advanced solid malignancies, including lung, breast, ovarian, and colon cancer. In November 2001, at the Chemotherapy Foundation Symposium held November 7-10, 2001 in New York City, Dr. Howard A. Burris III, of the Sarah Cannon Cancer Center (Nashville, TN), the principal investigator (PI) of the phase I clinical trial of S-8184, reported that, as of the date of the presentation, there were 2 PR among 16 patients. This trial was initiated in January 2001 to determine if the formulation's lower toxicity would result in a reduction or possible elimination of premedications and permit administration of a higher dose of paclitaxel. One patient with nsclc, treated with S-8184, experienced PR at a dose of 175 mg/m^2, as indicated by two consecutive CT scans, and remained on the study. This patient's tumor had progressed after previous treatment with both Taxol and Taxotere. Another patient with colorectal cancer who also experienced PR as indicated by one CT scan, is being treated with S-8184 at a dose of 225 mg/m^2. This patient also remained on the study, and subsequent imaging will be required to confirm the PR. Another 2 patients with nsclc, refractory to previous taxane treatment, exhibited a minor response and disease stabilized in 2 patients with breast and ovarian cancer also refractory to previous taxane therapy.

Dose escalation in the phase I trial is continuing, and MTD of S-8184 is still to be determined. Side effects seen to date include transient Grade 4 neutropenia in two patients. There has been no severe (≥Grade 3) neuropathy. One DLT (neutropenia) was seen at 125 mg/m^2 in a patient with extensive hepatic metastases, but not in other patients at this dose. One Grade 1 hypersensitivity reaction was seen during initial dosing in one patient, but not with subsequent doses. Based on this trial, S-8184 can be safely delivered via IV push. PK parameters indicate high peak paclitaxel concentrations, 5-fold higher AUC, slower clearance, and 2-fold longer elimination half-life compared with Taxol infusion. The longer elimination half-life may be attributable to P-gp inhibition and passive tumor targeting (Burris III H, etal, AACR-NCI-EORTC01, Abs. 128).

In January 2002, Sonus entered into a multiyear supply agreement with Indena for paclitaxel.

SP5.210C

SP5.210C, under development by Supratek (Montreal, Canada), is a targeted formulation of a proprietary, less toxic, formulation of paclitaxel (SP1010C) combined with SP5.2, a ligand that targets vascular endothelial growth factor (VEGF) receptor 1 (Flt-1) sites. Because Flt-1 is known to be overexpressed in the tumor surrounding endothelium, SP5.2 provides the formulation with specific affinity to the tumor compartments, leading to a higher accumulation of the drug in the tumor, and also produces an antiangiogenic effect in the tumor which is synergistic to the anticancer effect of paclitaxel. Experiments using human cerebral endothelial cell monolayers which is the *in vitro* model of the human blood brain barrier, have demonstrated that SP5.2 selectively inhibits VEGF-induced, Flt-1-mediated angiogenesis. Direct receptor-binding experiments demonstrated that SP5.2 selectively binds human and murine Flt-1 receptors, but does not interact with other VEGF receptors or other relevant molecules.

Supratek has incorporated paclitaxel in a water-soluble complex using its Biotransport carrier technology. Incorporation of the peptide in a Biotransport carrier increased the potency of binding of the ligand to the receptor 1000-fold. This new formulation does not require solubilizers used in Taxol.

Taxoprexin

Protarga (formerly Neuromedica; Conshohocken, NJ) synthesizes novel formulations of existing compounds using its Targeceutical technology that links therapeutic agents to fatty acid molecules that are preferentially taken up by the cells targeted for treatment. Taxoprexin, a Targeceutical compound synthesized by linking paclitaxel to docosahexaenoic acid (DHA), increases the amount of paclitaxel that can be safely administered to patients and its resident time in cancer cells. DHA is a natural omega-3 fatty acid that is used by the body as an energy source, or a component of cellular structure, and is necessary for the correct functioning of certain cell types. DHA also crosses the blood-brain barrier and is the most prevalent fatty acid in the brain, accounting for 25% of such acids that comprise 40% of the brain's weight. Protarga has been awarded two USA composition-of-matter patents for Taxoprexin.

In Taxoprexin, DHA is covalently conjugated via ester linkage to the 2'-OH position of paclitaxel. DHA-paclitaxel is an inert prodrug that is only activated when the chemical bond between the DHA and paclitaxel is cleaved. DHA-paclitaxel is designed to deliver more therapeutic agent to tumors and sustain therapeutic concentrations in tumor cells for longer periods than possible with the unconjugated drug. DHA-paclitaxel is minimally converted to paclitaxel in human plasma but produces higher sustained paclitaxel exposure in mouse M109 tumors than achievable by administration of unconjugated paclitaxel (Bradley MO, etal, AACR01, Abs. 42:371).

