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STATE-OF THE-ART IN THE MANAGEMENT OF CANCER

LUNG CANCER — PART VI
NOVEL AGENTS/FORMULATIONS IN DEVELOPMENT

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NOVEL AGENTS/FORMULATIONS IN DEVELOPMENT

There is an incredible amount of ongoing basic, preclinical, and clinical research in an effort to develop effective drugs against lung cancer. Numerous clinical trials have been completed or are ongoing (see FO, pp 1169-1181, and 1119-1124) to ascertain if agents already in the clinic against other types of solid tumors have a role, alone, or in combination and/or multimodality regimens in the treatment of lung cancer.

The effort to discover new therapeutics based on novel mechanisms and technologies is spurred by the dismal performance of existing treatment approaches, and by the magnitude of the lung cancer problem in the USA and worldwide (see FO, pp 1053, 1048, 1047, 1044, and 1043). Currently, it has been shown that drug therapies, even using marginally effective agents, are somewhat beneficial as interventions in advance disease, and as adjuvants to surgery and/or radiotherapy (RT) in early/localized disease. Therefore, use of chemotherapy is expanding rapidly. Candidates for chemotherapy in the USA alone are optimally estimated at 224,134 annually (Exhibit 1), resulting in a potential annual domestic market of over $2.2 billion.

Novel drugs/formulations that are being specifically evaluated, either preclinically or clinically, in lung cancer are presented in Exhibit 2. In addition, many other agents, currently in clinical trials against other malignancies, may also be applicable to the treatment of lung cancer. Also, numerous agents, in preclinical development against solid tumors that have not been tested in preclinical models of lung cancer, may ultimately target this malignancy as well. According to NEW MEDICINES's Oncology KnoweledgeBASE (nm|OK) over 280 novel agents/formulations are in all stages of development, worldwide, that may be applicable in the management of lung cancer.

In addition to chemotherapeutics that represent improvements over standard drugs against lung cancer, promising novel investigational approaches take advantage of information learned in the laboratory, by targeting specific mutations or proteins, either as a means of:

- correcting an abnormality, such as gene therapy approaches to replace mutant p53 or Rb function
- silencing oncogenes as is the case of ras inhibitors
- removing disease-associated proteins
- acting as signal transduction modulators of known pathways leading to disease
- delivering such agents as toxins, or radioisotopes, or cytotoxic drugs to tumors
- functioning as immune therapies/vaccines
- preventing/reversing tumor invasion and angiogenesis.

NOVEL CHEMOTHERAPEUTICS

Numerous novel cytotoxic chemotherapeutics are in development against lung cancer. Although many are analogs/formulations of commercially available agents, some are novel agents exhibiting higher effectiveness, particularly against multidrug resistant (MDR) tumors, offering better administration options, and/or exhibiting a more favorable side effects profile.

Spindle Poisons

The success of paclitaxel (Taxol; Bristol-Myers Squibb) in the treatment of many cancers, including nsclc, has created the impetus for the development of analogs of paclitaxel, and novel drugs with a similar mechanism of action. According to nm|OK over 41 different spindle poisons are in various stages of development. Although several are generic forms of Taxol, many are improved formulations of paclitaxel, and several [D-24851, RPR 109881A, TXD-258, IDN5109, 96023 and 97013, 0-deacetylbaccatin III (DAB) derivatives, bromotaxol, 2'Br-C16-HTD, epothilones, discodermolide, etc.] are novel agents with unique mechanisms of action. Eventually, most of these drugs will be evaluated in lung cancer. Those in phase I clinical trials are being tested against various advanced and, mostly, refractory solid tumors.

Anhydrovinblastine (AVLB), under development by IGT Pharma (Vancouver, Canada), is a semisynthetic precursor of vinblastine, 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 present in the parent structure (Goodbody AE, etal, Planta Med, Apr 1988;54(2):136-40). In March 1999, phase I (protocol IDs: RPCI-DS-9844, NCI-G99-1517, IGT-RPCI-DS-9844) clinical trial of AVLB in the treatment of refractory solid tumors, including nsclc, was initiated at the Roswell Park Cancer Institute (Buffalo, NY) with Gary N. Schwartz, MD, as the Study Chair. Approximately 30 patients will be accrued for this study. Although this phase I study involves patients who may have various forms of cancer, further studies will enroll only patients with nsclc.

