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ANTICANCER DRUGS AND MARKETS

UPDATE ON SPINDLE POISONS — PART II VINCA ALKALOIDS AND ANALOGS/FORMULATIONS

MEETING COVERAGE

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UPDATE ON SPINDLE POISONS — PART II VINCA ALKALOIDS AND ANALOGS/FORMULATIONS

This is the second part of a comprehensive series on spindle poisons. The first part covered taxanes and the third part will describe novel agents, both synthetic versions and analogs or derivatives of natural products as well as designed drugs acting on antimitotic mechanisms.

MECHANISM OF ACTION OF VINCA ALKALOIDS

The best known spindle poisons acting on a different mechanism than the taxanes are the Vinca alkaloids. Vinca alkaloids were isolated from *Catharanthus roseus* leaves in the late 1950s, independently, by a group headed by Professor Noble at the Western University of Ontario (London, Canada), and by researchers at the Eli Lilly Laboratories (Indianapolis, IN). Various Vinca alkaloids have been commercially available for over three decades. Currently, the four commercially available compounds within this category are vinblastine, vindesine, vincristine and vinorelbine. Vinorelbine was discovered and identified as a new type of Vinca alkaloid by an intensive program using novel chemistry approaches. Another Vinca alkaloid, anhydrovinblastine is in clinical trials, and a newer Vinca alkaloid, vinflunine, is currently in late-stage clinical development worldwide.

Spindle poisons are agents that selectively disrupt microtubule dynamics, either by targeting a specific tubulin isotype, like the taxanes, or a particular stage of cell division, thus disrupting proper chromosome function. The mitotic spindle ensures accurate chromosome segregation. Vinca alkaloid-site interacting agents appear to inhibit cell proliferation by affecting the dynamics of spindle microtubules. Microtubules are formed by the polymerization of the heterodimeric protein tubulin. There are at least 14 tubulin isotypes in higher eukaryotes, some of which are expressed in a tissue specific manner, i.e. are

often very different between cell types. Observation of microtubule polymerization *in vitro* indicated that they are intrinsically dynamic structures that are continually in a state of flux. This property, termed dynamic instability, was subsequently shown to also occur *in vivo*. Importantly, microtubule dynamics have been shown to change during the cell cycle. It is this dynamic nature of microtubules that allows them to mediate various cellular functions. Vinca alkaloids destabilize microtubule dynamics by forming alternate lattice contacts and polymers at microtubule ends. The most sensitive action of the Vinca alkaloids is on cells in mitosis, classifying these agents as antimitotics.

The Vinca alkaloid class of agents, based on their mechanism of action, may be divided into two groups, the first generation agents such as vinblastine, and second generation agents such as vinorelbine and its derivative vinflunine. Although it has already been shown that all these agents affect microtubule dynamics and chromosome movement during mitosis, blocking mitosis at the metaphase/anaphase transition and inducing formation of aberrant spindles, there are significant differences between the actions of these drugs. Rather than strongly suppressing the rate and extent of microtubule shortening *in vitro* as is the case with vinblastine, vinorelbine and vinflunine suppress the rate and extent of microtubule growth events (Ngan VK, etal, Cancer Res 2000;60:5045). When the effects of Vinca alkaloids on the dynamic behavior of spindle microtubules were quantitated, it was shown that vinflunine suppressed mitotic microtubule dynamics reducing tension across centromeres and preventing the cell-cycle signal from progressing into anaphase (Okouneva T, etal, AACR02, Abs. 1334:268).

It is possible that these differences, resulting in alternative mitotic spindle organization schemes, may account for the superior antitumor activities of the second-generation Vinca alkaloids. In all these drugs, mitotic block was a major contributor of antiproliferative action. Mitotically blocked cells exhibited aberrant spindles, consistent with induction of block by suppression of microtubule dynamics. Despite differences in their actions on individual dynamic instability parameters, morphologically detectable differences in spindle effects among these drugs were minimal, indicating that overall suppression of dynamics may be more important in blocking mitosis than specific effects on growth or shortening. Peak intracellular drug concentration at the mitotic IC_{50} value was highest for vinflunine (4.2 ± 0.2 μM), intermediate for vinorelbine (1.3 ± 0.1 μM), and more than 10-fold lower for vinblastine (130 ± 7 nM), suggesting that intracellular binding reservoir(s) may be partially responsible for vinflunine's high efficacy and less serious side effects (Ngan VK, etal, Mol Pharmacol, Jul 2001;60(1):225-32).

In preclinical studies, vinflunine exhibited superior antitumor activity to that of other Vinca alkaloids, including vinorelbine from which it was synthetically derived. When the effects of vinflunine and vinorelbine on microtubule dynamic instability and treadmiling was analyzed, it was found that these drugs exert effects on microtubule dynamics that differ significantly from vinblastine. The major effects of vinflunine and vinorelbine on dynamic instability were a slowing of the microtubule growth rate, an increase in growth duration, and a reduction in shortening duration. In contrast to the action of vinblastine, they neither reduced the rate of shortening nor increased the percentage of time the microtubules spent in an attenuated state, neither growing nor shortening detectably. In addition, vinflunine and vinorelbine suppressed treadmiling, but less strongly than vinblastine. The diverse actions of these drugs on microtubules are likely to produce different effects on mitotic spindle function, leading to different effects on cell-cycle progression and cell killing. Nontumor cells with normal checkpoint proteins may tolerate the relatively less powerful inhibitory effects of vinflunine and vinorelbine on microtubule dynamics better than the more powerful effects of vinblastine (Ngan VK, etal, Cancer Res, 15 Sep 2000 Sep 15;60(18):5045-51).

In addition to agents on the market or in development, hundreds of derivatives of these agents have been synthesized and evaluated, with the majority being modified in the vindoline moiety, bearing several reactive centers. Vinblastine and vinorelbine analogs have been synthesized by reacting new versatile electrophilic vindoline derivatives with various 3-substituted indoles. The resulting compounds have been evaluated for their antimitotic properties, but were less potent in comparison with the standard binary Vinca alkaloids (Fahy J, etal, Bioorg Med Chem Lett, 11 Feb 2002;12(3):505-7).

COMMERCIALLY AVAILABLE VINCA ALKALOIDS

Vinblastine

Vinblastine (Velban; Lilly), originally extracted from the periwinkle plant, inhibits microtubule formation in the mitotic spindle, resulting in arrest of dividing cells at the metaphase stage. It interferes with metabolic pathways of amino acids leading from glutamic acid to the citric acid cycle and to urea. However, therapeutic responses are not fully explained by cytologic effects, as these changes are sometimes observed clinically as well as experimentally in absence of oncolytic effects. Vinblastine may also interfere with cell-energy production required for mitosis and with nucleic acid synthesis.

The drug is administered IV. Among approved indications in the USA are Hodgkin's disease (HD), lymphocytic or histiocytic lymphoma, mycosis fungoides, advanced testicular cancer, Kaposi's sarcoma (KS), nonlipid histiocytosis (Letterer-Siwe disease), refractory choriocarcinoma, and refractory advanced breast cancer. The most common adverse reactions, in decreasing order of frequency, are leukopenia, alopecia, constipation, hypertension, malaise, bone pain, pain in tumor-containing tissue, and jaw pain, with leukopenia usually being the dose-limiting toxicity (DLT). With the exception of epilation and leukopenia, adverse reactions generally do not last for more than 24

hours. Neurologic side effects, including numbness of digits, loss of deep tendon reflexes, peripheral neuritis, mental depression, headache, and convulsions, are not common, but may last for more than 24 hours when they do occur. Animal studies suggest that teratogenic effects may also occur.

Vinblastine is currently being evaluated in several clinical trials in the USA and abroad in combination with other cytotoxics, hormone modulators, or biological response modifiers, and in multimodality approaches for various cancer indications. In the USA, combination trials incorporating vinblastine are ongoing for such indications as advanced, or recurrent lymphoma, lung cancer, malignant melanoma, bladder cancer, kidney cancer, etc.

Vincristine

Vincristine, originally launched as Oncovin by Eli Lilly, acts similarly to vinblastine. It is a cell-cycle, M-phase-specific agent which arrests cell growth in mitosis. The drug, also administered IV, has been approved in the USA for treatment of acute leukemia. It is also used to treat HD and non-Hodgkin's lymphoma (NHL), small-cell lung cancer (sclc) and a variety of other cancers. Vincristine's patent has expired and the drug is currently available from multiple sources, being evaluated in numerous clinical trials in combination with other cytotoxics, radiotherapy, stem cell/bone marrow transplantation, and with regulatory agents for treatment of solid tumors and hematologic malignancies. A common combination involves rituximab (Rituxan; Idec Pharmaceuticals) for NHL indications. The drug is also being evaluated in combination with other cytotoxics in childhood hematologic malignancies and solid tumors.

Vindesine

Vindesine (Eldisine; Lilly) is an amido derivative of vinblastine that was registered in Europe in 1980, and is now available in several countries, including the UK, Germany, France, Italy and other European countries, Canada, Australia, Argentina, and South Africa, among others. Vindesine is not commercially available in the USA. Administered IV, the drug is indicated for treatment of pediatric acute lymphocytic leukemia (ALL), non-small-cell lung cancer (nsclc), hormone-refractory breast cancer, chronic myelogenous leukemia (CML), kidney cancer, malignant melanoma, and NHL.

Vinorelbine

Vinorelbine (5'nor-anhydro-vinblastine), a semisynthetic derivative modified in the velbenamine or upper part of the molecule, is a widely available cytotoxic created by C' ring contraction of anhydrovinblastine. The first semisynthesis of a natural dimeric Vinca alkaloid created anhydrovinblastine in 1974 through a biomimetic coupling reaction of catharanthine and vindoline. This event was a milestone in Vinca alkaloid chemistry, allowing preparation of larger amounts of active compound, approximately 10 times more than what was possible with vinblastine extracted from natural sources. Vinorelbine was then biogenetically produced from anhydrovinblastine in the 1980s by chemists at Pierre Fabre, and launched in 1989 as Navelbine. Vinorelbine represents a new class of a bisindole alkaloid from the structural point of view, easily accessible in large quantity by semisynthesis. This agent exhibited antitumor efficacy with lower toxic side effects than the other Vinca alkaloids. The fact that it exhibits less activity than other vinca alkaloids against axonal microtubules may account for its reduced neurotoxicity in the clinic.

Intravenous Navelbine was approved by the FDA for the treatment of advanced nsclc in December 1994, 16 months after an NDA (20-388) was filed for this indication, and one year after it was recommended for approval by ODAC. Navelbine was indicated as monotherapy in patients with metastatic nsclc and in combination with cisplatin in ambulatory patients with advanced nsclc. Subsequently, the drug was approved for anthracycline-resistant advanced breast cancer. Major side effects of Navelbine include neutropenia, inflammation or discomfort at the injection site, nausea, vomiting, constipation, and numbness or pain in fingers and toes; granulocytopenia was the major DLT. The usual initial dose of Navelbine is 30 mg/m^2 administered weekly. The recommended method of administration is IV injection over 6 to 10 minutes. Navelbine is now registered in more than 80 countries for the treatment of lung and breast cancer. Vinorelbine is marketed in North and South America by GlaxoSmithKline, while Pierre Fabre Médicaments, a business group of bioMerieux-Pierre Fabre (Boulogne, France) is marketing vinorelbine in Europe and Asia, except Japan, where it is licensed to Kyowa Hakko Kogyo (Tokyo, Japan). Navelbine (KW-2307) was launched in Japan in 1999. In 2001, it is estimated that 130,000 patients were treated with Navelbine-based regimens.

Like its relatives the taxanes, vinorelbine is being evaluated in numerous clinical trials in combination with other cytotoxics and in multimodality therapies, as well as in combination with novel regulatory agents targeting a variety of markers/pathways. Vinorelbine, also like the taxanes, may be a radiosensitizer. Vinorelbine has been and continues to be extensively evaluated in Europe (see Exhibit 1), probably because its developer and marketer are both headquartered abroad.

Oral vinorelbine, also developed by Pierre Fabre, has been registered and is available in 20 mg and 30 mg capsules, in France, Portugal and Finland, and its registration file is under evaluation in several other European countries. In a phase I dose-escalation clinical trial, conducted at Centre Oscar Lambret (Lille, France) to determine MTD of a once weekly regimen of oral vinorelbine in patients with locally advanced or metastatic breast cancer, 26 patients previously exposed to <2 chemotherapeutic regimens, were treated with weekly vinorelbine doses ranging

from 60 to 100 mg/m^2. MTD was 100 mg/m^2 per week, determined by the occurrence of dose-limiting neutropenia, nausea/vomiting and constipation in 5/6 patients. Toxicities at 80 mg/m^2/week were manageable, with Grade 3/4 neutropenia, seen in 10/13 patients, being the main toxicity. Nausea, vomiting and diarrhea were common but rarely severe. Objective tumor responses were reported in 6 of 14 evaluable patients treated with weekly doses ≥80 mg/m^2. This weekly dose level is feasible but requires regular monitoring of neutrophil counts (Bonneterre J, etal, Ann Oncol, Dec 2001;12(12):1683-91).

A randomized phase II clinical trial of oral versus IV vinorelbine was conducted at the Medical University of Gdansk in Poland, to determine the efficacy and safety of oral vinorelbine using intrapatient dose escalation in previously untreated patients with advanced nsclc. Between December 1997 and April 1999, 115 patients with Stage IIIb or IV nsclc were randomized (2 to 1) to either oral vinorelbine at a weekly dose of 60 mg/m^2 for the first three administrations and then at 80 mg/m^2 in the absence of severe neutropenia, or weekly IV vinorelbine at 30 mg/m^2. Among 114 patients (76 in the oral arm and 38 in the IV arm) treated, 98 (86%) were eligible and assessable. Response rates in evaluable patients were 14% in the oral arm and 12% in the IV arm. Median PFS with oral and IV vinorelbine was 3.2 months and 2.1 months, respectively, and MST was 9.3 and 7.9 months, respectively. The most common hematologic toxicity was neutropenia, which was severe (Grade 3/4) in 46% of patients and in 7% of administrations in the oral arm, and in 62% of patients and 25% of administrations in the IV arm. Nonhematologic toxicities including nausea, vomiting, anorexia, weight loss, diarrhea, and constipation were generally mild-to-moderate. The activity and safety profile of oral and IV vinorelbine in advanced nsclc appear to be comparable. Therefore, oral vinorelbine may be considered a good alternative to the IV formulation (Jassem J, etal, Ann Oncol, Oct 2001;12(10):1375-81).

A multicenter phase II trial being conducted in the USA and Canada, is evaluating the clinical efficacy and safety of oral and IV Navelbine administered as a single agent for the treatment of chemotherapy-naïve patients with inoperable Stage IV nsclc, or elderly patients with inoperable Stage IIIb nsclc who are not candidates for combination chemotherapy. Objectives are to determine effectiveness in terms of reducing tumor size or alleviate symptoms. QoL is also being assessed for both groups. According to the protocol, eligible participants will be randomly assigned to either IV or oral Navelbine, administered weekly. Approximately 150 eligible patients are being enrolled in this trial.

Based on a multivariate analysis comparing treatment costs of oral and IV vinorelbine with paclitaxel, docetaxel and gemcitabine in treating nsclc, a standard weekly cost saving of $120 would be achieved if oral vinorelbine is used in preference to gemcitabine, and of $210 to $296 if used in preference to the taxanes. Over a period of 52 weeks, use of oral vinorelbine would result in savings of $1,500 per patient compared to gemcitabine and $2,600 to $3,600 compared to the taxanes (Launois R, etal, 12th International Congress on Anticancer Treatment, Paris, February 4-7, 2002).