Although Taxoprexin lacked *in vitro* microtubule assembly activity in cell culture, it arrested cells at the G2/M phase of the cell cycle, presumably by intracellular conversion to paclitaxel. At an equimolar dose to the paclitaxel MTD, Taxoprexin activity was equivalent to that of paclitaxel against M109 lung carcinoma in syngeneic mice. However, Taxoprexin's MTD was 6 times higher than that of paclitaxel. At MTD, Taxoprexin induced CR in all mice while no CR was observed with paclitaxel. Increased Taxoprexin activity may be attributable to a higher, sustained and preferential concentration in tumor cells of paclitaxel derived from Taxoprexin (Wolff AC, etal, ASCO00, Abs. 921E:236a).

When the disposition of DHA-paclitaxel and paclitaxel was examined in patients treated with Taxoprexin (880 mg/m^2-1100 mg/m^2), >99.5% of DHA-paclitaxel was bound to plasma proteins. At the 880 mg/m^2 (n=2) and 1100 mg/m^2 (n=6) dose levels, the mean DHA-paclitaxel blood:plasma ratio was 0.486 (0.202) and 0.536 (0.152), respectively; the low blood:plasma ratios suggest that the majority of DHA-paclitaxel was associated with the plasma fraction. It appears that DHA-paclitaxel exhibits extensive plasma protein binding, which may explain, in part, the small volume of distribution and low clearance. The AUC of unbound concentration of paclitaxel, achieved following administration of Taxoprexin at a dose of 1100 mg/m^2, is similar to that noted following administration of Taxol on clinically relevant dose schedules (E Brouwer E, etal, Drug Metab Dispos 2000;28:1141), and may be associated with the dose-limiting neutropenia observed following treatment with Taxoprexin (Baker SD, etal, AACR-NCI-EORTC01, Abs. 121).

Taxoprexin is administered IV as a 2-hour infusion with Cremophor EL-P and ethanol (<80% than Taxol on a molar basis). In a phase I clinical trial, 4.6 times as much drug could be administered to patients relative to the current FDA-approved paclitaxel dose. In addition, in animal studies, a therapeutic concentration can be maintained within tumors 10 times longer with DHA-paclitaxel compared to paclitaxel alone.

Protarga had filed an IND in March 1999 and, in May 1999, began a phase I clinical trial with Taxoprexin in patients with such refractory solid tumors as breast, colorectal, lung, prostate and ovarian cancer, at Johns Hopkins Oncology Center (Baltimore, MD), under the direction of Dr. Ross Donehower. In an interim report involving 10 patients treated with 30 cycles of Taxoprexin at 200 mg/m^2 (1 patient/4 cycles), 400 mg/m^2 (3/10), 660 mg/m^2 (6/14), and 880 mg/m^2 (1/2) mg/m^2, the main drug-related toxicity was Grade 3 (2 patients/cycle 1 and 2/2), and Grade 4 (1/1 and 1/3) neutropenia at 660 mg/m^2. Grade 1 neurotoxicity (cycle 1) was observed at 400 mg/m^2 in one patient heavily pretreated with paclitaxel. No alopecia was observed. An additional 12 patients were to be accrued once MTD is determined (Wolff AC, etal, ASCO00, Abs. 921E:236a).

As of October 2001, 8 separate multicenter phase II clinical trials were ongoing with Taxoprexin in eight types of cancer (breast, colorectal, kidney, lung, pancreas, prostate, skin and stomach) conducted at 29 hospitals in the in the USA and Europe, to enroll over 400 cancer patients. In 2001, the Royal Marsden Hospital (London, UK) also begun a study of Taxoprexin in combination with carboplatin. A phase II clinical trial in nsclc was initiated in March 2001, under the direction of Paul Ellis, MD, at Guy's Hospital (London, UK).

In October 2001, Protarga initiated 2 multicenter phase II clinical trials of Taxoprexin by 2-hour infusion for first-line treatment of hormone-refractory prostate cancer and advanced breast cancer. Michael Carducci, MD, of Johns Hopkins Oncology Center (Baltimore, MD) is the prostate cancer study's PI. Study objectives are to determine response rate, survival, toxicity profile, QoL, and resource utilization. The breast cancer study is being conducted at the Royal Marsden Hospital (London, UK) under PI Stephen Johnston, MD.

In June 2001, Protarga commenced a multicenter phase II clinical trial (protocol IDs: THERADEX-P01-00-07; CCF-IRB-4046; PROTARGA-P01-00-07) of Taxoprexin in advanced (Stage III or Stage IV), or unresectable, renal cell carcinoma, being conducted at the Cleveland Clinic Cancer Center (Cleveland, OH) under PI Ronald M. Bukowski, MD. Study objectives are to determine tumor response rate, duration of response, and time-to-disease progression, and overall survival; to establish the toxicity profile of this drug in these patients; and to assess QoL. According to the protocol, patients are treated with DHA-paclitaxel IV over 2 hours on day 1, repeated every 21 days in the absence of disease progression or unacceptable toxicity. QoL is assessed at baseline, every 2 courses, and at completion of treatment. Patients are followed every 3 months. A total of 21-50 patients will be accrued for this study.