According to a preliminary report on 6 patients (squamous cell carcinoma of the lung =1, adenocarcinoma of the colon =2, adenocarcinoma of the breast =1, and soft tissue sarcoma =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. 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. Four patients went off the study after 2 cycles because of progressive disease, disease stabilized in one patient at the 10 mg/m^2 dose level after four cycles, and one patient at the 16.5 mg/m^2 dose level was not as yet evaluable for response (Schwartz GN, etal, AACR00, Abs. 3895:612).

BMS-184476, a paclitaxel analog under development by Bristol-Myers Squibb, exhibits greater solubility than paclitaxel. In a phase I ongoing clinical trial which began in November 1997 at the San Antonio Cancer Institute (San Antonio, TX), escalating doses of BMS-184476 (20 mg/m^2-80 mg/m^2) are administered weekly, on days 1, 8 and 15, by a 1-hour infusion, repeated every 21 days, without premedication, in patients with solid tumors to evaluate determinants of MDT, DLT, and recommend phase II dose (Hidalgo M, etal. ASCO99, Abs. 645:168a). About 20-40 patients will be accrued for this study.

Maytansinoid immunoconjugates may also prove effective in the treatment of lung cancer. The maytansinoid DM1 is 100- to 1000-fold more cytotoxic than anticancer drugs currently in clinical use. ImmunoGen (Norwood, MA) has developed two such agents, linking the maytansinoid compound DM1, licensed from Takeda Chemical Industries (Osaka, Japan), to anti-CD56 humanized MAb huN901, for the treatment of sclc, or to antimucin humanized MAb huC242, licensed from Pharmacia, for treatment of various refractory solid tumors, including nsclc. The latter has entered phase I clinical trials while the former is expected to do so by the end of 2000. An immunotoxin, N901-bR, also developed by ImmunoGen, linking MAb N901 to a modified (blocked) ricin molecule,

completed a phase I clinical trial in 1996 in relapsed or refractory sclc, but its development of this construct was subsequently discontinued. Although there was only one PR among 21 patients, the trial demonstrated that an antibody directed against a surface marker of neuroendocrine differentiation is a feasible *in vivo* treatment approach.

Exhibit 1
Potential Numbers of Chemotherapy Regimens for the Treatment of Lung Cancer

Type of Treatment	Number of Patients (#)		
	Non-small-cell lung cancer (nsclc)	Small-cell lung cancer (sclc)	Total
First-line adjuvant (perioperative) chemotherapy	12,032		12,032
First-line chemotherapy in advanced disease	26,206	22,220	48,426
First-line radiosensitization in any stage disease treated by radiotherapy	75,286	16,096	91,382
Second-line chemotherapy	64,517	7,777	72,294
Total	178,041	46,093	224,134

Note: For additional information see FO, pp 1117, 1153 and 1154

PG-TXL (CT-2103) under development by Cell Therapeutics (CTI; Seattle, WA) consists of paclitaxel in a polyglutamate carrier. A phase I clinical trial commenced in the UK, in January 2000, being conducted by Cancer Research Campaign (London, UK). This trial will enroll 30 patients with advanced solid tumors who failed conventional cancer therapy. Phase I/II studies of PG-TXL are planned for later in 2000 in the USA and the UK. In preclinical evaluations, PG-TXL exhibited significant therapeutic activity against a broad range of tumors (Li C, etal, AACR99, Abs. 1909:287-8).

Taxoprexin, a conjugate of the fatty acid docosahexaenoic acid (DHA) and paclitaxel, under development by Protarga (Conshohocken, PA), is undergoing a phase I clinical trial (Wolff AC, etal, ASCO00, Abs. 921E) at Johns Hopkins Oncology Center (Baltimore, MD).

T67 (also known as T138067), and its analog, T607 (also known as T900607), are novel spindle poisons under development by Tularik (South San Francisco, CA). Both drugs bind specifically and irreversibly to β tubulin, thereby disrupting the process of cell replication, and causing tumor shrinkage. Also, both were active against MDR tumors. T67 is currently being evaluated in a multinational phase I/II clinical trial in refractory hepatocellular carcinoma with plans to also initiate a similar clinical trial in nsclc, and T607 entered a phase I clinical trial in solid tumors in the first quarter of 2000.

Topoisomerase I Inhibitors

Topoisomerase I (topo I) inhibitors have demonstrated activity against lung cancer and commercially available topo I inhibitors such as irinotecan (CPT-11) and topotecan are being investigated alone and in combination with various other agents in lung cancer (see FO pp 1164, 1165, 1178).