APPLICATIONS OF VINCA ALKALOIDS IN DEVELOPMENT

Vinca alkaloids have been used in oncology for over 30 years. Even as older drugs were gradually replaced with newer versions, they remained part of many standard regimens until the advent of the taxanes. Currently, although the original drugs are still in use, only the newer drug vinorelbine is considered an equally effective antimitotic as the taxanes for similar indications such as lung and breast cancer. Recently reported results from combination trials are summarized in Exhibit 1.

Breast Cancer

Vinorelbine is in various clinical trials, mostly overseas, for the treatment of metastatic breast cancer and in combination with other cytotoxics as well as novel regulatory agents. Both two and multiple drug combination and multimodality trials are being conducted, mostly in treating metastatic, often refractory disease.

Ongoing trials are investigating vinorelbine, in combination with capecitabine (Xeloda; Roche) in advanced or metastatic breast cancer. The rational here is validated by a recently reported trial of capecitabine in combination with another spindle poison, docetaxel (Taxotere; Aventis). Results from a phase III clinical trial of the combination of Taxotere and Xeloda, reported in the June 15 issue of the Journal of Clinical Oncology (JCO), demonstrated that this combination conferred a statistically significant longer MST of 14.5 months compared to 11.5 months with Taxotere monotherapy. In addition, the combination demonstrated a statistically significant superior objective tumor response of 42% compared to 30% with Taxotere monotherapy. Also, time-to-disease progression was significantly longer (median 6.1 months) with the combination versus 4.2 months with Taxotere alone, which translates into a 35% risk reduction for tumor progression in patients treated with the combination compared to Taxotere alone. A randomized phase II clinical trial was initiated in Europe comparing vinorelbine and capecitabine with docetaxel and capecitabine chemotherapy in metastatic breast cancer.

Among other currently ongoing clinical trials of vinorelbine and capecitabine chemotherapy are:

- a phase I/II clinical trial (protocol IDs: EU-99007, SWS-SAKK-25/99) in elderly women with metastatic breast cancer with or without bone involvement being conducted in Europe
- a multicenter phase II study of this combination in patients with advanced/metastatic breast cancer refractory to anthracyclines, also being conducted in Europe

- a randomized phase II clinical trial (protocol IDs: EU-99037, RMNHS-TOPIC2) of vinorelbine and epirubicin versus vinorelbine and mitoxantrone versus cyclophosphamide and doxorubicin as neoadjuvant chemotherapy in women with early-stage breast cancer, is also being conducted in Europe

Vinorelbine is also being investigated in a phase II clinical trial (protocol ID: SWOG-S0102), being conducted by the SouthWest Oncology Group (SWOG), combined with docetaxel and filgrastim (G-CSF) in women with HER2-negative Stage IV breast cancer.

A phase II multicenter study of concurrent bevacizumab (Avastin; Genentech) and vinorelbine in patients with Stage IV breast cancer (protocol IDs: DFCI-01013, NCI-2716) was initiated in March 2001 at the Dana-Farber Cancer Institute (Boston, MA) with Harold J. Burstein as Study Chair. IV bevacizumab is administered over 30-90 minutes every other week and IV vinorelbine over 6-10 minutes weekly. Treatment is continued every 8 weeks in the absence of disease progression or unacceptable toxicity. Between 19 and 37 patients will be accrued for this trial within 1 year.

Lung Cancer

As is the case with the taxanes, the Vinca alkaloids, particularly vinorelbine, are being aggressively evaluated for treatment of all stages of lung cancer. Actually, vinorelbine as well as docetaxel, gemcitabine, or paclitaxel represent novel approaches to combination therapy in advanced nsclc. However, despite intensive clinical trial activity in nsclc, it remains a stubborn target with little progress made to date to effectively combat the disease. In a meta-analysis of large (>100 patient) randomized phase III clinical trials, conducted between 1991 and 2001 in advanced nsclc, investigators from Columbia University (New York, NY) reported little benefit from chemotherapy. As shown below, although newer cisplatin combinations were associated with somewhat longer survivals than older standards or carboplatin plus taxanes in this time period, the incremental improvement was marginal (Raftopoulos H, etal, ASCO02, Abs. 1284:322a).

Regimen	# of Patients	MST (months)
Cisplatin monotherapy	783	7.2
Cisplatin and etoposide	509	7.8
Cisplatin standard regimens (cisplatin and vindesine, or vinblastine, or teniposide, or MVP, or MIC)	928	9.0
Cisplatin and new agents (docetaxel, gemcitabine, paclitaxel, or vinorelbine)	4648	9.2
Carboplatin and taxanes	1600	8.6

Among the marketed Vinca alkaloids, vinorelbine has shown the most promise in treating advanced/metastatic lung cancer as monotherapy or as a component of various combination regimens (see Exhibit 1). In randomized clinical trials of combination chemotherapies in nsclc, vindesine has not performed as well as other agents. In a large randomized phase III clinical trial of first-line chemotherapy in Stage IV nsclc, docetaxel and cisplatin resulted in a significantly higher response rate than vindesine and cisplatin (Kubota K, etal ASCO02, Abs. 1180:296a). In addition the QoL profile of docetaxel and cisplatin was superior to that of vindesine and cisplatin in this setting (Ohashi Y, ASCO02, Abs. 1497:375a).

Vinblastine is a member of the mitomycin/vinblastine/cisplatin (MVP) chemotherapy combination regimen used in the treatment of locally advanced or metastatic nsclc. In a phase II clinical trial in this setting, MVP resulted in an ORR of 33% and an MST of 30 weeks. Subsequently, other combinations, such as vinorelbine and cisplatin, or gemcitabine and cisplatin improved these results.

Vinorelbine is also part of multimodality regimens. In a phase III randomized trial, conducted at Hallym University College of Medicine (Seoul, Korea) to investigate whether induction chemotherapy followed by RT influences survival as compared with radiation alone, 101 patients with unresectable, locally advanced (Stage IIIa or IIIb) nsclc were stratified by performance status, weight loss, histology and stage, and then randomized to either combined chemoradiotherapy or RT alone. RT was administered in 1.8 Gy to 2.0 Gy daily standard fractions, 5 times weekly, for a total dose of 60 Gy to 65 Gy. Patients in the chemoradiotherapy group were treated with an induction regimen of cisplatin, etoposide, and vinblastine (PEV) chemotherapy. Among 89 evaluable patients (combined=43, RT alone=46) eligible for analysis, response rates for the combined and RT groups were 65% (28/43) and 70% (32/46), respectively. MST was 13.8 months in the chemoradiotherapy group compared to 8.5 months in the RT alone group. MST in patients with nonsquamous histology was strikingly prolonged in the chemoradiotherapy group at 14 months compared with the RT group at 3.6 months, and MST in patients with Stage IIIb disease was significantly prolonged in the chemoradiotherapy group as compared with the RT group (11.1 months versus 7.2 months). Together, MST of the high-risk group with nonsquamous or Stage IIIb nsclc was significantly higher in the combined group than that in the RT group (11.6 months versus 8 months), whereas MST of the low-risk group, defined as having both squamous histology and Stage IIIa disease, was similar in the two treatment groups (18.3 months versus 20.8 months). Induction PEV chemotherapy plus RT is superior to RT alone in high-risk subsets of unresectable, locally advanced nsclc. Also, therapeutic strategy should be based on the identification of prognostic factors (Kim TY, etal, Am J Clin Oncol, Jun 2002;25(3):238-243).

In a phase III randomized clinical trial conducted at Hospital de Pulido Valente (Lisboa, Portugal) from June 1998 to June 2001, four cisplatin-containing regimens, administered every 28 days, were evaluated in the treatment of advanced nsclc. The primary endpoints of the trial were response rate and survival. A total of 248 patients (62 per arm) were treated, stratified by stage (III versus IV) and performance status. Results are summarized below:

Regimen	Objective Response Rate (%)	MST of Stage III patients (months)	MST of Stage IV patients (months)
Mitomycin (6 mg/m^2) vinblastine (6 mg/m^2) and cisplatin (100 mg/m^2) on day 1 (MVP)	27.0	6.4	5.4
Cisplatin (100 mg/m^2) on day 1 and vinblastine (30 mg/m^2) on days 1, 8, 15	37.1	9.0	7.5
Cisplatin (100 mg/m^2) on day 1 and gemcitabine (1000 mg/m^2) on days 1, 8, 15	48.4	9.4	8.2
Gemcitabine (1000 mg/m^2) on days 1, 8, 15 and cisplatin (100 mg/m^2) on day 15	48.4	9.6	8.7

Grade 3/4 neutropenia was similar across all arms (range=56.5%-66.1% of patients), whereas Grade 3/4 thrombocytopenia was significantly more frequent (37% of patients) in the cisplatin and gemcitabine arm. Edema in the gemcitabine-based regimens and peripheral neuropathy in the cisplatin and vinblastine arm were the major nonhematologic side effects. After a median follow-up of 24 months (range=5-40+), 73% (86% Stage IV and 61% Stage III) of the patients had died. Estimated 1-year survival rates also reflected these Stage-related differences (Melo MJ, etal, ASCO02, Abs. 1205:302a).

Vinorelbine is also being evaluated as monotherapy in advanced nsclc. According to results from the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS), a phase III clinical trial that compared treatment with vinorelbine and best supportive care with best supportive care alone, single-agent vinorelbine improved survival and possibly improved overall QoL of elderly patients (≥70 years-of-age) with advanced (Stage IIIb/IV) nsclc ineligible for RT. Vinorelbine was administered IV on days 1 and 8 of a 21-day treatment cycle, for a total of 6 cycles. The trial was stopped early because of a low enrollment rate after 191 of the 350 targeted patients were randomly assigned between April 1996 and November 1997. Based on 161 evaluable patients, those treated with vinorelbine scored better than control patients on QoL functioning scales, and reported fewer lung cancer-related symptoms but experienced worse toxicity-related symptoms. MST increased from 21 to 28 weeks in the vinorelbine-treated group and the relative hazard of death in this group was 0.65 (JNCI, 6 Jan 1999;91(1):66-72).

In preclinical trials, at a minimally toxic concentration, vinorelbine moderately sensitizes human nsclc cells to radiation by causing accumulation of cells in the G2/M-phase of the cell cycle. Based on this observation, investigators at Nara Medical University (Kashihara City, Nara, Japan) and the National Cancer Center Research Institute (Tokyo, Japan) are conducting a preliminary study of vinorelbine and concomitant radiation in the treatment of the patients with locally advanced nsclc (Fukuoka K, AACR02, Abs. 3745:755).

Vinorelbine is also being evaluated in combination with tirapazamine (see Exhibit 1). In July 2000, Sanofi-Synthelabo (Paris, France) initiated a multicenter phase III randomized clinical trial (protocol ID: SANOFI-EFC3675) in patients with Stage IIIb/IV or recurrent nsclc. The trial objectives were to compare the overall survival of patients treated with vinorelbine and cisplatin with or without tirapazamine, as well as CR rates, time-to-disease progression, time-to-treatment failure, toxicity and safety, and QoL. Arm I patients are being treated with tirapazamine IV over 2 hours, followed by cisplatin IV over 1 day on day 1. Patients are also being administered vinorelbine IV over 6-10 minutes on days 1, 8, 15, and 22. Arm II patients are being administered cisplatin IV over 1 day on day 1, and vinorelbine IV over 6-10 minutes on days 1, 8, 15, and 22. Treatment is repeated every 28 days for 6 courses in the absence of disease progression or unacceptable toxicity. Approximately 800 patients were to be accrued for this study which had been closed as of April 2002.

A multimodality approach is investigating the role of chemoradiotherapy in the treatment on nsclc. In an NCI-sponsored phase I tritherapy clinical trial (RTOG-9810), tirapazamine is being evaluated as induction chemotherapy, in combination with cisplatin and vinorelbine, and subsequently, as a radiosensitizer in combination with RT, in patients with unresected locally advanced nsclc (Stage II, IIIa, or IIIb) without evidence of hematogenous metastases. The trial's objectives are to determine if acute and late treatment-related toxicity is increased by the addition of tirapazamine to induction chemotherapy, and subsequent chemoradiotherapy, and to establish the optimum dose of tirapazamine in this setting. According to the study protocol, patients are treated with vinorelbine IV weekly for 5 weeks, and tirapazamine IV over 2 hours, followed 1 hour later by cisplatin IV, administered over 30-60 minutes, on days 1 and 29. Beginning on day 50, patients also undergo RT daily, 5 times a week, for 7 weeks. Patients may also be treated with IV tirapazamine every other day, 3 times a week, during the first 2-4 weeks of RT, for a total of 0, 6, or 12 doses. Tirapazamine is escalated in cohorts of 7-12 patients during RT until the third dose level is achieved successfully or MTD is determined. Patients are followed every 3 months for 2 years, every 6 months for 3 years, and then annually thereafter. A max-

Exhibit 1
Results from Selected Phase II Clinical Trials of Combination/Multimodality Regimens Incorporating Vinca Alkaloids

Regimen	Toxicity	Results	Clinical Status➢ Location ❑ Indication ❑ Enrollment	Institution ❑ Reference
		Breast Cancer		
Vinorelbine + capecitabine (Vinocap)	Grade 3 neutropenia occurred in 3 (13%) patients; there were no Grade 4 toxicities; mild nonhematolgic toxicities were asthenia (n=4), abdominal pain (n=4), diarrhea (n=3), nausea/vomiting (n=2), and hand-foot syndrome (n=4)	Among 23 evaluable patients, the ORR was 61% and disease stabilized in 3 (13%)	Phase II (completed 5/02) ➢Lebanon ❑ metastatic breast cancer ❑ 30 patients (previously treated with adjuvant/neo-adjuvant chemotherapy=74%, anthracyclines=48%, taxanes=22%, and hormone therapy=74%)	Hotel-Dieu de France Hospital (Beirut, Lebanon) ❑ Ghosn M, etal, ASCO02, Abs. 1978:42b
Docetaxel + vinorelbine	Grade 3/4 toxicities included neutropenia (37.1%), anemia (8.5%), thrombocytopenia (2.9%), mucositis (5.7%), paresthesias (5.7%), and asthenia (8.5%); there was 1 toxic death	A total of 229 cycles were administered; ORR was 54.2% (19) with 5 (14.2%) CR and 14 (40%) PR; overall survival was 20 months and median TTP was 13 months	Phase II (begin 10/96, closed 2/01)➢Europe (Spain) ❑ advanced or metastatic breast cancer ❑ 35 patients (previous high-dose chemotherapy and peripheral blood-derived stem cell (PBSC) support=22 and multicyclic dose-intensive chemotherapy with PBSC support=14)	Clinica U (Pamplona, Spain) ❑ Rodriguez J, etal, ASCO02, Abs. 2072:65b
Gemcitabine + vinorelbine	Grade 4 neutropenia was observed in 2 patients at 1000 mg/m^2 of gemcitabine; Grade 4 neutropenia was experienced by 3 patients and Grade 3 anemia by 4; nonhematologic toxicities were moderate	MTD for gemcitabine was 1000 mg/m^2; optimal dose schedule was gemcitabine at 800 mg/m^2 and vinorelbine at 25 mg/m^2; ORR was 42% with 4 (8%) CR and 17 (34%) PR	Phase I/II (completed 5/02) ➢Europe (Italy) ❑ advanced or metastatic breast cancer ❑ 9 patients were entered into phase I and 50 into phase II (patients were previously treated with taxanes and/or anthracyclines)	Multicenter ❑ Morabito A, etal, ASCO02, Abs. 2064:63b
Trastuzumab + vinorelbine	Neutropenia was the only Grade 4 toxicity; there were no cases of symptomatic heart failure; 3 patients experienced Grade 2 cardiac toxicity, associated with prior cumulative doxorubicin dose >240 mg/m^2 and borderline pre-existing cardiac function; this regimen was well tolerated	Responses were observed in 30/40 patients for an ORR of 75%; ORR was 84% in patients treated with trastuzumab and vinorelbine as first-line therapy for metastatic disease, and 80% among HER2 +3 positive patients; high response rates were also seen in women treated with second- or third-line therapy, and among patients previously treated with anthracyclines and/or taxanes; this was a highly active regimen in women with HER2-overexpressing advanced breast cancer	Phase II (completed 01) ➢USA ❑ Her2+ metastatic breast cancer ❑ 40 women with HER2+3 (n=30) or HER2+2 or HER2+ (n=10) breast cancer; 82% had prior chemotherapy as part of adjuvant (30%), metastatic (25%), or both (28%) treatment, including substantial portion of patients exposed to anthracyclines (20%), taxanes (15%), or both (38%)	Dana-Farber Cancer Institute ❑ Burstein HJ, etal, J Clin Oncol, May 2001;19(10): 2722-30
Pegylated liposomal doxorubicin + vinorelbine	Of 33 patients evaluable for toxicity, Grade 4 neutropenia occurred in 15, and neutropenic fever in 3; palmoplantar syndrome in 17; Grade 1 and 2 alopecia in 14 and 4 patients, respectively; mucositis was mild and frequent; Grade 1 allergic reaction occurred in 1 patient and 2 patients had reversible decline in LVEF	33 patients were evaluable for response; ORR was 36% including 1 CR and 11 PR and disease stabilized in 12 patients for 4+ months; 3/12 patients with prior taxane therapy had an objective response	Phase II (begin 12/98, closed 2/01)➢Spain ❑ metastatic breast cancer ❑ 35 patients (12 had been previously treated with taxanes and 3 with high-dose chemotherapy)	Hospital U San Carlos (Madrid, Spain) ❑ Martin M, etal, ASCO02, Abs. 1965:38b