Several multicenter phase II clinical trials were initiated in 2001 in various advanced or metastatic solid tumors, to determine tumor response rate, duration of response, and time-to-disease progression, and overall survival and toxicity of this drug and assess QoL. A multicenter phase II clinical trial (protocol IDs: THERADEX-P01-00-03; PROTARGA-P01-00-03; VMRC-8770) of DHA-paclitaxel in metastatic (Stage IVa or IVb) or recurrent pancreatic cancer, was initiated in June 2001. According to the protocol, patients are treated with DHA-paclitaxel IV over 2 hours on day 1, repeated every 21 days in the absence of disease progression or unacceptable toxicity. QoL is assessed at baseline, every 2 courses, and at completion of treatment. Patients are followed every 3 months. A total of 21-50 patients will be accrued for this study. Another multicenter phase II clinical trial (protocol ID: THERADEX-P01-00-01; ABCCC-010505; PROTARGA-P01-00-01) in patients with metastatic (Stage IV) or recurrent colorectal cancer was initiated in May 2001. A total of 18-50 patients will be accrued for this study. Both of these studies are being conducted by Theradex (Princeton, NJ) with Ross C. Donehower as Study Chair.

Taxosomes/Dermos

Aphios has developed a liposomal version of IV paclitaxel (Taxosomes), and topical paclitaxel (Dermos), based on its nanotechnology drug delivery system targeting water-insoluble (hydrophobic) anticancer molecules. These formulations are based on phospholipid nanosomes for the IV or topical administration of proteins, genes, hydrophilic molecules and hydrophobic anticancer drugs.

NOVEL TAXANES AND ANALOGS

Numerous taxane analogs have been created in an attempt to retain/enhance the cytotoxic attributes of the existing drugs but reduce/eliminate their many toxicities (Exhibit 5).

BAY 59-8862 (IDN5109)

IDN5109 (SB-T-101131, Bay 59-8862), was synthesized by Indena (Milano, Italy), in collaboration with scientists at Roswell Park Cancer Institute (Buffalo, NY) and SUNY (Stony Brook, NY), by means of semisynthesis starting from 14-OH DAB (14-β-hydroxybaccatin III), a molecule extracted from leaves of the Taxus genus. In March 2000, Indena signed an exclusive worldwide agreement to supply Bayer with IDN 5109. Indena will manufacture the agent and Bayer will be responsible for clinical development and commercialization. Other derivatives originating from 14-OH DAB, similar to IDN 5109, were patented and also licensed to Bayer. Also see FO, pp 1036-37.

BAY 59-8862 is a novel second-generation taxane being investigated in a phase I clinical trial. BAY 59-8862 exhibited 20- to 30-fold more potent cytostatic and cytotoxic activity against P-gp-expressing breast, colon and renal tumor cell lines compared to either paclitaxel or docetaxel. BAY 59-8862 facilitated G2/M arrest in the P-gp-transfected MDA435/LCC6mdr1 breast cell line at much lower drug concentrations than paclitaxel. However, at equitoxic doses there was less G2/M arrest seen with BAY 59-8862 than with paclitaxel, indicating that there may be multiple sites of action for BAY 59-8862. BAY 59-8862 also induced apoptosis at significantly lower drug concentrations than paclitaxel, although again, at equipotent levels, it induced less apoptosis than paclitaxel. In P-gp-expressing tumor cell lines, BAY 59-8862 increased the intracellular levels of P-gp substrates rhodamine 123 (Rh-123) and doxorubicin, suggesting P-gp modulation (Vredenburg MR, etal, AACR01, Abs. 4356:812).

In mice bearing Ca7860 renal tumor xenografts that are resistant to paclitaxel, levels of BAY 59-8862 were higher than those of paclitaxel when administered at equitoxic doses. P-gp does not appear to play a relevant role in BAY 59-8862 activity. In a distribution study in nude mice treated at MTD with IV BAY 59-8862 (60 mg/kg) or IV paclitaxel (25 mg/kg), BAY 59-8862 was cleared more slowly than paclitaxel, with an elimination half-life of 4.7 hours

compared to 1.2 hours for paclitaxel. The plasma AUC/tissue ratio for BAY 59-8862 and paclitaxel was 2.5 and 0.2 in brain, 5.4 and 3 in kidney, 3.7 and 8 in liver, and 5 and 1.7 in heart, respectively (Zucchetti M, etal, AACR01, Abs. 2051:381). BAY 59-8862 accumulation in the brain resulted in a substantial increase in the CNS:plasma ratio compared to paclitaxel. This drug was also active against human glioma xenografts.

A multicenter phase I clinical trial is being conducted in patients with advanced solid tumors who had been administered from none to 5 prior chemotherapy regimens. Among 10 patients (colorectal carcinoma=4, pancreatic cancer=2, leiomyosarcoma=2, laryngeal carcinoma=1, mesothelioma=1) with normal bone marrow, hepatic and renal function, treated with IV BAY 59-8862 at 15-75 mg/m^2 by a 1-hour infusion, every 3 weeks, 9 were evaluable for toxicity. After a total of 19 complete courses and 1 incomplete course, at doses of 15 mg/m^2 (n=1), 30 mg/m^2 (n=3), 50 mg/m^2 (n=3) and 75 mg/m^2 (n=3), toxicities (>Grade 2) during course 1 were Grade 2 paresthesias, malaise and tumor pain at 30 mg/m^2 (infusion was discontinued in 1 patient who experienced throat discomfort and chest pain during treatment); Grade 3 fatigue and muscle weakness (n=1), Grade 2 anemia and hyponatremia (n=1) and Grade 2 muscle pain (n=1), at 50 mg/m^2; and Grade 3 neutropenia, nausea, anorexia, constipation, and hyponatremia and Grade 2 weakness (n=1) and Grade 2 muscle pain (n=1), at 75 mg/m^2. There was one MR in hepatic lesions of a patient with pancreatic cancer (Ramnath N, etal, AACR-NCI-EORTC01, Abs. 777).