Exatecan mesylate (DX-8951f), under development by Daiichi Pharmaceuticals (Tokyo, Japan), entered a phase II clinical trial in nsclc in Europe, after phase I clinical trials indicated that the drug may be effective in this solid tumor. Exatecan mesylate (0.5mg/m^2) was administered IV over 30 minutes, daily, for 5 days, every 3 weeks, for a maximum of six cycles, without routinely prescribed antiemetics. Among 23 patients (squamous cell cancer=8, adenocarcinoma=6, large cell cancer=4, and mixed/other cancer=5) with previously untreated advanced (Stage IIIb=11 and Stage IV=12) nsclc enrolled, the DLT was neutropenia. Major hematologic toxicities included neutropenia (Grade 4=4 patients, Grade 2/3=7 and Grade 0/1=7), anemia (Grade 2/3=7 and Grade 0/1=11), and thrombocytopenia (Grade 2/3=3 and Grade 0/1=15). Other toxicities included fatigue (Grade 2/3=7 and Grade 0/1=11), emesis (Grade 2/3=5 and Grade 0/1=13), alopecia (Grade 1=6, and Grade 2=2), and Grade 1 constipation (n=4), diarrhea (n=3), and rash (n=1). Among 16 patients assessable for response, there were 3 PR (18%), and disease stabilized in 6, and progressed in 7 (Talbot DC, etal, ASCO00, Abs. 2166).

TAS-103 (BMS-247615), under development by Taiho Pharmaceutical (Saitama, Japan, and NY, NY), in collaboration with Bristol-Myers Squibb, is a novel quinoline derivative that is a dual topoisomerase I and II inhibitor in phase II clinical trials. In a phase I clinical study conducted at the Sarah Cannon Cancer Center (Nashville, TN) and sponsored by Bristol-Myers Squibb, 16 patients with refractory solid tumors, including 5 with nsclc and 1 with sclc, were administered TAS-103 on a weekly dosing schedule, using three dose levels (80, 120, and 160 mg/m^2/week). Although there were no major responses, disease stabilized in 2 patients with nsclc administered 4 cycles each. Results of this study suggest that TAS-103 is well-tolerated at a dose of 120 mg/m^2/week (Burris HA, etal, ASCO00, Abs. 742). Results of another phase I study, conducted at the University of Chicago (Chicago, IL), suggested that a phase II dose of 160 mg/m^2 was feasible. In this study, escalating doses (50 mg/m^2-200 mg/m^2) of TAS-103

were administered as a 1-hour IV infusion, weekly, for 3 weeks, with a 2-week rest period between cycles (Ewesuedo RB, etal, ASCO99, Abs. 630:164a).

XR5000, under development by Xenova Group (Berkshire, UK), is a novel synthetic dual topo I and II inhibitor with activity in MDR cancer. Xenova has established collaborations with Cancer Research Campaign Technology (CRCT; London, UK) and the Auckland Cancer Research Laboratory in New Zealand, which were the original source of XR5000, and which have continued to provide Xenova access to topoisomerase technology and expertise for additional drug leads, and to a chemical design and medicinal chemistry program for a new series of second generation oral topoisomerase inhibitors. XR5000 is undergoing a multicenter phase II open-label clinical trial (protocol ID: EORTC 16991N) in 25 patients with advanced nsclc. Patients enrolled in this study may be administered up to 6 cycles of therapy, delivered on an outpatient basis with the use of an ambulatory pump. Recruitment for this trial is mostly complete, and final data will be available during 2000. According to recently released results from a phase II clinical trial in colorectal cancer, no CR or PR with XR5000 treatment were observed; disease stabilized in 2/15 and progressed in 13/15.

Antifolates

Commercially available antifolates such as raltitrexed (Tomudex; AstraZeneca), as well as the widely used thymidylate synthase (TS) inhibitor fluorouracil, have not been particularly effective in treating lung cancer. For instance, raltitrexed (3 mg/m^2), administered as a 15-minute IV at 21-day intervals, was found ineffective in a phase II clinical trial involving 21 patients with advanced extensive-disease sclc (Woll PJ, etal, Br J Cancer 1997; 76(2):264-5). Also, a combination of cisplatin, 5-FU, and etoposide, in the treatment of advanced nsclc, did not prove superior to other cisplatin-containing regimens and exhibited considerable toxicity (Kucuk O, etal, Am J Clin Oncol, Aug 2000;23(4):371-5). However, new antifolates are proving as effective as other standard therapies in this setting.