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Vinorelbine + raltitrexed	There was no interaction between the two drugs and the regimen exhibited acceptable toxicity	Among 9 pretreated patients evaluable for efficacy there were 3 objective responses (1 CR and 2 PR) of mean duration of 26 weeks (range=17-38)	Phase I (completed 02) ➢Europe (France) ❑ refractory advanced breast cancer ❑ 12 patients with advanced breast cancer, most refractory to taxane and anthracycline combination therapy	Centre Antoine Lacassagne (Nice, France) ❑ Ferrero J-M, etal, AACR02, Abs. 2759:555
Gemcitabine + vinorelbine	Main toxicity was hematologic with Grade 3/4 neutropenia occurring in 13 patients; there was 1 case of Grade 4 oral mucositis; there were 2 deaths from pneumonia and one patient developed febrile neutropenia that completely resolved with IV antibiotics and standard measures	The intent-to-treat ORR was 44%; among 21 patients evaluable for response (2 declined therapy and 2 died), there were 2 CR of hepatic metastases with duration of 22 and 20+ weeks; disease stabilized in 12% and progressed in 28%; median duration of response was 21 weeks and median event-free survival was 17 weeks; a randomized clinical trial is ongoing to compare this combination with vinorelbine monotherapy in patients with metastatic breast cancer who failed anthracycline and taxane regimens	Phase II (begin 4/98, closed 12/00)➢Europe (Spain) ❑ metastatic breast cancer ❑ 25 patients (10 had been treated with only adjuvant therapy with anthracyclines, and 15 with one or two lines of chemotherapy, including taxanes in 11 cases); a maximum of two lines of chemotherapy for metastatic disease was allowed	Multicenter ❑ Lobo F, etal, ASCO02, Abs. 2032:55b
Capecitabine + vinorelbine	Grade 3/4 neutropenia occurred in 22.2% of cases, Grade1/2 hand-foot syndrome in 20.6%/7.1%, Grade 2 neuropathy in 2.4% and stomatitis in 8.7%; there was no Grade 3/4 diarrhea or stomatitis; there was only 1 case of febrile neutropenia; there were no treatment-related deaths; capecitabine dose was reduced in 11.1% of cycles and vinorelbine could not be administered in 25.4% of cycles on day 8 because of Grade 3/4 neutropenia; the dose of day 8 vinorelbine was reduced in 24.6% of cycles because of Grade 2 neutropenia	At a median follow-up of 126 days, among 19 patients evaluable for response, ORR was 52.6% (1 CR and PR 9) and median response duration was 119 days (range= 7+-321); median TTP was 168 days (range 28-462+). Preliminary data show that the combination of capecitabine and vinorelbine is feasible and effective in heavily pretreated patients previously exposed to anthracycine and taxane regimens	Phase II (begin 4/00, ongoing 5/02)➢Korea ❑ refractory metastatic breast cancer ❑ 24 female patients previously treated with anthracycline and taxane regimens; the study continues until 60 patients are enrolled	U Ulsan College of Medicine (Seoul, Korea) ❑ Ahn J-H Sr, etal, ASCO02, Abs. 2030:55b
Docetaxel + vinorelbine	Among 30 patients evaluable for safety, Grade 3 or 4 neutropenia occurred in 13% of cycles and 38% of patients, and febrile neutropenia in 1 cycle (1%). Other Grade 3/4 toxicities were leukopenia, in 17% of patients, fever in 17%, mucositis in 10% and infection in 10%; there were no toxic deaths	Among 17 patients evaluable for efficacy, there were 3 CR and 8 PR for an ORR of 65%; 12 patients were not evaluated for response (9 of them had not completed the first 6 cycles and 3 were prematurely withdrawn because of adverse events including febrile neutropenia, prolonged fever and malaise); this is an active first-line treatment of metastatic breast cancer with an acceptable toxicity profile	Phase II (completed 02) ➢Europe (Spain) ❑ metastatic breast cancer, first-line ❑ 30 patients; prior treatment included surgery in 93%, RT in 61%, hormone therapy in 53% and neoadjuvant chemotherapy in 67% with anthracyclines in 63%; sites of metastasis were bone in 47%, liver in 33% and pleura/lung in 33%; 70% of patients had 2 or more metastatic sites	Multicenter ❑ Mayordomo JI, ASCO02, Abs. 2014:51b

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Docetaxel + vinorelbine	Hematologic toxicities were Grade 3/4 neutropenia (n=28), febrile neutropenia (n=12), Grade 3/4 anemia (n=2), and Grade 3/4 thrombocytopenia (n=1); nonhematologic toxicities included alopecia, and severe stomatitis (n=2), vomiting (n=2), and diarrhea (n=1)	Among 40 patients, ORR was 40% including 6 (15%) CR and 10 (25%) PR and disease stabilized in 6 (15%) patients and progressed in 18 (45%); median duration of response was 8 months and median TTP was 6 months	Clinical (completed 5/02) Europe (Greece) ❑ metastatic breast cancer ❑ 40 patients (12 were previously treated with anthracyclines)	St. Savas Hospital (Athens, Greece) ❑ Barbounis V, etal, ASCO02, Abs. 1974:41b
Epirubicin + vinorelbine + docetaxel	Among 34 patients evaluable for toxicity, adverse events included dyspnea, obstructive ictericia, and allergic reaction observed in 7 patients; other toxicities included Grade 3/4 neutropenia, asthenia, nail disorders, and nausea	A total of 114 cycles were administered to 35 patients; among 28 evaluable patients, ORR was 71% with 6 CR and 14 PR; median TTP and duration of response had not been reached at the time of this report	Phase II (ongoing 5/02)➢ Europe (Spain) ❑ metastatic breast cancer ❑ 37 patients; metastasis were observed in liver (28%), bone (28%), and lung (28%)	Multicenter ❑ Morales S, etal, ASCO02, Abs. 2041:57b
Vinorelbine + 5-fluorouracil (5-FU) + leucovorin	Main toxicities were Grade 3 leukopenia and Grade 3/4 neutropenia; other toxicities were Grade 1/2 infection, and stomatitis, Grade 1/4 diarrhea and Grade 1 sensory neurotoxicity	Among 20 evaluable patients, ORR was 65.0%, with 1 CR and 12 PR; MST had not been reached at the time of this report	Phase II (completed 5/02) ➢Taiwan ❑ advanced breast cancer ❑ 20 patients (recurrent advanced breast cancer=14; previous anthracycline-containing adjuvant chemotherapy=7; and hormonal therapy=12)	Multicenter ❑ Yeh KH, etal, ASCO02, Abs. 2006:49b
Vinorelbine + methotrexate + 5-FU	Grade 3 hematologic toxicity occurred in 23%, 36% and 50% and Grade 4 in 39%, 32% and 50% in Group I, II, and III, respectively; Grade 3 infections were observed in 15%, 9% and 10% in Group I, II and III, and Grade 4 infections in 5% and 10% in Group II and III, respectively; nonhematologic toxicity of vinorelbine included neurotoxicity manifesting as muscle weakness,epigastric pain and constipation in the majority of patients; serious convulsions after vinorelbine administration occurred in 1 patient in Group III who also developed granulocytopenic sepsis; all symptoms were reversible; there were no treatment-related deaths	In Group I there were 4% CR, 46% PR, and disease stabilized in 39% and progressed in 11%; in Group II, there were 4% CR, 50% PR, and disease stabilized in 23% and progressed in 23%; in Group III there were 22% CR, 22% PR, and disease stabilized in 45% and progressed in 11%. MST was 26, 23, 16 months and median TTP was 7, 10, 8 months in Groups I, II and III, respectively; vinorelbine doses 20+20 and 30+10 mg/m^2 administered on day 1 and 8 were better tolerated and more efficacious than 40 mg/m^2 administered on day 1	Phase II (completed 02) ➢Europe (Finland) ❑ metastatic breast cancer ❑ 60 patients in 3 treatment arms	Helsinki U Central Hospital (Helsinki, Finland) ❑ Elomaa I, etal, ASCO02, Abs. 1977:41b
Docetaxel + epirubicin + vinorelbine	At dose levels I and II, Grade 3/4 hematologic toxicities were neutropenia (63%) and febrile neutropenia (7%); Grade 2-3 nonhematologic toxicities included alopecia (75%), mucositis (30%), nausea/vomiting (30%), mild edema (10%), nail changes (10%), and diarrhea (6%)	Among 40 evaluable patients, the objective response was 60% (24 patients)	Phase I/II (completed 5/02)➢Europe (Spain) ❑ metastatic breast cancer ❑ 43 patients with metastases in the liver (n=15), bone (n=17), soft tissue (n=11), and lung (n=12)	Multicenter ❑ Lacave AJ, etal, ASCO02, Abs. 1954:36b
Cisplatin + epirubicin + vinorelbine	Grade 3/4 hematologic toxcities included leucopenia, neutropenia, febrile neutropenia, and Grade 1/2 anemia; nonhematologic toxicities included Grade 3 nausea/vomiting (n=15), Grade 3 asthenia (n=4), and alopecia in all patients	Among 93 evaluable patients administered 288 treatment cycles, there were 10 CR, 59 PR, 15 MR, and disease stabilized in 9	Phase II (begin 6/97, completed 5/02)➢Europe (Italy) ❑ Stage T2-3/N0-2 breast cancer ❑ 93 patients	Multicenter ❑ Barni S, etal, ASCO02, Abs 1961:37b

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Vinorelbine + cisplatin + 5-FU	Toxicities included mild myelosuppression, Grade 4 granulocytopenia (18%), and diarrhea (n=1), Grade 3 diarrhea (2%), nausea (4%), stomatitis (4%), fatigue (1%), fever (1%), photosensitivity (1%), and hand-foot syndrome (1%); right diaphragmatic supra elevation occurred in 11 patients, and central venous catheter-associated deep vein thrombosis in 8	ORR was 55%; among 96 evaluable patients, there were 4 CR (4%) and 49 PR (51%); after a median follow-up of 10.2 months, median duration of response was 5.2 months, and TTP was 6.8 months	Phase II (completed 1/01) ➢Europe (Italy) ❑ advanced, metastatic breast cancer ❑ 100 patients (52% had previous chemotherapy; 61% with anthracyclines, 5% with taxanes, and 29% with 5-FU)	European Institute of Oncology-Division of Medical Oncology (Milan, Italy) ❑ Nole F, etal, Ann Oncol, Jan 2001;12(1):95-100
Doxorubicin + vinorelbine + cyclophosphamide + 5-FU	The main toxicity was Grade 3/4 neutropenia	ORR was 86%; in 17 patients there were no tumor cells in the breasts and nodes following pathologic review; 7 patienst had *in situ* carcinoma in the breast; at a median follow-up of 82 months, 29 patients relapsed; as of December 2001, MST was 71% and DFS was 52%; among 72 patients, CR rate was 34%	Clinical (begin 91, closed 98)➢Europe (France) ❑ high risk, operable breast cancer ❑ 72 patients	Centre Jean Perrin and INSERM (Clermont-Ferrand, France), ICIG (Villejuif, France) ❑ Chollet PJ, etal, ASCO02, Abs. 1958:37b
		Lung Cancer		
Gemcitabine + vindesine	All patients were evaluable for toxicity; treatment was well tolerated; Grade 3/4 anemia, neutropenia and thrombocytopenia were observed in 5.3%, 12.5% and 3.5% of patients, respectively; nonhematologic toxicities were moderate, including Grade 2 fatigue in 16% of cases and Grade 2 or Grade 3 paresthesias in 19.6% and 10.7%, respectively	Following a minimum of 2 cycles, all patients were evaluable for response; there were 22 (39.3%) PR, and disease stabilized in 18 (32.1%) and progressed in 16 (28.6%); after a median follow-up of 18 months, 39/56 patients had died; MST was 9 months, and the estimated 1-year survival rate was 37.5%; clinical benefit occurred in 50% of patients; this very promising regimen is being evaluated in comparison to gemcitabine monotherapy in an ongoing phase III clinical trial	Phase II (begin 1/98, closed 6/01)➢Europe (Italy) ❑ unresectable nsclc, in elderly or poor-performance status patients ❑ 56 patients with nsclc [Stage IIIb=10 (17.8%) and Stage IV=46 (82.2%]; squamous cell carcinoma =26 (46.4%), adenocarcinoma=18 (32.1%), undifferentiated=5 (8.9%), and large-cell tumors=7 (12.5%)	Gruppo Interdisciplinare Veronese Oncologia Polmonare (GIVOP), U Verona (Verona, Italy) ❑ Santo A, etal, ASCO02, 2678:215b
Irinotecan + vinorelbine	Among 41 patients evaluable for toxicity, Grade 4 fatigue was experienced by 1 patient who subsequently discontinued treatment; other toxicities included Grade 2/3 diarrhea (12.1%), Grade 3 alopecia (12.1%), and Grade 3 neurotoxicity (2.4%)	Among 40 evaluable patients, ORR was 31.6% with 2 CR and 12 PR, and disease stabilized in 18 (43.9%); in the intent-to-treat population, there were 6 (14.6%) PR, and disease stabilized in 10 (24.3%), and progressed in 15 (36.5%); median TTP was 5 months, MST was 7.8 months, and 1-year survival rate was 37%; this regimen was well tolerated with prolonged 1-year survival	Phase II (completed 5/02) ➢Europe (Greece) ❑ advanced, refractory nsclc ❑ 41 patients refractory or resistant to platinum or taxanes (histologic types were squamous cell carcinoma =34.1%, adenocarcinoma= 31.7%, large cell carcinoma=4.8%, and undifferentiated nsclc=29.4%	Multicenter ❑ Pectasides DG, etal, ASCO02, Abs. 1307:327a
Paclitaxel + cisplatin + vinorelbine	Hematologic toxicities were Grade 3/4 neutropenia (43%), thrombocytopenia (2%), and anemia (17%); febrile Grade 4 neutropenia occurred in 11 (24%) patients; nonhematologic toxicities included Grade 3/4 nausea/vomiting (20%) and Grade 2-3 neurotoxicity (17%); there was 1 treatment-related death	Among 46 evaluable patients, ORR was 39% with 1 patient achieving CR; median PFS was 14.3 weeks and median overall survival was 31.3 weeks; the 1-year survival rate was 34% and the 2-year survival rate was 9%	Phase II (begin 4/94, closed 1/98)➢Europe (Spain) ❑ metastatic nsclc ❑ 46 chemotherapy-naive patients	Clinica U (Pamplona, Spain) ❑ Aramendia JM, etal, ASCO02, Abs. 2743:231b