BMS-184476

BMS-184476 is a 7-methylthiomethyl ether derivative of paclitaxel, that displayed *in vitro* potency at nanomolar concentrations against paclitaxel-resistant human tumor cell lines with MDR mediated by P-gp and altered tubulin. This agent exhibited efficacy superior to paclitaxel against human tumor xenografts, producing significantly more cures. Although BMS-184476 and Taxol exhibited similar cytotoxic potency in cell lines of various origins that did not contain mutated tubulin, or high levels of MDR, BMS-184476 demonstrated improved cellular effects in cell lines containing Taxol-specific resistance. This activity may contribute to the *in vivo* superiority of BMS-184476 (Menendez AT, AACR00, Tubulin-Drug Interactions III Minisimposium).

A randomized phase IIb clinical trial (protocol ID: CA154-008) of two schedules of BMS-184476, in the treatment of refractory metastatic breast cancer, was initiated in April 2001, in the USA and Canada. A phase IIb is also underway in the USA in lung cancer.

In a phase I clinical trial, conducted at the University of Pennsylvania (Philadelphia, PA), BMS-184476 was administered as a 1-hour IV infusion followed by cisplatin (75 mg/m^2), every 21 days, in 24 patients with various solid tumors. Overall, 84 cycles of therapy were administered at doses of BMS-184476 ranging from 40 mg/m^2 to 60 mg/m^2 with a fixed cisplatin dose. At the planned final dose level of BMS-184476 (60 mg/m^2) and cisplatin (75 mg/m^2), DLT occurred in the form of Grade 3/4 diarrhea (n=2), Grade 3 nausea and vomiting (n=5) and Grade 4 neutropenia lasting 5 days (n=1). After instituting a prophylactic regimen of ondansetron, dexamethasone, metoclopramide and loperamide, no further DLT was observed in 6 additional patients. Mild to moderate (Grade 1/2) peripheral neuropathy (n=4) was infrequent, as was alopecia. There were 3 PR in patients with mesothelioma, and esophageal and head and neck cancer, 2 MR in cholangioma and mesothelioma, and disease stabilized in 4. BMS-184476 pharmacokinetic parameters were not significantly different in this combination compared to single-agent observations at similar doses (Gallagher ML, etal, ASCO01, Abs. 420:106a). Drug-related toxicities included Grade 2 arthralgia/myalgia, peripheral neuropathy, nausea/vomiting, diarrhea and stomatitis. None of the patients experienced hypersensitivity.

In 1999, Millennium Predictive Medicine (MPMx), a subsidiary of Millennium Pharmaceuticals (Cambridge, MA) executed a pharmacogenomics agreement with Bristol-Myers Squibb related to certain drug classes in the BMS oncology pipeline, including BMS-184476. BMS also entered into a similar agreement with Karolinska Institute (Stockholm, Sweden) in March 2000.

BMS-188797

BMS-188797, a paclitaxel analog, is being currently evaluated in several phase I clinical trials, alone or in combination with platinum-based therapy. In a phase I clinical trial, conducted at Stanford University Medical Center, between April and November 2000, IV BMS-188797 was well tolerated and showed broad antitumor activity when dosed as monotherapy on a weekly infusion schedule. The main objective of this trial was to establish MTD and DLT of this agent, administered as a 1-hour infusion weekly on days 1, 8, and 15, every 21 days, to 18 patients with advanced malignancies (ovarian=4, lung=3, colon=2, GI stromal=2, sarcoma=2, others=5), previously treated with a median of 2.5 chemotherapy regimens. Three dose levels, 35 mg/m^2 (n=3), 50 mg/m^2 (n=9) and 65 mg/m^2 (n=6) were evaluated. The 50 mg/m^2 dose that was well tolerated was established as the MTD. Only 1/9 patients experienced a DLT at this dose, consisting of Grade 4 febrile neutropenia. Other transient Grade 2 toxicities included nail changes (n=4), fatigue (n=3), edema (n=3), nausea (n=3), diarrhea (n=2) and neuropathy (n=1). Among 13 patients evaluable for response there were 2 PR (ovarian 6+ months and lung 4+), 2 MR (lung 4+ and esophageal 3+), and disease stabilized in 2 (ovarian 6 and rectal 3). All responders had been previously treated with a paclitaxel-containing regimen (Advani R, etal, ASCO01, Abs. 422:106a).