Alimta, also known as multitargeted antifolate (MTA; LY231514), under development by Eli Lilly, has been evaluated as first-and second-line treatment in advanced nsclc in a variety of patient populations, including chemotherapy-naive patients, those who have relapsed following prior platinum-containing therapy or chemotherapy which did not contain platinum. In chemonaive patients, single-agent MTA produced similar responses (14%-23%) as other active agents in nsclc such as gemcitabine and the taxanes. Additionally, when MTA was studied in chemotherapy-naive patients, in combination with cisplatin, the response rate was 42% (Manegold C, etal, ASCO99, Abs. 1780: 462a), comparable to other modern combination regimens (Postmus PE and Green MR, Semin Oncol, Feb 1999;26(1 Suppl 4):31-6). In another cisplatin-based combination trial, ORR was 43%, median duration of response was 5.8 months, and the MST was 7.3 months (Shepherd FA, etal, ASCO00, Abs. 1984). In February 1999, at the International Congress on Anticancer Therapies, Eli Lilly reported that Alimta has also shown activity in mesothelioma.

S-1, under development by Bristol-Myers Squibb, under a license from Taiho Pharmaceutical, was effective in nsclc, and its toxicities were tolerable, according to results of a phase II clinical trial, conducted by the S-1 Cooperative Study Group (Lung Cancer Working Group) in Tokyo, Japan, that evaluated the antitumor activity and assessed the toxicity profile of S-1 in 62 chemotherapy-naive patients with Stage IIIb or IV nsclc, enrolled between June 1996 and May 1998. S-1 (40 mg/m^2) was administered orally, twice daily, after meals, with one course consisting of consecutive administration for 28 days, followed by 14 days of rest, and repeated, if there was no disease progression, until 4 courses were delivered. Among 59 (Stage IIIb=22 and Stage IV=37) of 61 patients treated with S-1, the response rate was 22.0%. The median follow-up was 281 days, MST was 309 days, and 41.1% of patients were alive at 1 year. Toxicities were generally mild and reversible. Toxicities >Grade 3 included anemia (1.7%, 1/59), neutropenia (6.8%, 4/59), thrombocytopenia (1.7%, 1/59), proteinuria (1.7%, 1/59), anorexia (10.2%, 6/59), diarrhea (8.5%, 5/59), stomatitis (1.7%, 1/59) and fatigue (6.8%, 4/59) (Niitani H, etal, ASCO00, Abs. 1995).

Nucleosides

Nucleosides, and their analogs, are being evaluated in the treatment of lung cancer, based on the effectiveness of gemcitabine, currently approved for the treatment of this malignancy (FO, pp 1161).

Decitabine, a nucleoside analog that acts through modulation of DNA methylation, is under development by SuperGen (San Ramon, CA). In experimental models, decitabine was shown to reactivate tumor suppressor genes that are turned off in many types of cancer because of excessive DNA methylation. Data from a phase I clinical trial, conducted at the Hospital Center of the University of Montreal in Canada, under the supervision of Dr. Richard Momparler, was presented at the 10th International Congress on Anticancer Treatment (January 31-February 3, 2000). The trial examined the safety and administration schedule of decitabine in 15 patients diagnosed with Stage IV nsclc. Probable MST for patients treated with 2 or more cycles of decitabine was greater than 15 months.

FMdC, under development by Matrix Pharmaceutical (Fremont, CA), is a nucleoside analog with similar activity to gemcitabine that, in combination with cisplatin, may exhibit activity against nsclc. An earlier phase II clinical trial of single agent FMdC as first line therapy in advanced nsclc, that was initiated in February 1999, was discontinued in October 1999, when preliminary analysis of evaluable