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Paclitaxel + cisplatin + vinorelbine or gemcitabine	All patients were evaluable for toxicity; there was 1 treatment-related death; hematologic toxicities included Grade 3/4 neutropenia (31%) and thrombocytopenia (4%), including 6 (23%) cases of febrile Grade 3/4 neutropenia; nonhematologic toxicities were mild except for Grade 3/4 neurotoxicity (4%)	Among 26 patients, 25 were evaluable for response; intracranial response was observed in 10 patients; there was 1 CR and disease stabilized in 8 (31%); median overall survival was 21.4 weeks and median TTP was 12.8 weeks	Phase II (begin 6/94, closed 12/00)➢Europe (Spain) ❑ brain metastases from nsclc ❑ 26 chemotherapy-naive patients	Clinica U (Pamplona Spain) ❑ Cortes J, etal, ASCO02, Abs. 1297:325a
Cisplatin + gemcitabine + vinorelbine	In 33 evaluable patients, hematologic toxicities included Grade 3 leucopenia (27%), thrombocytopenia (33%), and anemia (24%), and Grade 4 leucopenia (15%); nonhematologic toxicities were mild nausea, vomiting, and peripheral neuropathy	Among 25 chemotherapy-naive patients, there were 5 (20%) PR, and disease stabilized in 12 (4%), and progressed in 8 (32%)	Phase II (completed 5/02) ➢Europe (Austria) ❑ advanced nsclc ❑ 33 patients (25 chemotherapy naïve)	Vienna General Hospital (Vienna, Austria) ❑ Doweik L, etal, ASCO02, Abs. 2748:232b
Gemcitabine + cisplatin + vinorelbine	Grade 3/4 neutropenia occurred in 46% of cycles and 68% of patients, infection in 10% of cycles and 25% of patients, thrombocytopenia in 5% of cycles and in 1 patient, and fatigue in 52% of patients	There were 14/28 (50%) PR	Phase I/II (begin 6/00, closed 8/01)➢Brazil ❑ metastatic nsclc ❑ 28 chemonaive patients	Arnaldo Vieira de Carvalho Cancer Institute (Sao Paulo, Brazil) ❑ Martins SJ, etal, ASCO02, Abs. 2698:220b
Paclitaxel + gemcitabine + vinorelbine	If all the 183 delivered cycles are considered, Grade 3/4 neutropenia and thrombocytopenia occurred in 23 (46%) and 6 (12%) patients, respectively; red blood cell transfusions were required in 5 patients; fatigue, constipation, and peripheral neuropathy were the most common nonhematologic toxicities (severe in 5 patients); nausea and vomiting were generally mild	There was 1 CR and 17 PR for an ORR of 36% among 50 evaluable patients	Phase I (closed 6/01) ➢Europe (Italy) ❑ locally advanced or metastatic nsclc, first-line ❑ 50 patients (Stage IIIb=18, Stage IV=32)	Multicenter ❑ Luigi Maiorino L, etal, ASCO02, Abs. 2695:219b
Tirapazamine + cisplatin + vinorelbine	Among 34 patients evaluable for toxicity, 76.5% experienced leucopenia (Grade 3/4=17 patients) and 67.6% developed granulocytopenia (Grade 3/4=21); nausea and vomiting were severe in 4 patients; asthenia was reported in 52.9% (Grade 3/4=4) and pain in 44.1% (Grade 3/4=4); leg cramps were observed in 58.8% and were moderate (Grade 3/4= 2); involuntary muscle contractions occurred in 19% of patients, 26.5% experienced constipation, and 47.1% diarrhea (Grade 3/4=2)	According to a preliminary review there were 14 objective responses (41%), and disease stabilized in 10 (29%)	Phase II (begin 6/99, closed 01)➢Europe (Germany) ❑ Stage III or IV nsclc ❑ 34 patients (Stage III=1, Stage IIIb=10 and Stage IV=23); there were 8 squamous cell carcinoma, 17 adenocarcinoma and 9 other cell types	Asklepios Fachkliniken Muenchen-Gauting (Gauting, Germany), Krankenhaus Grosshansdorf (Germany) ❑ von Pawel J, etal, ASCO01, Abs. 2737:246b

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Vinorelbine + cisplatin + tirapazamine	Among 42 patients evaluable for toxicity, Grade 3/4 neutropenia was experienced by 88% and febrile neutropenia by 41% (1 patient with Grade 5); their toxicities included Grade 1 tinnitus (40%), hearing loss (14%), cramps (57%), Grade 3/4 diarrhea (5%), severe nausea/vomiting (14%), and 5 patients had transient intestinal obstruction	Among 37 patients evaluable for response, an objective response (OR) was observed in 18 (49%) and disease stabilized in 11; among Stage IIIb and Stage IV patients, OR was 55% and 45%, respectively; MST had not been reached at the time of this report	Phase II (begin 2/97, closed 99)➢Europe (France) ❑ advanced nsclc ❑ 54 patients (Stage IIIb=12 and Stage IV=42); cancer types included squamous cell carcinoma (n=24), adenocarcinoma (n=23), and large-cell carcinoma (n=7)	Institut Gustave Roussy (Villejuif, France) ❑ Le Chevalier T, etal, ASCO99, Abs. 1894:491a
Cisplatin + vinorelbine + hyperfractionated accelerated RT (HART)	Grade 3+ toxicities included neutropenia (n=25), anemia (n=3), thrombocytopenia (n=2), infection (n=5), esophagitis (n=5), nausea (n=3), radiation pneumonitis (n=3), and dermatitis (n=1); there were 2 deaths from radiation pneumonitis	All patients were administered 2 cycles of cisplatin and vinorelbine therapy and 1 did not complete HART; ORR was 83%. MST had not been reached at the time of this report; 1-year and 2-year survival was 68% and 58%, respectively; median PFS was 10 months and 1-year PFS was 43%	Pilot (begin 7/99, closed 3/01)➢Japan ❑ Stage IIIa/b nsclc ❑ 30 patients	National Cancer Center Hospital East (Kashiwa, Japan) ❑ Ishikura S, etal, ASCO02, Abs. 1283:321a
Cisplatin + vinorelbine + docetaxel + RT	Of 47 patients, 6 were not evaluable after the 2 induction cycles because of death (n=3), Grade 4 renal hemoptysis (n=1), and Grade 3 infection (n=2); 1 patient died from febrile neutropenia, 1 from massive hemoptysis and 1 from disease progression. Major toxicities in 32 patients who continued with RT and docetaxel were Grade 3 esophagitis (n=6) and Grade 3 pneumonitis (n=3); there was 1 death from pulmonary embolism	Among 47 patients treated with cisplatin and vinorelbine, there were 20 (42.5%) PR and disease progressed in 7 (14.9%). Among 32 patients who continued treatment with docetaxel and RT, there were 15 (46.9%) PR and disease progressed in 8 (25%); local recurrence occurred in 2 patients and distant relapses including brain and liver metastases, in 6	Phase II (begin 7/00, closed 9/01)➢Europe (France) ❑ locally advanced nsclc ❑ 59 patients	Multicenter ❑ Vergnenegre A, etal, ASCO02, Abs. 1271:318a
Head and Neck Cancer				
Cisplatin + vinorelbine	Among 42 patients, 1 died of febrile neutropenia and 1 of unknown causes after the second cycle; Grade 3/4 neutropenia was observed in 35% of patients; other serious toxicities included Grade 3 nausea/vomiting (10%) and anemia (5%); other toxicities were mild	Doses were reduced in 43% of patients because of neutropenia; among 40 patients evaluable for response, CR rate was 10% and PR rate 23%, for an ORR of 33%; median duration of response and median overall survival were both 6 months	Phase II (completed 02) ➢Europe (Spain) ❑ recurrent or metastatic squamous cell carcinoma of the head and neck ❑ 42 patients	Multicenter ❑ Espinosa E, etal, ASCO02, Abs. 933:234a
Methotrexate + vinblastine + doxorubicin + cisplatin	Severe leukopenia was seen in 55% of patients during the first cycle; 81% of patients displayed severe leukopenia during the entire treatment course	Among 35 patients evaluable for response after 4 cycles, ORR was 46%; there were 2 CR among 18 responders; median TTP was 19 weeks, and 1-year PFS rate was 17%; MST was 49 weeks and 1-year survival rate was 43%. Among 22 patients with unresected residual or recurrent disease, median TTP was 11 weeks, 1-year PFS rate was 14%, MST was 24 weeks, and the 1-year survival rate was 36%. Among 13 patients with metastatic disease, median TTP was 26 weeks, 1-year PFS rate was 23%, MST was 54 weeks, and the 1-year survival rate was 54%	Phase II (begin 4/93, closed 2/96)➢USA ❑ unresectable, recurrent, or metastatic squamous cell carcinoma of the head and neck ❑ 36 patients	North Central Cancer Treatment Group (NCCTG) ❑ Okuno SH, etal, Cancer 2002 Apr 15;94(8):2224-31

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Vinorelbine + cisplatin (JM-8) + RT + carboplatin	Grade 3 and 4 hematologic toxicities occurred in 4 (12.5%) and 8 (25%) patients, respectively; Grade 4 GI toxicity was seen in 2 patients (6.25%) and mucositis in 2 (6.25%)	Among 22 evaluable patients, there were 7 (31.8%) CR and 11 (50%) PR; disease progressed in 4 patients (18.1%); another 10 patients were still being treated and could not be evaluated	Clinical (closed 02) ➢Europe (Italy) ❑ head and neck cancer and/or esophageal carcinoma ❑ 32 patients	Azlenda Ospedaliera di Padova (Padova, Italy) ❑ Koussis H, etal, ASCO02, Abs. 2562:186b
Vinorelbine + ifosfamide + cisplatin; surgery + RT	Toxicities included Grade 1/2 anemia (92%), Grade 3 anemia (8%), Grade 1/2 neutropenia (51%), Grade 3 neutropenia (34%), Grade 4 neutropenia (15%), and Grade 1/2 thrombocytopenia (32%); patients with neutropenia recovered without hospitalization or parental antiobiotics; anorexia and nausea were controlled with ondansetron; alopecia and leukopenia were also observed	Among 8 evaluable patients, there were 3 CR and 5 PR for an ORR of 100%	Clinical (completed 02) ➢India ❑ squamous cell carcinoma of the head and neck ❑ 12 patients	Tata Memorial Hospital (Mumbai, India) ❑ Pai VR, etal, ASCO02, Abs. 2578:190b
Other Malignancies				
Mitoxantrone + vinorelbine + prednisone	Hematologic toxicities include Grade 3/4 leukopenia (11), and Grade 3/4 anemia (3); infectious complications was experienced by 2 patients.	After a median of 6 treatment cycles per patient, among 23 evaluable patients, there were 8 (35%) PR, and disease stabilized in 6 (26%), and progressed in 9 (39%); median duration of response was 7.3 months; survival was significantly better among responders	Phase II (begin 6/98, closed 6/01)➢Europe (Italy) ❑ hormone-resistant, metastatic prostate cancer ❑ 28 patients (13 previously treated with RT); metastatic sites included bone, lymph nodes, liver, and lung	Centro di Riferimento Oncologico (Aviano, Italy) ❑ Bernardi D, etal, ASCO02, Abs. 2444:157b
Cisplatin + vinblastine + dacarbazine + interleukin-2 (IL-2) + interferon (IFN) α-2b	Grade 3/4 neutropenia occured in 18.4% of 60 cycles, and fever and chills in 51%, Grade 3/4 vomiting in 6%; there was 1 episode of severe hypotension; there was no renal toxicity or febrile neutropenia	Among 14 evaluable patients the ORR was 28.6%; there were 2 CR and 2 PR while disease progressed in 10; after a 2-year follow-up the disease-free period was 10 months	Phase II (begin 1/98, completed 6/01)➢Peru ❑ metastatic malignant melanoma ❑ 14 patients (1 previously treated with IFN in the adjuvant setting)	Edgardo Rebagliati Hospital (Lima, Peru) ❑ Flores D, etal, ASCO, Abs. 2783:241b
Carboplatin + vincristine + fluvastatin; surgery + RT	There was no significant toxicity in any of the 64 courses administered	The mean residual tumor bulk after surgery was 39.3 cm^2 and after the 4th course it was reduced by 45% to 17 cm^2; overall survival at 12 months was 60%	Phase II (completed 02) ➢Mexico ❑ pediatric, low-grade astrocytoma (LGA) of the thalamus, brain stem or optic quiasm, first-line ❑ 8 chemonaive patients with LGA (brainstem=5, thalamus=3) with residual tumor after surgery (pylocitic histology=4 and fibrillar=4)	Hospital de Pediatria, Centro Medico Nacional Siglo XXI IMSS, Mexico ❑ Aguilar Enrique Lopez, etal, ASCO02, Abs. 2104:73b
Interleukin-2 (IL-2) + vinorelbine + gemcitabine	Chemotherapy-related toxicities included Grade 1/2 neutropenia at 1000 and 1200 mg/m^2 of gemcitabine, Grade 3/4 neutropenia at 1400 mg/m^2, Grade 4 thrombocytopenia at 1400 mg/m^2, and Grade 2 anemia at 1200 mg/m^2	MST was 10+ months; MST of responders and those with stable disease was 11+ months, while MST of those with progressive disease was 7 months; there was 1 CR and 2 PR among 6 patients treated with 1000 mg/m^2 of gemcitabine, while disease stabilized in 2 patients for 21+ and 11 months; at 1200 mg/m^2, among 6 patients, there were 3 PR and disease stabilized in 1 for 9+ months; at 1400 mg/m^2, among 4 patients there were 2 PR and disease stabilized in 1 for 4+ months	Phase II (completed 5/02) ➢Europe (Italy) ❑ metastatic renal cell carcinoma ❑ 16 patients; metastatic sites were lung/pleura (n=10), bone (n=4), liver (n=4), and lymphnodes (n=3)	Oncology Institute (Bari, Italy), U Bari-Urology Clinic (Bari, Italy) ❑ Guida M, etal, ASCO02, Abs. 2420:151b

— continued on next page

Vinorelbine + cisplatin	Among 37 evaluable patients, hematologic toxicities included Grade 3 neutropenia (19%), anemia (12%), and Grade 3/4 infection (11%); Grade 3/4 nausea/vomiting was observed in 50% of patients	A total of 171 treatment cycles were administered; among 37 evaluable patients, there were 21 (56.7%) PR and 3 (8%) CR; PFS was 13.2 months, median duration of response was 17.5 months, and MST was 20.6 months	Clinical (begin 4/96, closed 11/98)➢South Africa ❑ Stage III/IV cervical carcinoma ❑ 42 chemotherapy-naive patients	National Hospital (Bloemfontein, South Africa), U Pretoria (Pretoria, South Africa) ❑ Goedhals L, etal, ASCO02, Abs. 858:215a
Docetaxel + vinorelbine	Severe toxicities were granulocytopenia (35%), leukopenia (31%), and febrile neutropenia (20%)	Among 39 patients evaluable for response there were 3 (6.5%) CR and 8 (17.5%) PR for an ORR of 24%; disease stabilized in 30%; at a medium follow-up of 30 months, TTP was 5.5 months, relapse-free survival was 6 months, median DFS was 13 months, and overall survival was 9 months	Phase II (completed 02) ➢Europe (Greece) ❑ recurrent ovarian cancer ❑ 46 patients with paclitaxel-pretreated ovarian cancer	Hellenic Cooperative Oncology Group (Athens, Greece) ❑ Aravantinos G, etal, ASCO02, Abs. 895:224a
Cisplatin + vinorelbine	Treatment was well tolerated; toxicities included Grade 3/4 myelosuppression and mild neurotoxicity and acute pain syndrome at the tumor site in 1 patient	Among 35 patients, there were 20 major objective responses for an ORR of 57%; there were 4 CR (11%) with a median PFS of 814 days and 16 PR (46%) with a median PFS of 184 days; disease stabilized in 6 patients and progressed in 9; median overall survival was 240 days, 855 in those with CR and 300 in those with PR	Phase II (completed 6/01) ➢Europe (Italy) ❑ recurrent, metastatic endometrial adenocarcinoma ❑ 35 patients	University of Palermo-Istituto Clinica Medica, Policlinico (Palermo, Italy) ❑ Gebbia V, etal, Ann Oncol, Jun 2001;12(6):767-72

***TTP**=time-to-progression **PFS**=progression-free survival*

imum of 36 patients will be accrued for this study, which is being chaired by Walter John Curran, Jr, MD, of the Radiation Therapy Oncology Group (RTOG).