A phase I clinical trial was undertaken at H. Lee Moffitt Cancer Center (Tampa, FL) to establish MTD and DLT of BMS-188797 when administered in combination with car-

boplatin. In this study, a total of 21 patients were enrolled in several different dosage cohorts. All patients were pretreated with standard regimens consisting of a steroid, and histamine H1 and H2 antagonists. The initial dose level included BMS-188797 (100 mg/m^2) in combination with carboplatin (AUC=6). When dose escalation to 125 mg/m^2 was not possible because of DLT (febrile neutropenia and prolonged recovery from neutropenia), the carboplatin dose was lowered to AUC=5, and dose escalation of BMS-188797 was reinstituted. DLT involving febrile neutropenia occurred at the BMS-188797 dose of 150 mg/m^2. MTD was again reached at a BMS-188797 dose of 125 mg/m^2 in combination with carboplatin at AUC=5. All cases of DLT were hematologic and they all occurred during the first course of treatment. There were no other serious (Grade 3 or 4) toxicities. The pharmacokinetic parameter estimates for BMS-188797 when administered in combination with carboplatin, are similar to those reported for single-agent BMS-188797. Currently, a cohort of patients is being treated at a BMS-188797 dose of 135 mg/m^2, in combination with carboplatin at AUC=5 (Sullivan DM, etal, AACR-NCI-EORTC01, Abs. 786).

BMS-275183

BMS-275183 is an orally bioavailable taxane synthesized by BMS scientists from taxanes that contain a docetaxel sidechain (3'N tBoc). Several sidechain modifications in one core series led to this compound that is highly bioavailable and efficacious. BMS-275183 exhibits robust oral efficacy against subcutaneous murine tumors and human tumor xenografts in mice (Kadow JF, etal, AACR-NCI-EORTC01, Abs. 771). BMS-275183 was orally bioavailable in both rats and dogs with taxane-like systemic myelosuppression observed in dogs (Hansel SB, etal, AACR-NCI-EORTC01, Abs. 391).

Dose-related toxicity, pharmacokinetics, oral bioavailability and pharmacodynamic effects are being investigated in the first clinical trial of BMS-275183, at the University of Pittsburgh (Pittsburgh, PA). The starting dose of this phase I dose-escalation clinical trial was 20 mg/m^2, administered orally once every 3 weeks, that was subsequently escalated to 40 mg/m^2 and 80 mg/m^2. No toxicity was observed in 13 patients treated with BMS-275183. Preliminary pharmacokinetic analysis demonstrates that BMS-275183 is detectable in the blood up to 72 hours after dosing at all dose levels studied. According to preliminary assessment in 5 patients, the absolute bioavailability was 23% with low variability. Preliminary pharmacodynamic analysis carried out by measuring drug-related changes in tubulin polymerization in peripheral blood mononuclear cells (PBMC) indicated an increase in polymerized tubulin in PBMC following administration of BMS-275183 at the second dose level of 40 mg/m^2. These data indicate that BMS-275183 is orally bioavailable. Dose-escalation is continuing in order to define this drug's toxicity and pharmacology (Trump D, etal, ASCO01, Abs. 433:109a).

Another phase I clinical trial of BMS-275183, designed to establish the effect of food on the drug's oral bioavailability, is ongoing at the Karmanos Cancer Center at Wayne State University (Detroit, MI) under PI Patricia LoRusso, DO.

DJ-927

DJ-927, under development by Daiichi Pharmaceutical (Tokyo, Japan), is an orally active novel taxane, with higher solubility, better safety profile and higher antitumor activity. While the tubulin inhibitory effect of DJ-927 was comparable to those of currently available taxanes, its cytotoxic activity against various types of human tumor cell lines was about 10-fold and 3-fold stronger than those of paclitaxel and docetaxel, respectively. In particular, DJ-927 exhibited much greater cytotoxicity against MDR cell lines that constitutively overexpressed P-gp. Orally administered DJ-927 also showed potent antitumor activity against various types of human solid tumors that were xenografted into nude mice. The antitumor effects of DJ-927 were superior to those of IV paclitaxel and docetaxel in P-gp-overexpressing tumors.

When the cytotoxicity of DJ-927 was compared with those of paclitaxel and docetaxel on 10 different human tumor cell lines with various levels of P-gp expression, DJ-927 exhibited the highest cytotoxic activity against most of the tumor cell lines including the P-gp positive ones. While the cytotoxic activities of paclitaxel and docetaxel were inversely related to the expression of P-gp in tumor cells, that of DJ-927 showed no correlation with P-gp levels. Against solid tumors that were subcutaneously inoculated into nude mice, DJ-927 was effective against 9 (including 5 P-gp-positive) out of 10 tumor cell lines while paclitaxel and docetaxel were ineffective against the P-gp-positive tumors. DJ-927 also showed the highest activity in the inhibition of *in vitro* colony formation of P-gp-positive M5076 murine histiocytoma cells. Simultaneous addition of verapamil, a P-gp modulator that enhances the activity of paclitaxel and docetaxel, had no effect on the activity of DJ-927. In a solid tumor model and a liver metastasis model using M5076 tumor cells, orally administered DJ-927 exhibited potent growth-inhibitory effects and prolonged life significantly, whereas IV administered paclitaxel and docetaxel were not effective. In human lung tumor cells (PC-6 and its P-gp-overexpressing variant, PC-6/Tax1-1), relative intracellular amounts of DJ-927 were higher than those of paclitaxel and docetaxel, and those differences were larger, particularly in MDR tumor cells. These results suggested that the stronger effects of DJ-927 against P-gp-expressing tumor cells might be attributable to its higher intracellular concentrations (Shionoya M, etal, AACR-NCI-EORTC01, Abs. 773).