Exhibit 2
Selected Agents in Development for the Treatment of Lung Cancer

Developer ❑ Affiliate(s)	Generic Name ❑ Number ❑ Brand Name	Description ❑ Administration Route	Status➢ Location ❑ Indication(s)
Abbott Laboratories	FTI-2148 and FTI-2128	Non-thiol tetrapeptide mimic of the ras carboxyl terminal cysteine-aliphatic-aliphatic-methionine (CAAM), a potent inhibitor of farnesyltransferase (FTase), and of oncogenic H-ras processing and signaling ❑ IV	Preclin (o10/99)➢USA ❑ lung cancer
Abgenix ❑ Japan Tobacco, Immunex	ABX-EGF	Human anti-EGFr MAb ❑ IV	Phase I (o7/00)➢USA ❑ solid tumors expressing EGFr
Aeterna Laboratories, NCI	[AElig]-941 (AE-941) ❑ Neovastat	A novel antiangiogenic shark cartilage liquid extract; matrix metalloproteinase (MMP) inhibitor (MMPI); interacts with the VEGF receptor sites ❑ PO	Phase III (b5/00)➢USA, Canada ❑ locally recurrent nsclc
Agouron Pharmaceuticals (Pfizer) ❑ Hoffmann-La Roche (terminated)	AG3340 ❑ Prinomastat	Synthetic selective inhibitor of certain MMP enzymes such as gelatinase A and B, stromelysin-1 and collagenase-3; angiogenesis inhibitor ❑ PO	Phase III (b8/99; o3/00)➢USA, Canada, Europe, Australia ❑ advanced, unresectable nsclc (combination)
Allos Therapeutics ❑ NCI	RSR-13	Synthetic hemoglobin allosteric modifier that increases the release of oxygen from hemoglobin ❑ central venous access continuous IV	Phase II (b10/98, o1/00)➢USA ❑ locally advanced, unresectable, Stage IIIa or IIIb nsclc
AltaRex	MAb AR20.5 ❑ BrevaRex	Murine MAb that binds with high affinity to MUC-1 tumor-associated antigen ❑ injection	Phase I (c1/00)➢USA ❑ solid tumors expressing MUC-1
American Home Products (AHP)	CYA-246	Bacterial cell wall mimetic that is a potent cytokine inducer ❑ IV	Phase II (o2/00)➢USA ❑ nsclc (in combination)
Antisoma ❑ Imperial Cancer Research Fund (ICRF), U California, BioInvent International	TheraFab	Yttrium-90-labeled fragment of murine IgG1 MAb HMFG1 recognizing polymorphic epithelial mucin (PEM) ❑ IV	Preclin (o6/00)➢UK ❑ lung cancer
Aronex Pharmaceuticals ❑ U Texas M. D. Anderson Cancer Center	AR726 (L-NDDP) ❑ Aroplatin (formerly known as Platar)	Liposomal formulation of a novel platinum analog ❑ IV, intraperitoneal	Phase II (o3/00)➢USA ❑ mesothelioma
AstraZeneca	ZD1839 ❑ Iressa	A quinazoline-derivative that selectively inhibits EGFr tyrosine kinase (EGFr-TK) ❑ PO	Phase I (o11/99)➢USA, Europe, Canada; phase II (o3/00)➢USA ❑ advanced solid tumors
AstraZeneca ❑ AnorMED, Cancer Research Campaign	ZD0473 (was AMD473)	A novel sterically hindered platinum complex designed primarily to be less susceptible to inactivation by thiols; third generation compound with activity against cisplatin- or carboplatin-resistant tumors ❑ infusion, PO	Phase II (b12/99)➢USA, Europe ❑ advanced solid tumors
Aventis Pharmaceuticals ❑ NCI	Flavopiridol ❑ NSC 649890, L86-8275, HMR-1275	Semisynthetic analog of rohitukine, isolated from the bark of the Indian tree *Dysoxylum binectariferum*, that is a potent CDK1 inhibitor; arrests cell cycle progression in either G1 or G2 ❑ continuous IV	Phase II (c98)➢USA ❑ previously untreated Stage IV nsclc; phase II (p00)➢USA ❑ nsclc (combination)
Battelle Pulmonary Therapeutics ❑ Abbott Laboratories		Aerosolized doxorubicin ❑ inhalation	Phase I (o4/00)➢USA ❑ unresectable pulmonary malignancy
Beaufour Ipsen	BN 50730	A ginkgolide (ginkgo extract) shown to be a platelet activating factor (PAF) antagonist; angiogenesis inhibitor ❑ IV	Preclin (o3/00)➢Europe ❑ solid tumors