In another multimodality approach, in a multicenter phase I clinical trial conducted in Japan, RT was administered in conjunction with vinorelbine combined with mitomycin and cisplatin. Among 29 patients with Stage III, unresectable nsclc, 22 (76%) responded to therapy. The recommended phase II dose is 6 mg/m^2 of mitomycin, 80 mg/m^2 of cisplatin and 20 mg/m^2 of vinorelbine (Atagi S, etal, ASCO02, Abs. 2683:216b).

In addition to evaluating vinorelbine in combination with other cytotoxic agents, clinical trials are ongoing combining this agent with novel regulatory agents. Cell Pathways (Horsham. PA) and GlaxoSmithKline are conducting an initial phase I/II clinical trial (protocol ID: EX2004) to study the combination of exisulind (Aptosyn) and vinorelbine as a first-line treatment for elderly patients with advanced nsclc. The two companies are sharing costs of this effort as well as information, while maintaining all rights to their respective products. The initial phase I/II safety and efficacy study, being conducted at the University of Wisconsin (Madison, WI), under the direction of principal investigator Joan Schiller, MD, is evaluating escalating doses of Aptosyn capsules (125-250 mg) twice daily on day 1 in combination with a standard regimen of IV vinorelbine (25 mg/m^2), administered weekly on a 4 week schedule.

Bladder Cancer

Vinblastine is being evaluated in combination regimens in advanced bladder cancer. A controlled, randomized, multinational, multicenter, phase III clinical trial was conducted by the International Collaboration of Trialists of the MRC Advanced Bladder Cancer Group to see whether addition of neoadjuvant CMV to radical surgery or RT, would improve survival in muscle-invasive transitional cell carcinoma of the bladder [T2 (Grade III), T3, T4a, N0/NX, M0]. Methotrexate (30 mg/m^2) and vinblastine (4 mg/m^2) were administered on days 1, 8 and cisplatin (100 mg/m^2) on day 2 of each cycle for 3 cycles. From November 1989 to July 1995 a total of 976 (CMV=491) patients (T3=58%, N0=65% and G3=88%) were entered by 106 centers in 20 countries. First results with a median follow-up of 4 years, reported in 1999 (Lancet, 14 Aug 1999;354(9178):533-40), showed a statistically nonsignificant 15% decrease in the risk of death after CMV (hazard ratio 0.85). After a median follow-up of approximately 7 years, a total of 559 patients have died. This is the largest trial making this comparison (Hall RR, ASCO02, Abs. 710:178a).

Long term follow-up of a prospective study of 3 courses of primary cisplatin, methotrexate and vinblastine chemotherapy with selective bladder preservation for muscle invasive carcinoma of the bladder after deep transurethral resection (TUR) of the primary bladder tumor in 40 consecutive patients with muscle invasive (Stage T2-T4 NX M0) transitional cell carcinoma (TCC) of the bladder was conducted at the Hospital Universitario Doce de Octubre (Madrid, Spain). Patients with disease in complete clinical remission after cycle 3 of therapy were treated with 3 additional chemotherapy courses. Patients in whom CR persisted after cycle 6 were closely followed with no further therapy until disease progression. CR was achieved in 21 (53%) patients after the first 3 cycles of therapy and PR occurred in 10 (25%), for an overall response rate (ORR) of 78%. Within a median follow-up of 78 months (range=70 to 109), the estimated 7-year progression-free and overall survival rates were 40% and 35%, respectively. The 7-year survival rate with a functional bladder for those in CR was 52%. Low grade, small tumor, absence of concomitant carcinoma *in situ* (CIS) and response to therapy, were all significant predictors for an increased probability of bladder preservation in univariate analysis. However, response to therapy was the only variable with independent prognostic value in the multivariate analysis. TUR of bladder tumor, followed by cisplatin, methotrexate and vinblastine chemotherapy, resulted in long-term bladder preservation in a significant proportion of responding patients, and may be an acceptable alternative to radical surgery in select patients with muscle invasive bladder cancer (De La Rosa F, etal, J Urol, Jun 2002;167(6):2413-8).

Other Cancers

Vinca alkaloids have been or are being investigated in a variety of solid tumors and hematologic malignancies.

Vinblastine has been investigated in combination with estramustine in hormone-refractory prostate cancer (HRPC). According to final results from a randomized, multicenter, phase III clinical trial, conducted by the Hoosier Oncology Group and Fox Chase Network, a combination regimen of estramustine and vinblastine improved survival of patients with HRPC. This trial compared single-agent IV vinblastine (4 mg/m^2), administered to 98 patients weekly for 6 weeks every 8 weeks, with the combination of vinblastine plus oral estramustine phosphate (600 mg/m^2), administered daily to 95 patients. The combination arm was clearly superior to vinblastine monotherapy for secondary endpoints of PFS (3.7 months versus 2.2 months) and proportion with sustained ≥50% decrease of serum PSA (25.2% versus 3.2%). Regarding toxicities, in the combination arm incidence of Grade 3/4 granulocytopenia was significantly lower (8% versus 27%), although nausea and edema were more frequent. MST was 12.5 months in the combination arm and 9.4 months in the vinblastine monotherapy arm. Potential prognostic factors were pretreatment serum LDH, hemoglobin (Hgb), alkaline phosphatase, baseline PSA and post-treatment decrease of PSA by >50% within the first 8 weeks were significant in the univariate analysis. Significant factors in the multivariate model were LDH, alkaline phosphatase, and Hgb. Pretreatment and post-treatment PSA change did not improve the multivariate survival model. Positive results with this older regimen strengthen the hypothesis that the antimicrotubule properties of estramustine combined with other microtubule inhibitors is a more effective treatment for HRPC (Hudes G, etal, ASCO02, Abs. 704:177a).

In digestive malignancies, although vinorelbine has not shown significant activity in advanced pancreatic adenocarcinoma, the drug may be useful in 5-FU-resistant metastatic colorectal cancer. Vinorelbine has also shown activity in advanced, refractory squamous cell carcinoma of the esophagus (SCCE), either as monotherapy or in combination with other drugs and/or RT (Exhibit 1). In a phase II clinical trial, conducted at the Istituto Nazionale per lo Studio e la Cura dei Tumori (Milan, Italy), 17 patients with advanced or relapsed SCCE, were treated with vinorelbine (30 mg/m^2) every two weeks; 11 patients had been previously treated with chemotherapy (cisplatin and 5-FU) and/or RT at the time of first diagnosis. There were 4 (25%) PR among 16 patients assessable for activity; 3 of the responders had been pretreated. A significant improvement of dysphagia was seen in 4 of 11 symptomatic patients. Toxicity was mild, with only one episode of Grade 4 neutropenia and constipation. Single-agent vinorelbine was active against SCCE, even in patients previously treated with cisplatin and 5-FU. Its good tolerability and the possibility of relieving symptoms such as dysphagia strongly suggest the addition of vinorelbine to combination regimens with cisplatin as front-line chemotherapy for SCCE (Bidoli P, etal, Tumori 2001 Sep-Oct;87(5):299-302). In a recently completed phase II clinical trial of a vinorelbine and cisplatin combination in 71 patients with metastatic SCCE, the response rate was 37% with a median duration of response of 7.7 months. Main toxicities were hematologic with a 41% incidence of Grade 3 /4 granulocytopenia and infection, vomiting and fatigue. This 2-day regimen appears at least as active and less toxic than the standard 5-day 5-FU and cisplatin regimen (Conroy T, Crit Rev Oncol Hematol, May 2002;42(2):173-8).

Vinca alkaloids are also being combined with regulatory agents to treat various malignancies. A multicenter phase I/II clinical trial (protocol ID: UCLA-0011010; NCI-4292; UCLA-NCI-4292) was initiated in May 2001 to study the effectiveness of combination chemotherapy (daunorubicin, vincristine and oral prednisone) plus STI571 (Gleevec; Novartis) in 46 patients with chronic myelogenous leukemia (CML) or acute lymphocytic leukemia (ALL). Ronald Paquette of the Jonsson Comprehensive Cancer Center (Los Angeles, CA) is Study Chair. Patients not previously treated with STI571 are treated with oral STI571 on days 1-35. Those treated with STI571 for at

least 28 days are administered oral STI571 on days 22-35. All patients are treated with IV daunorubicin over 2-3 minutes on days 1-3, IV vincristine over 1 minute on days 1, 8, 15, and 22, and oral prednisone on days 1-28. A second course, in the absence of disease progression or unacceptable toxicity, is administered to patients with more than 5% residual blasts in bone marrow on day 28. Cohorts of 3-6 patients are treated with escalating doses of daunorubicin until MTD is determined.

In an NCI-sponsored dose-escalation phase II clinical trial (protocol ID: 00-C-0044), vinorelbine is being coadministered with XR9576 (tariquidar), a selective potent inhibitor of the action of the P-gp pump to prevent MDR under development by Xenova (Berkshire, United Kingdom), in collaboration with QLT (Vancouver, BC, Canada), in up to 30 patients to analyze the interaction between these two agents. Patients undergo baseline technetium 99m sestamibi scanning on day 1, and are treated by XR9576 IV over 30 minutes, followed by technetium 99m sestamibi scanning on days 3 or 4 of course 1. At least 10 days following the initial XR9576 dose, patients are administered course 2 of therapy consisting of vinorelbine IV over 6-10 minutes on day 1 and XR9576 IV over 30 minutes followed 30 minutes later by vinorelbine IV over 6-10 minutes on day 8. Some patients are treated with the combination of XR9576 and vinorelbine on day 1, and vinorelbine IV alone on day 8 for course 2. Patients are administered subsequent courses of therapy on day 8 of course 2, consisting of XR9576 followed by vinorelbine on days 1 and 8. Treatment repeats every 3 weeks in the absence of disease progression or unacceptable toxicity, with vinorelbine dose escalation until MTD is determined. The study's PI is James Abraham of the NCI.

In another trial, the effectiveness of XR9576, combined with docetaxel, doxorubicin, or vinorelbine, is being investigated in an NCI-sponsored phase I clinical trial (protocol ID: NCI-01-C-0091A) in 24 children with relapsed or refractory solid tumors. IV XR9576 is administered over 30 minutes on days 1 and 3 of course 1, and on day 1 of all subsequent courses, and IV doxorubicin over 15 minutes on day 3 of course 1 and on day 1, IV vinorelbine over 10 minutes on days 3 and 10 of course 1 and days 1 and 8, or IV docetaxel over 60 minutes on day 3 of course 1 and on day 1 of all subsequent courses. Patients treated with doxorubicin or docetaxel are treated with filgrastim (G-CSF) subcutaneously beginning on day 5 of course 1 and day 3 of all subsequent courses and until blood counts recover. This study is being conducted under the direction of Frank Milton Balis, MD, of the Pediatric Oncology Branch of the NCI (Bethesda, MD).

NOVEL VINCA ALKALOID ANALOGS AND FORMULATIONS

With the exception of vinflunine, there has been little activity in the development of novel Vinca alkaloids.

Anhydrovinblastine (AVLB)

Anhydrovinblastine (AVLB), a precursor of vinblastine, is prepared by the enzymatic coupling of catharanthine and vindoline using an iron-containing compound such as peroxidase. AVLB differs from vinblastine in that it possesses a double bond at the 3',4' position of the catharanthine nucleus rather than the hydroxyl group that is present in the parent structure (Goodbody AE, etal, Planta Med, Apr 1988;54(2):136-40).

In preclinical studies involving human tumor xenografts of nsclc and cervical cancer, AVLB showed superior activity to that of both vincristine and vinorelbine at equitoxic doses. In studies conducted at the British Columbia Cancer Center (Vancouver, BC, Canada) AVLB has shown significant cytotoxic potential against a panel of human cancer cell lines, and significant activity against the human H460 nsclc tumor xenograft in SCID/Rag-2 mice. In addition, *in vitro* cytotoxicity assays have shown AVLB to have IC_{50} values ranging from 20-24 nM against the H460 human nsclc, C-4 human cervical carcinoma, K562 human leukemia, and A431 human epidermoid cell lines. Although AVLB was approximately 10-fold less active than vinorelbine when tested *in vitro* against the same cell lines, in solid tumor efficacy experiments *in vivo* it was found to be more potent (Natashia L, etal, AACR98, Abs. 1137:166).

In March 1999, an open label, dose-escalation phase I clinical trial (protocol IDs: RPCI-DS-9844, NCI-G99-1517, IGT-RPCI-DS-9844) of AVLB in the treatment of refractory solid tumors, including nsclc, was initiated at the Roswell Park Cancer Institute (Buffalo, NY), and Dartmouth-Hitchcock Medical Center (Hanover, NH) with Nithya Ramnath of Roswell Park as Study Chair. Investigators are also determining drug kinetics, and looking for evidence of antitumor activity. Although this phase I study involves patients who may have various forms of cancer, further studies will only enroll patients with nsclc. In this trial, AVLB was infused IV over 1 hour at doses of 2.5 mg/m^2 (n=1), 5 mg/m^2 (n=3), 10 mg/m^2 (n=l), or 16.5 mg/m^2 (n=1), administered every 3 weeks for 2 or more cycles. According to a preliminary report on 6 patients with squamous cell carcinoma of the lung (n=1), adenocarcinoma of the colon (n=2), adenocarcinoma of the breast (n=1), and soft tissue sarcoma (n=2), treated with prior chemotherapy, who enrolled in the phase I trial of AVLB, one patient treated at 5 mg/m^2 developed Grade 2 right abdominal pain, anorexia and an elevated serum amylase shortly after one cycle; no other drug-related toxicities >Grade 1 were observed. In terms of results, 4 patients went off the study after 2 cycles because of progressive disease, disease stabilized in one patient after four cycles, at the 10 mg/m^2 dose level, and 1 patient at the 16.5 mg/m^2 dose level was not as yet evaluable for response (Schwartz GN, etal, AACR00, Abs. 3895:612).

According to final results, among 24 patients (nsclc=11, colorectal cancer=5, soft tissue sarcoma=4, and miscella-

neous=4) previously exposed to a median of 3 chemotherapy regimens (range=1-6), treated with 51 courses of AVLB at doses ranging from 2.5 to 30 mg/m^2, Grade 2 toxicities including infusional hypertension, anemia and dizziness were noted in 3 patients at 16.5 mg/m^2. Among 6 patients treated at 25 mg/m^2, DLT included Grade 4 constipation and Grade 3 nausea and vomiting in 2 patients. Because this dose exceeded the MDT and only mild toxicities were seen at 16.5 mg/m^2 and the increment from 16.5 mg/m^2 to 25 mg/m^2 represented a 50% increase, an intermediate dose of 21 mg/m^2 was evaluated in 7 patients (6 were evaluable for toxicity). MDT was established at 21 mg/m^2, based on 1 case of Grade 3 nausea and vomiting (DLT) and Grade 2 constipation. Stable disease was noted in 1 patient with metastatic sarcoma to the lungs, treated at 10 mg/m^2 and in 3 patients with metastatic nsclc treated at doses of 21 mg/m^2 and 25 mg/m^2 (Ramnath N, etal, ASCO02, Abs. 421:106a).