The preclinical efficacy and safety profile of DJ-927 was superior to those of paclitaxel and docetaxel. In terms of its toxicity profile, primary toxicities that were observed in mice after a single oral administration of DJ-927, were myelo-

suppression and gastrointestinal distress, which were also observed in paclitaxel- and docetaxel-treated mice. In contrast to paclitaxel and docetaxel, there were no clinical signs or histologic changes with DJ-927 that indicated neurotoxicity in mice (Tohgo A, etal, AACR-NCI-EORTC01, Abs. 782 and Ono C, etal, AACR-NCI-EORTC01, Abs. 775). DJ-927 is currently in phase I clinical trials in the USA.

RPR109881

RPR109881 (RPR-109881A), under development by Aventis, is a novel highly potent taxane analog, being investigated in ongoing phase I and II clinical trials, in various regimens and tumors (for results of various phase I clinical trials see FO, p 1036). A phase I multicenter clinical trial (protocol IDs: CAN-NCIC-IND101, NCI-V96-1096), which began in September 1996, conducted by the NCIC-Clinical Trials Group with Karen A. Gelmon, MD, as Study Chair, in advanced solid tumors such as refractory breast cancer, was closed in March 1998. In this trial, RPR 109881A was administered as a 1-hour weekly IV infusion to 30 patients with advanced solid tumors.

In a phase I study conducted at the National Cancer Center Hospital (Tokyo, Japan), 19 patients with advanced solid tumors were administered RPR 109881A as a 1-hour IV infusion every 3 weeks at doses ranging from 15 mg/m^2 to 75 mg/m^2. Febrile neutropenia and fatigue were the DLT at doses of 60 mg/m^2 and 75 mg/m^2, and seemed to be dose-related. Thrombocytopenia and anemia were infrequent, and nonhematologic toxicities were generally mild. Pharmacokinetic studies indicated that RPR 109881A plasma disposition was bi- or triphasic, with a high total plasma clearance, a large volume of distribution, and a long terminal half-life. The AUC and peak concentration of RPR 109881A seemed to increase with increasing dose proportionally, suggesting linear pharmacokinetics. Among 18 assessable patients, two partial and two minor responses were documented. The recommended dose for phase II study was established as 60 mg/m^2 administered as a 1-hour infusion every 3 weeks (Kurata T, etal, J Clin Oncol, Sep 2000;18(17):3164-71).

RPR116258A

RPR116258A, a semisynthetic third-generation, potent taxane derivative, is a weak substrate for P-gp and able to cross the blood brain barrier. In preclinical evaluations, RPR116258A demonstrated broad antitumor activity in tumor models, including cell lines expressing mdr-1, and against B16 paclitaxel-resistant melanoma cell lines. This drug was also able to cross the blood brain barrier.

A phase I clinical trial evaluated the safety and pharmacokinetic profile of RPR116258A administered as a 1-hour infusion every 3 weeks in minimally-pretreated patients with advanced cancer. No prophylactic antiemetics or treatment to prevent hypersensitivity reactions were permitted in cycle 1. Among 14 patients enrolled, 49 treatment courses were evaluable at dose levels of 10 mg/m^2 (n=3), 15 mg/m^2 (n=6), 20 mg/m^2 (n=3), and 25 mg/m^2 (n=2). The main toxicity was short-lasting Grade 4 neutropenia in one patient at 25 mg/m^2 and Grade 3 diarrhea at 15 mg/m^2 (n=1) and 25 mg/m^2 (n=1) that was well controlled by loperamide. Minor Grade 1 or Grade 2 toxicities included diarrhea (n=3), fatigue (n=3), nausea (n=3), vomiting (n=2), neutropenia (n=5), thrombocytopenia (n=1), and Grade 1 neurosensory disorders (n=1). There were no hypersensitivity reactions or fluid accumulation. One unconfirmed PR was reported in a patient with transitional cell carcinoma (TCC) of the bladder and minor responses were reported in two patients with prostate cancer and osteosarcoma. RPR116258A was well tolerated at the studied dose levels up to 25 mg/m^2. Preliminary pharmacokinetic results indicate a long terminal half-life justifying an intermittent dosing schedule every 3 weeks (Goetz AD, etal, ASCO01, Abs. 419:106a and Denis LJ, etal, NCI–EORTC-AACR00, Abs. 568).