AVLB was licensed from the University of British Columbia (Vancouver, BC, Canada) by IGT, now Prescient NeuroPharma (Vancouver, BC, Canada). In January 2000, the University of British Columbia was issued patent #6,011,041 by the United States Patent and Trademark Office (USPTO) covering the use of AVLB as an antineoplastic agent in the therapeutic treatment of cancer.

In January 2002, Prescient NeuroPharma finalized an agreement to license exclusive rights to AVLB to Access Oncology (New York, NY), to develop and market AVLB worldwide, with the exception of Latin America and the Far East. Including development costs, the value of the deal is in excess of $25 million plus royalties. Access Oncology agreed to make upfront payments of $1.25 million, milestone payments of $17.5 million, pay royalties on net sales and fund all further development of AVLB, including the completion of phase II and III clinical trials.

Liposomal Formulations of Vinblastine and Vinorelbine

Inex Pharmaceuticals (Burnaby, BC, Canada) has been evaluating the antitumor activity of liposomal formulations of vinblastine and vinorelbine in comparison to free drug. Both Vinca alkaloids have been encapsulated in 100 nm sphingomyelin:cholesterol (SM:CH) vesicles at high trapping efficiency (>90%) using an ionophore loading procedure. The liposomal formulations of vinblastine and vinorelbine exhibited good drug retention and stability properties. These vesicles containing vinblastine or vinorelbine at high drug-to-lipid (D/L) ratios exhibited therapeutically optimal drug release properties. Improved antitumor efficacy of these liposomal formulations compared to free drug has been demonstrated in several murine and human xenograft models, including leukemia P388, melanoma B16, renal cancer RXF393, breast cancer MX-1, and nsclc H460 for vinblastine and colon cancer HT29 for vinorelbine (Hope MJ, etal, AACR02, Abs. 2081:419).

Vincristine Sulfate Liposome Injection (VSLI)

Vincristine sulfate liposome injection (VSLI), also referred to as Onco TCS, is a proprietary construct under development by a joint venture formed by Inex Pharmaceuticals and Elan (Dublin, Ireland and New York City, NY). Onco TCS is a proprietary lipid envelope-based drug delivery system that optimizes delivery of IV drugs to tumors. The key component of TCS technology is PEG-ceramide, a fusion regulator and exchangeable polymer that consists of ceramide lipids, derived from sphingomyelin and cholesterol (55:45 mole ratio), linked to an immunologically inert polymer, polyethyleneglycol (PEG) molecule; the lipids are used to form liposomes containing various biological agents or drugs (Webb MS, etal, Biochim Biophys Acta, 17 Jul 1998;1372(2):272-82). PEG-ceramide's role is to stabilize the TCS formulation for a sufficient length of time to allow accumulation at the disease site. Thereafter, PEG-ceramide dissipates from the formulation, promoting intracellular delivery of the drug. Vincristine-loaded TCS has demonstrated an 80- to 100-fold increase in circulation time over conventional doses of the free drug.

Targeted delivery enables high concentrations of the drug to accumulate at the tumor site, improving the effectiveness and reducing side-effects to healthy tissues (Boman NL, etal, Cancer Chemother Pharmacol 1996;37(4):351-5). The stability of Onco TCS enables it to circulate in the bloodstream for several hours after injection and to preferentially accumulate at the tumor site, while the optimized release rate of vincristine from the TCS enables the drug to attack tumor cells through a number of cell life cycles. In preclinical evaluations, VSLI exhibited a prolonged circulation time relative to free vincristine sulfate, and also released vincristine at a slow rate. In tumor-bearing mice administration of VSLI resulted in the accumulation of liposomes in tumor tissues, thus enhancing drug levels within target tissues. When VSLI and free vincristine were compared at the same dose in murine tumor models, VSLI demonstrated enhanced activity. VSLI conferred greater therapeutic activity than did free vincristine in five xenograft tumor models of breast, lung and prostate cancer and Kaposi's sarcoma (Sweet H, etal, AACR02, Abs. 1330:268).

One of the leading indications for Onco TCS is non-Hodgkin's lymphoma (NHL). Onco TCS has demonstrated the capacity to significantly reduce the size of tumors in patients with advanced-stage NHL, after standard chemotherapy treatments have failed. An IND was filed with the Canadian HPB to begin phase II clinical trials for this indication in September 1997 and these trials began in January 1998, conducted by lead investigator Andreas Sarris, MD, at M. D. Anderson Cancer Center (Houston, TX). All trial participants were diagnosed to have either low- or intermediate-grade NHL. Included in the response group were patients with B-cell and T-cell lymphomas as well as a patient with mantle-cell lymphoma. For the first

21 evaluable patients, ORR was 45%. In every patient who responded to Onco TCS treatment, tumor size was reduced at least 50%. Onco TCS was well tolerated.

In another phase II trial conducted at M. D. Anderson Cancer Center, heavily pretreated (median number of prior regimens=3, range=1-10, including vincristine in all patients, of whom 51% were refractory to their last regimen) patients with relapsed NHL or acute lymphocytic leukemia (ALL) were treated with IV liposomal vincristine (2.0 mg/m^2), over 60 minutes, every 14 days. Of the 155 administered injections, 138 (89%) were at the 2.0 mg/m^2 level. Median injected dose was 3.8 mg (range=2.6-4.8 mg), and median number of injections was 4 (range=1-12). Responders were administered up to 12 injections. Among 34/51 patients evaluable for response, there were 14/34 (41%) responders with NHL. Response rates were 10% for indolent, 71% for transformed, and 47% for aggressive NHL, but the 95% confidence intervals overlapped. Median PFS was 5.5 months for responders. Grade 3/4 motor or sensory neuropathy was seen in 11 patients; 5 who already had prior neuropathy, terminated therapy. Fever was detected in 3 patients, but there were no toxic deaths (Sarris AH, etal, Ann Oncol, Jan 2000;11(1):69-72). According to a later report, among 68 of 83 enrolled patients evaluable for response, there were 24 (35%) responses. Median number of prior regimens was 3 (range=1-25), and included vincristine in all patients and 10% were refractory to their initial and 40% to their last regimen. Of the 291 administered doses, 262 (90%) were at 2.0 mg/m^2 with median dose being 3.8 mg (range=2.6-5.0 mg); median number of injections per patient were 4 (range=1-12). Responses according to histology are shown below:

Indication	Indolent	Transformed	Aggressive	Post BMT	Total
Number (#)	15	12	38	3	68
CR+PR (#)	2	5	17	0	24
CR+PR (%)	13	42	45	0	35

Median PFS of responders was 5.5 months. Regarding toxicities, Grade 3/4 neuropathy was seen in 14 patients resulting in termination of therapy in 8. There was no serious myelosuppression or toxic deaths. Therefore, liposomal vincristine at full doses was feasible, active, and well tolerated (Sarris AH, etal, ASH99, Abs. 412).

In March 2001, a pivotal multicenter phase II clinical trial (protocol ID: DM00-009) of Onco TCS, in combination with rituximab as a first-line treatment for aggressive B-cell NHL, was initiated at the University of Texas, M. D. Anderson Cancer Center, under PI Maria Rodriguez, MD. Patients are treated with standard dose CHOP chemotherapy, and VSLI (2.0 mg/m^2) over 1 hour on day 1, plus rituximab (375 mg/m^2), administered every 21 days, for 6 to 8 courses. Objectives include determining tolerance and efficacy of this combination. Among 23 evaluable patients >60 years-of-age with aggressive NHL, there were 12 CR (52%), 5 unconfirmed CR (22%), and 1 (4%) PR, for an overall response of 78%. Treatment was discontinued after cycle 5 in one patient because of Grade 3 sepsis. Neuropathy was mild (Grade 0/2). After a median follow-up of 6 months, there were no recurrences. All in all, 73 patients had been enrolled in the study at the time of this report (Rodriguez MA, etal, ASCO02, Abs. 1132:284a).

As of March 2002, Inex had enrolled at least 100 patients in a phase II/III multicenter clinical trial (protocol ID: INEX-CA99002; UCLA-0002028; HSC-00-205; DS 00-18) at medical centers across North America, for treatment of relapsed aggressive NHL The trial was initiated in June 2000, after Inex obtained approval from the FDA in November 1999. Eligible enrollees were diagnosed with recurrent adult immunoblastic large-cell lymphoma, recurrent adult T-cell leukemia/lymphoma, recurrent adult diffuse large-cell lymphoma, and anaplastic large-cell lymphoma, who had failed previous chemotherapy. Objectives include evaluating tumor response and safety, and determining duration of response, TTP, and survival. Patients are being administered VSLI IV over 1 hour every two weeks for up to 12 cycles in the absence of disease progression or unacceptable toxicity. Myron Czuczman, MD, is the PI at the Roswell Park Cancer Institute and Christos Emmanouilides, MD, is the PI at the UCLA Jonsson Cancer Center. Barbara Gallimore of Inex Pharmaceuticals is the Study Chair.

In November 2001, Inex initiated two pilot phase II clinical trials to evaluate Onco TCS, in combination with etoposide, in 35 patients with relapsed aggressive NHL. The primary objectives of the study are to generate safety data of this combination and preliminary efficacy data. Patients are being administered etoposide every day for 14 days, every 28 days, and Onco TCS every two weeks for up to 12 cycles. The first trial commenced at Norfolk and Norwich University Hospital in the UK, under the direction of Gillian Turner, MD. The second pilot trial will be conducted at three centers in the USA.

In September 2001, Inex initiated two pilot open-label phase II clinical trials evaluating Onco TCS in combination with rituximab as a treatment for relapsed B-cell aggressive NHL. Each trial is evaluating Onco TCS with Rituxan in 14 patients. The primary objective of the trials is to generate safety data of the combination and preliminary efficacy data. One of the trials is being conducted at the University of Leeds, in the UK, under the direction of Gareth Morgan, MD, and the other is at the University of California, San Francisco, under the direction of Lawrence D. Kaplan, MD.

In addition to NHL, Onco TCS is being investigated in combination regimens in various solid tumors. In August 2000, Inex initiated a phase II clinical trial (protocol ID: HSC-00-140) in patients with sclc who relapsed after first-line treatment with a combination of etoposide and cisplatin, or who were refractory to or had relapsed after second-line

therapy, as well as those who could not tolerate etoposide and cisplatin, being conducted at the Arizona Cancer Center and the Southern Arizona VA HealthCare System (Tucson, AZ). In May 2002, according to interim results from the phase II clinical trial, Onco TCS was shown to be active in treating patients with sclc with a low toxicity profile. Results were based on 23 evaluable patients, among whom there were 2 PR while disease stabilized in 4. The trial is continuing and will enroll approximately 50 patients, with final results are expected to be released in 2003.

As of May 2002, a phase II clinical trial of Onco TCS was ongoing in children and adolescents with relapsed solid tumors and leukemia, being conducted at the University of Texas, M.D. Anderson Cancer Center. Tumor subgroups include soft tissue sarcoma, bony sarcoma, Wilms' disease, lymphoma, and ALL. In February 2002, Inex initiated a phase II clinical trial (protocol ID: ID01-597) of Onco TCS for the treatment of Hodgkin's disease. This trial is also being conducted at the University of Texas, M. D. Anderson Cancer Center. Andre Goy, MD, is the PI. The main objective of this trial is to generate preliminary safety and efficacy data for Onco TCS. A maximum of 35 patients will be accrued for this study.

Vinflunine

Vinflunine (20',20'-difluoro-3',4'-dihydro-vinorelbine), a novel bi-fluorinated derivative of vinorelbine, was created using rational design by modifications in the D' ring of anhydrovinblastine by chemists at Pierre Fabre. Vinflunine (Javlor) is a semisynthetic Vinca alkaloid obtained by the selective introduction, in superacidic medium, of two fluorine atoms at the 20' position of vinorelbine (Fahy J, Curr Pharm Des, 21 Sep 2001;7(13):1181-97). Vinflunine is a second-generation Vinca alkaloid.

Certain qualitative and quantitative differences between first- and second-generation agents became evident when the pharmacologic profile of vinflunine was compared, based on *in vitro* and *in vivo* experimental preclinical data, with its parent molecule and the classic Vinca alkaloids, such as vincristine or vinblastine. While vinflunine is an inhibitor of tubulin assembly, its tubulin-binding properties are qualitatively and quantitatively different. Like the first-generation drugs, vinflunine appears to interact at the Vinca binding domain, and to induce tubulin structural changes favoring an inhibition of GTP hydrolysis. However, at concentrations of ≤100 μM, vinflunine does not prevent vincristine binding to unassembled tubulin, and only weakly inhibits binding of vinblastine or vinorelbine. Based on *in vitro* analysis of the inhibitory effects of these agents on microtubule polymerization, their comparative capacities to bind to tubulin can be ranked as vincristine>vinblastine>vinorelbine>vinflunine (Kruczynski A, etal, Biochem Pharmacol, 1 Mar 1998;55(5):635-48, Ngan V, etal, AACR99, Abs. 1897, and Hill BT, Curr Pharm Des, 21 Sep 2001;7(13):1199-212).

In preclinical experiments vinflunine showed higher antitumor activity *in vivo* relative to vinorelbine when administered intraperitoneally (IP), and pronounced activity in 2/2 human melanoma xenografts as an IV injection. Major antitumor activity of vinflunine was first encountered using the IV-grafted P388 murine leukemia model when a single IP dose resulted in a 100% increased life span. When IV vinflunine was evaluated in 8 tumor models implanted subcutaneously in nude mice, significant antitumor activity was observed in 2/2 pancreatic cancers (PAXF 736 and PAXF 1657), in 1/3 nsclc (LXFA 629) and in 1/3 renal cancers (RXF 1220). Tumor regressions were observed in PAXF 1657, PAXF 736 and LXFA 629 xenografts while there was no change in the RXF 1220 model (Fiebig, H-H, etal, AACR02, Abs. 1331:268).

Using a P388 model and combining optimal single doses of vinflunine with those of three DNA damaging agents, namely mitomycin C, cisplatin or F11782, a novel epipodophylloid in development by Pierre Fabre, significantly superior results were obtained compared to single agent treatment. Body weight loss was minimal indicating increased antitumor activity without additional toxicity. Combining minimally effective doses of vinflunine with those of mitomycin C, F11782 or cisplatin, also proved additive. In contrast, a combination of vinflunine with either doxorubicin or etoposide did not enhance antitumor activity, while certain combinations of vinflunine and 5-FU resulted in a worse outcome (Kruczynski A, etal, AACR02, Abs. 1333:268).

Additional *in vivo* preclinical studies have shown that at low subtherapeutic doses, vinflunine significantly inhibited the bFGF-induced neovascularization in a pellet of reconstituted basement membrane (Matrigel) injected subcutaneously into C57BL/6 mice. Also, intermittent IV administration of vinflunine resulted in potent tumor growth inhibition of 92% of intracecally grafted LS-174T human colorectal tumors (orthotopic model). Vinflunine, administered IV as multiple injections at the highest nontoxic dose of 20 mg/kg, also reduced significantly the number of experimental hepatic metastases induced by intrasplenic injection of LS-174T colon cancer cells. These results demonstrate significant antitumor activity of vinflunine in human orthotopic colon cancer and experimental liver metastasis models, and suggests an antiangiogenic activity for vinflunine at low doses (Kruczynski A, etal, AACR02, Abs. 1332). The *in vivo* antivascular effects of vinflunine, identified at doses below those required for optimal antitumor activity, coupled with its demonstrated potential value as a component of combination regimens, and the finding that resistance to vinflunine was generated far less readily than to vinorelbine, augur wellfor the ongoing clinical development of this new agent.

Several phase I clinical trials with vinflunine were completed in Europe in 2000 using various dosing schedules. Phase II clinical trials with vinflunine in treatment of renal

and bladder cancer and malignant melanoma are currently being completed in Europe, South Africa and Australia.

In a multicenter, dose-escalation, phase I clinical trial of vinflunine, the drug's safety and pharmacokinetics were studied in patients with solid tumors, using weekly and every-3-weeks dosing schedules. Between October 1999 and June 2000, 14 patients (melanoma=3, mesothelioma=2, gastrointestinal cancer=3, other tumor sites=6) who had been treated with at least one line of chemotherapy for advanced disease were administered vinflunine as a 10-minute IV infusion at weekly doses ranging from 120 mg/m^2 to 190 mg/m^2. A dose-proportional increase in blood concentrations was observed for vinflunine and its metabolites, and hematologic toxicity appeared to be additive. At the 190 mg/m^2 weekly dose level, 2 of 3 patients experienced DLT in the form of Grade 4 infection (n=1) and Grade 3 transaminases (n=1); at 150 mg/m^2, 3 of 5 patients experienced DLT in the form of Grade 4 neutropenia (n=2) and Grade 4 febrile neutropenia (n=1). There was 1 MR in a patient with pretreated renal cell cancer. The recommended dose for phase II clinical trials using this schedule in pretreated patients was established as 120 mg/m^2 per week (Delord JP, etal, ASCO01, Abs. 441:111a, and Puozzo C, etal, ASCO01, Abs. 2107:89b).

Between October 1999 and July 2000, 16 patients with solid tumors (colorectal=4, mesothelioma=3, cervical cancer=2, sarcoma=2, melanoma=2, and other tumor sites=3) were treated with 10-minute IV infusions of vinflunine at doses ranging from 170 mg/m^2 to 210 mg/m^2, on days 1 and 8, every three weeks. At 210 mg/m^2, 3 of 6 patients experienced DLT during the first treatment cycle, with Grade 3/4 constipation occurring in 2 patients and Grade 3 myalgia in 1. At 190 mg/m^2, 2 of 3 patients experienced DLT (Grade 3 constipation=1 and neutropenia=1). At 170 mg/m^2, only 2 of 6 patients developed DLT, one with Grade 4 constipation and febrile neutropenia, and one with Grade 3 chest pain. Based on these results, the recommended dose for vinflunine on this schedule was established as 170 mg/m^2 (Zorza G, etal, ASCO01, Abs. 2070:80b, and Johnson P, etal, ASCO01, Abs. 2100:88b).

In the first phase I clinical study, escalating doses of vinflunine were administered IV, once every 21 days, to patients with advanced malignancies. Between December 1998 and December 1999, 25 patients with a variety of cancers (unknown primary site=2, renal cell cancer=5, gastrointestinal cancer=8, breast cancer=2, ovarian cancer=1, nsclc=2, cervical cancer=1, and sarcoma=4) were treated at 8 different dose levels, with a starting dose of 30 mg/m^2 as a 10-minute infusion. DLT, consisting of Grade 4 neutropenia (n=1) and febrile neutropenia (n=1), Grade 3/4 abdominal cramps (n=2), Grade 3 constipation (n=1), and Grade 3 esophagitis (n=1), was experienced by 5 patients at 400 mg/m^2. At this same dose level, 1 patient with nsclc, previously irradiated for a superior vena cava syndrome, developed reversible Grade 3 heart failure and Grade 3 dyspnea, believed to be drug related. MTD was established as 400 mg/m^2 every 3 weeks. Both breast cancer patients (one with liver involvement) experienced a PR, as did one patient with renal cell carcinoma (Fumoleau P, etal, NCI-EORTC-AACR00, Abs. 576).

MEETING COVERAGE

REFLECTIONS FROM THE MEETINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR), ARRIL 5-10, 2002, SAN FRANCISCO, CA AND THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO), MAY 18-21, 2002, ORLANDO, FL

Although no breakthrough findings were reported at the 2002 meeting of either the AACR or ASCO, an incredible progress has been made in understanding the mechanism of action of the numerous agents in clinical or preclinical development acting on various regulatory pathways associated with tumorigenesis and metastasis. Looking collectively at early results from various clinical trials, one cannot help but surmise that the management of cancer as another chronic disease may be at hand. Combination chemotherapies using several cytotoxics acting on different mechanisms is resulting in high response rates without the severe toxic effects of high-dose approaches tried in the past. Looking at the results of phase II clinical trials of combination chemotherapies summarized in the article on Vinca alkaloids in this issue, it is obvious even very high response rates appear to be squandered as malignancy persists, continues to metastasize or returns. Although multidrug (MDR) resistance eventually diminishes the effectiveness of even the most well thought combinations, it may be that its effects will be mitigated by regulatory agents that start working where cytotoxics left off.

Have we already dealt cancer a major blow but don't know it yet? Although no one expressed such a sentiment in so many words, most investigators suggested that the less than spectacular results emanating from the many clinical trials of single-agent or combinations of regulatory/cytotoxic agents may be greatly enhanced by combining cytotoxic agents with a cocktail of modulators of various signaling pathways, angiogenesis inhibitors, and immunotherapeutics/vaccines. The next wave of clinical trials will consist of combinations of many different cytotoxics, cytostatics/regulatory agents and immunotherapies, addressing more than 20 major cancer indications, creating an incredibly complex clinical, translational, regulatory and commercial environment.

Rapidly expanding knowledge of the relevant pathways involved in tumorigenesis and progression, with hundreds of markers identified and their activity delineated, is helping create agents with high affinity for their targets. In addition, exquisitely accurate *in vivo* approaches allow

investigators to visualize the activities of these agents in real time, and *in vitro* diagnostic, prognostic and disease monitoring methodologies increase the physician's ability to design tailored therapies, intervene promptly, and provide vigilant follow-up. Evidence-based medicine (EBM) will have a great impact on the practice of oncology as new approaches become adopted into patient care. FUTURE ONCOLOGY plans to publish comprehensive reports on all the topics described below.

NOVEL AGENTS IN EARLY-STAGE CLINICAL DEVELOPMENT

Numerous novel agents are either in phase I clinical development or have completed phase I clinical trials with interim/final reports presented during the 2002 AACR and ASCO meetings (Exhibit 2). Many of these drugs have advanced or will be advancing to phase II clinical trials.

MODULATION OF SIGNALING PATHWAYS

Drugs targeting specific tumor characteristics, such as overexpression of certain well established markers (EGFr, ras, etc.), came up short both as monotherapies and in combination with cytotoxic agents in treating late-stage advanced or metastatic refractory or recurrent disease. It has become clear that additional research is required to better define the targets and the relevant disease pathways. Also, treatment success requires use of a combination of regulatory agents. It is imperative that developers of regulatory anticancer agents begin the arduous task of evaluating their drugs in combination with others acting on different mechanisms and addressing different tumor markers or signaling pathways.

Effective use of signaling pathway modulators will probably require a thorough understanding of the nature of each patient's tumor. Not only does the type, and stage/grade of the tumor must be established, but the tumor would need to be profiled in full regarding the status of several relevant markers. These may vary by type of cancer, stage/grade of tumor and by patient. In every group of patients treated by any approach deemed effective, amid all the failures, there are always a few long-term survivors. This at first glance irrational behavior of this disease must have a rational explanation which, in turn, may provide the key to unlock its mysteries and manage its course.

INHIBITION OF ANGIOGENESIS, LYMPHOANGIOGENESIS AND DESTRUCTION OF EXISTING TUMOR VASCULATURE

Angiogenesis inhibitors and antivascular agents that prevent tumor progression and metastasis have yet to revolutionize the treatment of cancer as promised several years ago. The learning curve proved to be longer than anyone expected. Interestingly, in some cases tumor growth was initially enhanced by administration of antiangiogenic agents, before subsequent evaluations demonstrated inhibition of new vessel formation. Now that lymphatic-specific vascular endothelial growth factors (VEGF-C and VEGF-D) and molecular cell-surface markers such as the VEGFR-3 receptor have been identified, the definition of angiogenesis in cancer needs to be updated. Recent developments have highlighted the importance of lymphatic epithelial cells, which could become the next focus for angiogenesis and metastasis research (Karkkainen MJ, etal, Nat Cell Biol, Jan 2002;4(1):E2-5).

CHEMOPREVENTION

Because transformation of normal tissue to precancerous and then to a fully malignant stage, involves a process that evolves over years, sometimes decades, it was always believed that early intervention would block disease progression. Although some precancerous conditions may be treated surgically, patients are reluctant to undergo such an invasive procedure that may need to be repeated throughout a patient's lifetime, as is the case with benign colon polyps.

Despite the rationale for early medical intervention, in the past, cumbersome methodologies required to establish efficacy, involving large trial populations and many years of follow-up, have discouraged companies from pursuing this line of research. The difficulty in conducting such research is illustrated by the fact that, currently, only five drugs have been approved for treating precancerous conditions, such as intraepithelial neoplasia (IEN) of the skin, bladder, breast, and colon.

However, all this should change if the recommendations of the AACR Task Force, cochaired by Drs. Joyce O'Shaughnessy, Gary J. Kelloff, Gary B. Gordon, and Richard Pazdur, and comprising over 50 survivor advocates and cancer researchers representing basic, translational, and clinical research from throughout the USA, are heeded by the FDA. The Task Force recommended that clinical trials of new drug treatments for IEN be designed to target high-risk populations only, i.e., groups at risk for developing the most severe kinds of IEN associated with a well established link between precancerous lesions and invasive cancer. The endpoint of such trials would be elimination of high-risk IEN. Examples of high-risk populations with IEN include those with severe Barrett's esophagus, high-grade prostatic intraepithelial neoplasia (PIN), women with cervical dysplasia, those with abnormal breast cells who have been previously treated for breast cancer or have a family history of breast cancer, etc. Change in endpoints from prevention of disease to documentation of local change in lesions or markers, represents a major departure from the long-standing methodology in assessing the efficacy of chemoprevention approaches and promises to revitalize clinical research in this sector.

EVIDENCE-BASED PRACTICE

In recent years, there has been increasing discussion of evidence based medicine (EBM). Its importance and ratio-

Exhibit 2
Novel Anticancer Agents in Phase I Clinical Trials as Reported at the 2002 Meetings of the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO)

Developer ❑ Affiliate(s)	Generic Name ❑ Number ❑ Brand Name	Description ❑ Administration Route	Status ❑ Indication(s)
Abbott Laboratories	ABT-510	Thrombospondin-mimetic peptide ❑ bolus, subcutaneous (SC)	Phase I (closed 02)➢Europe ❑ advanced solid tumors
Access Pharmaceuticals ❑ U London, Polymer Laboratories, NDDO Oncology	AP5280, AP-5280 (AP5070)	Platinum-polymer delivery system designed to deliver high concentrations of cisplatin directly to solid tumors; a soluble, synthetic polymer conjugate formulation of cisplatin ❑ IV	Phase I (begin 9/01, ongoing 5/02) ➢Europe (UK) ❑ first-line treatment of advanced solid tumors
AlbaPharm ❑ National Cancer Institute (NCI)	BL22 [RFB4(dsFv)-PE38]	Recombinant immunotoxin containing the variable domain (Fv) of the anti-CD22 MAb RFB4.20,21 fused to PE38, a fragment of Pseudomonas exotoxin, containing domains responsible for cell death but lacking the domain necessary for cell binding ❑ IV	Phase I (completed 02)➢USA ❑ refractory hairy-cell leukemia (HCL); phase I (begin 7/01, ongoing 5/02) ➢USA ❑ chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), B-cell, prolymphocytic leukemia; phase I (begin 12/98)➢USA ❑ B-cell NHL
AstraZeneca ❑ Angiogene Pharmaceuticals	ZD6126 (previously ANG453)	Colchicine prodrug that disrupts the tubulin cytoskeleton of neoendothelial cells causing selective destruction of tumor vasculature and producing massive tumor necrosis ❑ IV	Phase I (ongoing 5/02)➢USA, Europe; phase I (begin 1/02, ongoing 5/02)➢Europe (UK) ❑ refractory solid tumors
BattellePharma	Resmycin	Aerosolized doxorubicin ❑ inhaled	Phase I (begin 6/99, ongoing 5/02)➢USA ❑ pulmonary bronchioloalveolar carcinoma (BAC), extensive-stage or recurrent sclc, Stage IIIb or recurrent nsclc, or lung metastases; phase I (begin 2/00, ongoing 5/02)➢USA ❑ advanced solid tumors affecting the lungs
Bayer ❑ Onyx Pharmaceuticals, Chiron	BAY 43-9006	Small molecule that targets Raf-1 kinase, an enzyme that is part of the ras oncogene signaling pathway considered important during tumor development ❑ PO	Phase I (begin 7/00, ongoing 5/02)➢Europe (Germany, Belgium), USA, Canada ❑ refractory, locally advanced, or metastatic, solid tumors
Bayer ❑ Indena, Roswell Park Cancer Institute, State U New York at Stony Brook	IDN5109, SB-T-101131, Bay 59-8862 ❑ Orataxel	Semisynthetic, orally bioavailable taxane active against P-glycoprotein expressing tumor cells ❑ PO, IV	Phase I (completed 1/02)➢USA ❑ solid tumors
BioNumerik Pharmaceuticals	Karenitecin ❑ BNP1350	Highly lipophilic, silicon-containing, lactone stable, semisynthetic camptothecin analog ❑ PO, parenteral	Phase I (begin 2/99, completed 00)➢USA ❑ solid tumor; phase I (begin 2/00, ongoing 2/02)➢USA ❑ pediatric solid tumors
Bristol-Myers Squibb	BMS-214662	BMS-214662 blocks ras processing by inhibiting farnesyltransferase enzyme activity; (FTase) inhibitor (FTI) ❑ IV	Phase I (begin 11/00, ongoing 5/02)➢USA; phase I (ongoing 5/02)➢USA (combination) ❑ advanced solid tumors; phase I (ongoing 11/00)➢USA ❑ hematologic malignancy
Bristol Myers Squibb	Paclitaxel analog ❑ BMS-188797	Paclitaxel analog	Phase I (begin 4/00; completed 11/00)➢USA; phase I (ongoing 5/01)➢USA (combination) ❑ refractory, advanced, solid tumors