A different treatment schedule of RPR 116258A was investigated in a phase I clinical trial at Centre Rene Gauducheau (Nantes, France) and Hospital Vall d'Hebron (Barcelona, Spain), in patients with advanced solid tumors. In this trial, the drug was administered without premedication as a weekly 1-hour infusion on days 1, 8, 15, and 22, every 5 weeks, DLT was evaluated at 5 weeks after cycle 1, to establish MTD. Among 25 patients enrolled in the study, most had advanced breast cancer (n=15). In the dose-escalation phase, 17 patients were treated at 1.5 mg/m^2 (n=1), 3 mg/m^2 (n=1), 6 mg/m^2 (n=4), 8.4 mg/m^2 (n=5) and 12 mg/m^2 (n=6). A total of 48 cycles (range=1-8) were administered with treatment duration ranging from 2 to 40 weeks. MTD was reached at the 12 mg/m^2 dose level at which 2/6 patients experienced DLT during cycle 1 consisting of Grade 3 diarrhea. At subsequent cycles, other DLT reported at the 12 mg/m^2 dose level included Grade 3 fatigue (n=2) and diarrhea (n=1), and Grade 4 neutropenia lasting >5 days (n=1) and febrile neutropenia (n=1). At the 8.4 mg/m^2 dose level there was one incidence of Grade 3 fatigue.

To establish the recommended dose for phase II studies, 8 more patients were treated at the 8.4 mg/m^2 dose level. Neutropenia, the main hematologic toxicity, reached Grade 3 in one patient at this dose level. The main nonhematologic toxicities were diarrhea, including Grade 3 (n=3), occurring in 36.4% of patients, fatigue including Grade 3 (n=3), in 36.4%, and neurosensory toxicity in 22.7% with only 1 case at Grade 3 level. No neurocentral toxicity was reported, and only 3 cases of mild (Grade 1) hypersensitivity reaction were observed. At the 8.4 mg/m^2 dose level, the drug exhibited a high total body clearance, a very large volume of distribution, and a quite long terminal half-life of 31 hours. Although there was a trend towards higher plasma levels at later sampling times on day 22 than on day 1 at cycle 1, no drug was detected before treatment on day 22. There were 2 confirmed PR at the 8.4 mg/m^2 and 12 mg/m^2 dose levels, in breast cancer

refractory to previous taxane regimens, and disease stabilized in 12 patients with breast cancer (n=7), gastric and ovarian cancer, cholangiocarcinoma, carcinoid tumor, and nsclc. An intermediate dose level of 10 mg/m^2 is being explored (Fumoleau P, etal, AACR-NCI-EORTC01, Abs. 282).

TL-139

TL-139 is one of a large number of unique taxanes synthesized, characterized, and subjected to preclinical screening by Taxolog (Parsippany, NJ). Taxolog was established in 1997 by licensing patents covering paclitaxel analogs and related technology from MDS Research Foundation, a nonprofit organization created in 1995, and from Syncure, both established by Robert Holton, PhD, and located in Tallahassee, FL. Florida State University (FSU; Tallahassee, FL) and Holton are the patent holders for the semisynthetic version of paclitaxel currently marketed as Taxol by Bristol-Myers Squibb, and share the royalties from the sales of Taxol (see FO, p 1037).

To date, Holton and FSU have been awarded over 58 patents involving taxanes. Using the metal alkoxide process (MAP), invented at FSU, numerous analogs were synthesized having alternate substitutes on the C-13 paclitaxel sidechain. The Holton group also carried out an extensive program exploring the chemistry required to modify all of the other pendant groups on the 10-DAB nucleus. By varying the molecular groups on the outside of the 10-DAB molecule, which is the backbone of paclitaxel, Holton and colleagues created over 500 paclitaxel analogs, and tested them *in vitro* and *in vivo* with over 30 having been tested in mice bearing human xenografts. Taxolog owns the patents for these analogs.

A patent that was filed in 1995 by Chunlin Tao, a former research assistant to Holton, 90 days before the one submitted by FSU was invalidated in November 2001, by U.S. District Judge Roger Vinson in Tallahassee who ruled that Tao used confidential FSU information in 1995 to produce synthetic compounds for American BioScience when it was known as VivoRx Pharmaceuticals. The judge ruled that Holton and colleagues Hossain Nadizadeh and Li-Xi Yang are the rightful inventors. This ruling freed FSU to start up research again on taxane compounds that seem to work better with radiation. ABI plans to appeal the decision.

In July 2001 Wyeth-Ayerst Laboratories and Taxolog entered into a collaboration and license agreement to research novel compounds for use as potential antitumor agents to be exclusively developed, manufactured, and commercialized by Wyeth. TL-139 is the first compound to be jointly developed. In preclinical studies, TL-139 demonstrated outstanding activity against a broad range of human carcinomas *in vivo*, including significant antitumor activity against human tumor cell lines that are sensitive or resistant to currently marketed taxanes. A phase I clinical trial with TL-139 was initiated in July 2001.