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Bristol-Myers Squibb	BMS-275183	Oral formulation of paclitaxel ❑ PO	Phase I (ongoing 5/02)➢Europe, USA ❑ advanced, refractory solid tumors
Bristol-Myers Squibb ❑ Gesellschaft für Biotechnologische Forschung (GBF)	BMS-310705	Water-soluble and chemically stable semisynthetic epothilone B with potent parenteral and oral anti-tumor activity against models of taxane-sensitive and resistant human tumors *in vivo* ❑ PO, IV	Phase I (ongoing 5/02)➢Europe (Switzerland) ❑ refractory solid tumors; phase I (ongoing 5/02) ➢USA ❑ advanced cancer
Daiichi Pharmaceutical	DJ-927	Orally active novel taxane with higher solubility, a better safety profile, and higher antitumor activity ❑ PO	Phase I (ongoing 5/02)➢USA ❑ solid tumors
Dr. Reddy's Laboratories	DRF-1042	C-ring-modified novel camptothecin analog ❑ PO	Phase I (completed 6/02)➢India ❑ refractory solid tumors
Duke University Medical Center	1311-c81C6	Human/mouse chimeric anti-tenascin monclonal antibody (MAb) 81C6, radiolabeled with 1311 ❑ intracranial, intratumoral, intraventricular, intrathecal, intracavitary, intracystic	Phase I (completed 02)➢USA ❑ newly diagnosed malignant glioma; phase I (completed 96)➢USA ❑ neoplastic meningitis; phase I (completed 98)➢USA ❑ recurrent malignant glioma; phase I/II (begin 10/97, ongoing 4/01) USA; (begin 9/97, ongoing 6/00) USA ❑ primary, newly diagnosed, or recurrent brain tumors; phase I/II (begin 2/93, ongoing 2/01) USA ❑ primary or metastatic, anaplastic glioma
Eli Lilly	LY317615	Protein kinase C (PKC) β inhibitor with antiangiogenesis activity ❑ PO	Phase I (ongoing 6/02)➢USA ❑ advanced solid tumors
Eli Lilly	LY293111	Orally available small molecule with antineoplastic activity, known to be an LBT4 receptor antagonist, 5-lipoxygenase inhibitor, and PPAR-γ agonist ❑ PO	Phase I (completed 02)➢USA (combination), phase I (completed 02)➢USA ❑ advanced solid tumors
EntreMed ❑ Bristol-Myers Squibb, Children's Hospital at Harvard Medical School, Covance Biotechnology Services, Cell Genesys	Angiostatin, rhA ❑ rhAngiostatin	Recombinant, antiangiogenic 38-kDa internal fragment of plasminogen ❑ IV, SC	Phase I (closed 3/02)➢Europe (the Netherlands), phase I (ongoing 6/02)➢USA (combination) ❑ advanced solid tumors
Fujisawa Pharmaceutical	FK866	Inhibitor of nicotinamide adenine dinucleotide (NAD) biosynthesis ❑ continuous infusion	Phase I (ongoing 5/02)➢USA ❑ solid tumors
GenVec ❑ Varian Medical Systems, Asahi Chemical Industry	TNFerade	Delivers the human tumor necrosis factor (TNF)-α gene directly to tumors, via a proprietary adenovector gene delivery technology; once inside the tumor, standard radiation therapy triggers a "switch" known as the EGR-1 promoter initiating localized production of TNF-α ❑ intratumoral, injection	Phase Ib (begin 2/01, completed 2/02)➢USA ❑ refractory solid tumors; phase II (planned 02) ➢USA ❑ pancreatic cancer; phase II (planned 02)➢USA ❑ esophageal cancer; phase Ib (begin 10/01, ongoing 5/02)➢USA ❑ soft-tissue sarcoma
GlaxoSmithKline	GF120918	Potent inhibitor of multidrug (MDR) P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) ❑ PO	Phase I (ongoing 5/02)➢Europe (France) (combination) ❑ refractory, advanced, solid tumors
GlaxoSmithKline	GW572016	Selective dual inhibitor of tyrosine kinases EGFr and erbB2 ❑ PO	Phase I (completed 02)➢USA ❑ solid tumors
Ilex Oncology ❑ Hoffmann-La Roche	ILX23-7553	Vitamin D3 analog; inhibits cell proliferation and induces cell differentiation ❑ PO	Phase I (begin 6/99, completed 02)➢USA, Phase I (begin 3/00, ongoing 4/01)➢USA ❑ refractory solid tumors

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Ilex Oncology	Isocoumarin ❑ NM-3	Orally active, small molecule; angiogenesis inhibitor ❑ PO	Phase I (begin 00; ongoing 6/01) ➢Europe (France), phase I (begin 6/01)➢USA ❑ solid tumors
ImmunoGen ❑ Takeda Chemical Industries, British Biotech, GTC Biotherapeutics	huN901-DM1/ BB-10901TAP	Anti-CD56 humanized MAb huN901 conjugated to maytansinoid compound DM1 ❑ IV	Phase I/II (begin 5/01, ongoing 6/02)➢USA ❑ relapsed or refractory small-cell lung cancer (sclc)
ImmunoGen ❑ GlaxoSmithKline, Pharmacia, Takeda Chemical Industries	Cantuzumab mertansine ❑ SB-408075, huC242-DM1	Humanized MAb huC242 directed against CanAg, a mucin-type tumor-associated glycoprotein, and conjugated to a maytansinoid prodrug DM1; tumor-activated prodrug (TAP) ❑ IV	Phase I/II (begin 12/99, begin 9/00, ongoing 6/02)➢USA; phase I/II (begin 5/01, ongoing 6/02)➢USA (dose intensification) ❑ advanced, refractory, solid tumors (pancreatic cancer, nsclc, colorectal cancer)
Interpharma-Praha	Protaxel	Novel taxane; prodrug of paclitaxel ❑ IV	Phase I (ongoing 4/02)➢Europe, USA ❑ refractory ovarian cancer
Ivax ❑ National Institutes of Health (NIH)	TP-38	Immunotoxin consisting of a MAb MR1-1 which mutates MR1 in the CDR3 of the (VH) and (VL) chains to provide an antibody with especially good cytotoxicity that recognizes and binds to EGFrvIII, a mutant form of EGFr; the construct can be attached to an effector molecule, therapeutic moiety, or detectable label ❑ IV, intratumoral	Phase I (ongoing 02)➢USA ❑ glioblastoma multiforme (GBM)
Kosan Biosciences ❑ Memorial Sloan-Kettering Institute for Cancer Research, Stanford U, Harvard College	Epothilone D or desoxyepothilone B (dEpoB) ❑ KOS-862	Polyketide natural product belonging to a novel class that is structurally distinct from the other epothilones; inhibits cancer cell proliferation by a mechanism similar to that of paclitaxel but is effective against paclitaxel-resistant cells ❑ IV	Phase I (begin 10/01, ongoing 5/02) ➢USA ❑ refractory solid tumors
KuDOS Pharmaceuticals ❑ Cancer Research Ventures, Paterson Institute for Cancer Research, Trinity College	PaTrin-2	Orally administered powerful and irreversible inhibitor of alkyltransferase being evaluated as an inhibitor of DNA repair; it may widen the therapeutic window of current cancer treatment approaches and and make additional tumor types susceptible to existing therapies ❑ PO, IV	Phase I (completed 3/05)➢Europe (UK) (combination) ❑ advanced solid tumors
Merck KGaA	EMD 72000	Humanized MAb that targets EGFr-expressing tumors ❑ infusion	Phase I (completed 02)➢Europe (Germany) ❑ refractory solid tumors
Mojave Therapeutics ❑ Memorial Sloan-Kettering Cancer Center	Heat-shock protein (HSP)-based vaccine	Melanoma vaccine comprising two fusion peptides containing the Javelin sequence, a peptide motif with a high affinity for heat-shock proteins (HSP), and tyrosinase 370D (YMDGTMSQV) or GP100 209M (IMDQVPFSV) peptides, non-covalently bound to recombinant human HSP-70 ❑ injection	Phase I/IIa (completed 02)➢USA ❑ advanced or metastatic (Stage III or IV) malignant melanoma
NeoPharm ❑ Georgetown U, Isis Pharmaceuticals	LE-AON (Liposomal Encapsulated Antisense OligoNucleotide)	Liposome encapsulated formulation of antisense phosphorothioate oligonucleotide inhibitor of c-Raf-1 mRNA ❑ IV	Phase I/II (begin 3/01, ongoing 5/02)➢USA (monotherapy); phase I/II (begin 3/01, ongoing 5/02)➢USA (combination) ❑ radiation-resistant, or advanced, solid tumors

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NeoPharm ❑ National Cancer Institute (NCI)	SS1[dsFv]-PE38	Immunotoxin composed of a single chain MAb genetically engineered and linked to Pseudomonas exotoxin PE-38 ❑ IV	Phase I (begin 11/00, ongoing 5/02)➢USA, phase I (begin 2/01, ongoing 5/02)➢USA ❑ solid tumors
NeoPharm ❑ Center for Biologics Evaluation and Research	IL-13-PE38QQR	IL-13 linked to Pseudomonas exotoxin derivative; targeted cytokine that uses IL-13 receptor to deliver the bacterial toxin PE38QQR to cancer cells ❑ IV	Phase I (begin 9/99, ongoing 3/02) ➢USA ❑ refractory metastatic, renal cell carcinoma; phase I/II (begin 6/01)➢USA, phase I (begin 11/00, ongoing 9/01)➢USA, phase I (begin 10/00, ongoing 5/02)➢USA ❑ recurrent malignant glioma
NeoPharm	Liposome-entrapped mitoxantrone (LEM)	Electrostatic liposome encapsulation of mitoxantrone ❑ IV	Phase I (begin 8/01, ongoing 4/02)➢USA ❑ advanced or metastatic, refractory, solid tumors
NeoRx ❑ Stanford U	Pretarget Lymphoma	Radioimmunotherapy consisiting of an anti-CD20-streptavidin fusion protein (B9E9), followed by infusion of a clearing agent, and the radiotherapeutic 90-Y-biotin conjugate; based on Pretarget technology ❑ IV	Phase Ia (begin 1/01, ongoing 5/02)➢USA ❑ relapsed or refractory B-cell NHL; phase II (planned 4Q02) ➢USA ❑ diffuse large-cell lymphoma (DLCL); phase II (planned 4Q02) ➢USA ❑ follicular lymphoma
Northwest Biotherapeutics	DCVax-prostate (CaPVax)	Vaccine comprising mature dendritic cells loaded with recombinant human PSMA ❑ intradermal	Phase I/II (begin 00, ongoing 5/02) ➢USA ❑ metastatic, hormone-refractory prostate cancer
Novartis ❑ Variagenics	PKI166, PKI 166 (CGP 75166)	Orally bioavailable, potent dual inhibitor of both EGFr protein-tyrosine kinase activity and ErbB2 kinase ❑ PO	Phase I (completed 02)➢Europe (Switzerland), USA, phase I (ongoing 5/02)➢Europe ❑ advanced solid tumors
Novartis	LAF389	Synthetic analog of bengamide B, a natural product of Jaspidae sponges ❑ IV	Phase I (ongoing 5/02)➢USA ❑ refractory solid tumors
NS Pharma	HMN-214	Oral antimicrotubular agent with polo-like- and cyclin-dependent kinase inhibitory activities; stilbazole derivative; prodrug of HMN-176 ❑ PO	Phase I (ongoing 5/02)➢USA ❑ advanced solid tumors
Oxford BioMedica	TroVax	Gene based tumor vaccine; potential synergistic effect when used with MetXia-P450 ❑ intramuscular	Phase I/II (ongoing 2002)➢Europe (UK) ❑ advanced colorectal cancer
Pfizer ❑ OSI Pharmaceuticals	CP-547,632	Active inhibitor of vascular endothelial growth factor receptor 2 tyrosine kinase (VEGFr2-TK); angiogenesis inhibitor ❑ PO	Phase I (ongoing 4/02)➢USA ❑ advanced solid tumors
Pfizer Global Research and Development	AG2037	Antifolate; potent glycinamide ribonucleotide formyl transferase (GARFT) enzyme inhibitor ❑ IV, PO	Phase I (ongoing 5/02)➢USA ❑ advanced solid tumors
Pfizer Global Research and Development	CI-1040 (successor to PD0184352)	Small molecule oral inhibitor of the of the dual-specificity kinases, MEK1and MEK2 (MAPK/ERK/ kinase) ❑ PO	Phase I (completed 3/02)➢USA ❑ advanced cancer; phase II (pending 5/02) USA ❑ solid tumors
Pfizer Global Research and Development	CP-471,358	Oral inhibitor of matrix metalloproteinase ❑ PO	Phase I (completed 02)➢Europe ❑ advanced solid tumors
PharmaMar ❑ U Hawaii	Kahalalide F ❑ PM 92102	Small depsipeptide isolated from the mollusc, *Elysia rubefescens* from Oahu island with antitumor and antiviral properties; inhibits growth in several tumor cell lines ❑ IV	Phase I (begin 1/00, ongoing 8/01)➢Europe (Spain) ❑ solid tumors; phase I (ongoing 02) ➢Europe (the Netherlands) ❑ androgen-resistant prostate cancer

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PharmaMar	Dehydrodidemnin B ❑ Aplidin	Active didemnin isolated from the Caribbean tunicate *Aplidium albicans*; dehydroderivative of didemnin-B ❑ IV	Phase I (completed 02)➢Europe, phase I (begin 2/99, completed 10/01)➢Europe (Spain, France, UK), Canada ❑ refractory, advanced, solid tumors
Prescient NeuroPharma ❑ U British Columbia, Access Oncology	Anhydrovinblastine (AVLB)	Semisynthetic analog of vinblastine ❑ IV	Phase I (completed 01)➢USA ❑ refractory solid tumors
Prolx Pharmaceuticals	PX12	Asymetrical disulfide; novel thioredoxin (TRX) inhibitor	Phase I (ongoing 5/02)➢USA ❑ advanced metastatic cancer
Sigma-Tau	Gimatecan ❑ ST-1481/ST-1480	Camptothecin derivative ❑ PO	Phase I (ongoing 5/02)➢Europe ❑ advanced solid tumors
Solbec Pharmaceuticals ❑ Curacel International		Mixture of steroidal glycosides obtained from the plant *Solanum sodomaeum* (Devil's Apple) ❑ IV	Phase I (ongoing 5/02)➢Australia ❑ solid tumors
Sugen ❑ Esteve, Taiho Pharmaceutical	SU6668, SU006668, TSU-68 (Japan)	Synthesized inhibitor of receptor tyrosine kinases (RTK) present in receptors for various growth factors involved in tumor angiogenesis, including VEGF, fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) receptors ❑ IV, PO	Phase I (begin 10/98, closed 10/01)➢USA, Europe (IV), Phase I (begin 7/01, ongoing 5/02)➢USA (PO) ❑ advanced solid tumors
Taiho Pharmaceutical	TAS-102	Antitumor nucleoside with activity against primary tumors and metastases ❑ PO	Phase I (ongoing 5/02)➢USA ❑ advanced solid tumors
Teikoku Hormone	TZT-1027	Synthetic analog of dolastatin 10, a peptide isolated from the shell-less marine mollusk, *Dolabella auricularia*, an Indian Ocean sea hare; inhibits microtubule assembly and tubulin polymerization ❑ intraperitoneal (IP), IV	Phase I (completed 02)➢Japan ❑ solid tumors; phase I (ongoing 02)➢Japan ❑ advanced nsclc
Tularik	T607 (also known as T900607)	An analog of T67; targets tubulin and is active against MDR tumors; does not cross the blood-brain barrier (BBB) ❑ bolus injection	Phase I (ongoing 4/01)➢USA, Canada, Europe (UK) ❑ solid tumors
Xoma	ING-1 antibody (heMAb)	A high-affinity human-engineered IgG1 MAb to the tumor-associated Ep-CAM antigen expressed on epithelial cell cancers; destroys target cells by recruiting host immune system cells to induce apoptosis ❑ IV	Phase I (begin 11/00, closed 8/01) ➢USA, phase I (ongoing 5/02) ➢USA ❑ advanced, refractory adenocarcinoma

Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), June 2002; www.nmok.net

nale, limitations, underlying techniques, and specific applications will become relevant in a wide variety of diseases, and implementation will impact clinical and administrative decisionmaking. EBM is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. EBM involves integrating clinical practice with the best available external clinical evidence from systematic research (Sackett, etal, BMJ, 1996, 312, pp.72-3). Current best evidence is up-to-date information from relevant, valid research about the effects of different forms of health care, the potential for harm from exposure to particular agents, the accuracy of diagnostic tests, and the predictive power of prognostic factors (First Annual Nordic Workshop, National Institute of Public Health, Oslo, Norway, 1996).

EBM will have a tremendous impact on the practice of oncology and on the design and objectives of oncology clinical trials. Evidence-based oncology (EBO) methods and data will evolve into the most powerful approach in clinical care and policy decisions regarding coverage, as numerous competitive therapeutics are reaching the market. Phase II/III clinical trials performed to gain FDA registration will be included in EBO databases, which will in turn determine both clinical and policy decisionmaking.

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