Tumor-activated Prodrug (TAP)-Taxane Immunoconjugates

ImmunoGen (Cambridge, MA) has developed a tumor-activated prodrug (TAP) technology that couples cytotoxic agents with tumor-targeting antibodies. A TAP construct is comprised of a highly potent small-molecule effector drug, usually 100- to 1000-fold more potent than chemotherapeutics in current clinical use, conjugated to a tumor-targeting MAb that recognizes and binds directly to certain tumor cells. TAP are designed to act as prodrugs and remain nontoxic while circulating in the body, only to be activated once inside the target cell and not in the surrounding healthy tissue. In preclinical studies, all of ImmunoGen's TAP-based constructs have proven to be more potent and less toxic to animals than standard chemotherapeutics.

The lead products within the TAP group, currently under clinical evaluation, are two immunoconjugates that use DM1, a member of the maytansinoid family of spindle poisons, as the effector molecule. Maytansinoids act by a mechanism similar to the vinca alkaloids (e.g., vincristine, vinblastine) that inhibit tubulin polymerization. These constructs will be described in Part II of this series.

In February 2000, ImmunoGen entered into a research collaboration with the State University of New York (SUNY) at Stony Brook, to develop novel taxane compounds which can be used as new effector molecules with the TAP technology. Under the terms of the agreement, joint discoveries will be owned by both parties, and ImmunoGen has an exclusive option to license SUNY's ownership stake. Financial terms of the agreement were not disclosed.

In January 2002, ImmunoGen was issued patent #6,340,701, by the USPTO covering these novel taxane compounds and their use as effector molecules in conjunction with TAP technology. The issued patent covers the composition of matter of specific linkable taxane compounds and new cancer-killing constructs composed of these taxanes linked to cell-binding agents such as MAb. These taxanes are about 50-fold more potent *in vitro* than paclitaxel against the human tumor cell lines MCF-7, A-431 and A-549. They contain disulfide substitutes that renders them linkable to a MAb via disulfide bonds that are stable in circulation *in vivo*, but are cleaved inside a tumor cell to release active drug. These taxanes were converted into TAP by linkage to an anti-epidermal growth factor receptor (anti-EGFr) MAb. These linkable compounds were synthesized because commercially available taxanes are not sufficiently potent for use in TAP, and do not contain an appropriate chemical moiety for covalent attachment to a MAb.

TAP incorporating taxanes were effective in killing antigen-positive A-431 cells *in vitro*, with greater than 99.99% of cells killed at a concentration of 10 nM. Free antibody or an isotype-matched, non-binding antibody-taxane conjugate was not cytotoxic at this concentration, illustrating

the antigen specificity of the cytotoxic affect. Treatment *in vivo* of SCID mice bearing established subcutaneous A-431 xenografts at a conjugate dose of 10 mg/kg, every day for 5 days, resulted in eradication of the tumors, with no evidence of toxicity. Microscopic examination of the tumor site upon necropsy on day 72 indicated that all animals were tumor-free. An equivalent dose of free drug showed no antitumor effect. Because anti-EGFr antibody shows clinical benefit when used in combination with cytotoxic drugs, the efficacy of free antibody (20 mg/kg) administered IV every day for 5 days, IV doxorubicin alone and a combination of the two agents, were evaluated in the A-431 xenograft model. Treatment with doxorubicin, free antibody or a combination of the two, resulted in tumor growth delays of 1, 10, and 20 days, respectively. These agents were not as effective as the taxane-containing TAP. Thus, the targeted delivery of taxanes in the form of TAP enhances their antitumor efficacy (Chari RV, etal, the AACR-NCI-EORTC01, Abs. 114). While the MTD of this standard therapy only delayed tumor progression, the taxane-based TAP conjugate achieved tumor regressions at doses well below its MTD.

TXD258 (TAX-258)

TXD258 is an orally available taxane in development by Aventis. TXD258 is cytotoxic to MDR1-expressing tumor cells such as CaCo-2 (4.9 times more active than docetaxel), B16/docetaxel-resistant melanoma *in vivo*, and in cell lines with acquired resistance to doxorubicin, vincristine, vinblastine, paclitaxel and docetaxel. Antitumor activity was also obtained in nude mice bearing intracranial glioblastomas U251 and SF295, resulting in increases in life span values of 81% for SF295 and 202% for U251 (Bissery M-C, etal, AACR00, Abs. 1364:214, and Dykes DJ, etal, AACR00, Abs. 1916:301).

Oral TXD-258 was also effective in the advanced stage colon adenocarcinoma C38 cell line, against advanced stage pancreatic adenocarcinoma P03 and against advanced mammary adenocarcinoma MA17/A by both the oral and IV routes. Oral TXD258 was well tolerated at the active dose with a 14% mean body weight loss at nadir, occurring 4 days post last treatment with host recovery achievable approximately 15 days post therapy (Vrignaud P, etal, AACR01, Abs. 1975:367). All colon tumor models evaluated responded to intermittent IV administration of TXD258 with a high antitumor efficacy, observed at its total highest nontoxic dose against colon HCT 116. Antitumor activity was also observed in certain lung, kidney, pancreas, head and neck, and prostate cancer cell lines. TXD258 was also well tolerated (Vrignaud P, etal, AACR00, Abs. 1365).

NOVEL SPINDLE POISONS

A new generation of spindle poisons is currently being investigated. These novel agents are the topic of Part II of this series.

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