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BioChem Pharma ❑ Cytovia (Maxim Pharmaceuticals)	CV2105 series	A series of anticancer compounds identified by a proprietary high-throughput screening technology that were shown to induce apoptosis in certain cancer cells by activating specific caspase enzymes, and that may exhibit anticancer activity in cancer cells resistant to current chemotherapeutic agents	Preclin (o7/00)➢USA ❑ solid tumors
Biomira ❑ Imperial Cancer Research Fund (ICRF), Dana-Farber Cancer Institute	BLP-25	MUC-1 synthetic peptide vaccine encapsulated in liposomes ❑ IV	Phase IIb (b8/00)➢Canada ❑ nsclc
BioNumerik Pharmaceuticals ❑ Grelan Pharmaceutical	BNP7787	Second-generation platinum-protecting and taxane-protecting agent; thiol modulating agent ❑ PO, IV	Phase I (o2/00)➢USA, Europe
BioStratum (BST)	BST-1004 ❑ Collamer	Peptides from collagenous domains of type IV collagen with antimetastatic properties	Preclin (7/00)➢USA ❑ lung cancer
Bristol-Myers Squibb (BMS) ❑ Johnson Matthey	Satraplatin ❑ JM-216, BMS-182751	Novel oral platinum (IV) analog ❑ PO	Phase III (o6/99)➢USA, phase III (o6/98)➢Europe ❑ nsclc; phase II (c12/99)➢ Europe ❑ sclc
Bristol-Myers Squibb (BMS) ❑ Celltech Group	BMS-275291, D-2163	MMPI selective against specific MMP enzymes without affecting TNF or IL-1 release that is believed to play a key role in the inflammation process and may lead to side effects ❑ PO	Phase III (o2/00)➢USA, Europe (combination) ❑ advanced nsclc
Bristol-Myers Squibb (BMS)	BMS-184476	Paclitaxel analog that exhibits greater solubility than Taxol ❑ IV	Phase I (o4/00)➢Europe, USA ❑ advanced, refractory solid tumors
Bristol-Myers Squibb (BMS) ❑ Taiho Pharmaceutical	S-1	Thymidylate synthase inhibitor comprising ftorafur (an analog of 5-FU), which produces 5-FU, 5-chloro-2, 4-dehydropyrimidine (gimestat), which inhibits 5-FU degradation, and potassium oxonate (otastat), which reduces 5-FU toxicity in the digestive tract, at a molar ratio of 1:0.4:1 ❑ PO	Phase II (b6/96, c5/98)➢ Japan ❑ advanced (Stage IIIb or IV) nsclc
British Biotech ❑ Tanabe Seiyaku, Schering-Plough	Marimastat ❑ BB-2516	Synthetic, low-molecular weight MMPI; angiogenesis inhibitor ❑ PO	Phase III (b3/97, c12/99, o3/00)➢Europe, Canada ❑ sclc responsive to first-line treatment; phase II (o3/99) ➢Japan ❑ sclc (second-line); phase III (b5/99, o8/00) ➢USA, UK ❑ metastatic or locally advanced (Stage III) nsclc
Canji (Schering-Plough) ❑ Transgene, Genzyme Molecular Oncology	SCH58500 (rAd/p53; was ACN53)	Recombinant adenovirus encoding wild-type p53 ❑ intratumoral, bronchial lavage	Phase II (b11/98, o6/00)➢USA ❑ nsclc
Cell Genesys ❑ Bristol-Myers Squibb, Japan Tobacco, Fletcher International, Whitehead Institute, Johns Hopkins U	GVAX (autologous)	Irradiated and genetically modified tumor cells to secrete granulocyte macrophage-colony stimulating factor (GM-CSF) ❑ intradermal, subcutaneous	Phase I/II (b2/00)➢USA ❑ nsclc
Cell Pathways ❑ Paladin Labs	Exisulind ❑ FGN-1 ❑ Aptosyn	Sulfone metabolite of sulindac, an NSAID; selective apoptotic antineoplastic drug (SAAND) ❑ PO	Pilot study (o10/99)➢USA ❑ prevention of recurrence of lung cancer; phase I (o2/00)➢USA (combination) ❑ previously untreated nsclc
Cell Therapeutics (CTI) ❑ U Texas M. D. Anderson Cancer Center	Paclitaxel ❑ CT-2103 ❑ PG-TXL	Poly(L-glutamic acid) conjugate of paclitaxel, a water soluble form ❑ IV	Phase I (b1/00)➢USA, UK ❑ advanced solid tumors

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Cell Therapeutics (CTI)	Etoposide ❑ PG-Etoposide	Formulation of etoposide in water soluble form ❑ IV	Research (o3/99)➢USA ❑ lung cancer
Corixa ❑ U Pittsburgh		Epithelial mucin peptide, MUC-1, vaccine ❑ injection	Phase I (o7/00)➢USA ❑ pancreatic cancer
Corixa ❑ Glaxo SmithKline, U Washington, Southern Research Institute, Dana-Farber Cancer Institute	Her-2/neu vaccine	A microsphere-encapsulated, multivalent formulation HER2/neu peptide vaccine ❑ injection	Phase I (o7/00)➢USA ❑ solid tumors
Corixa ❑ Zambon Group		Novel lung cancer antigens, including those formulated using a microsphere delivery system, and proprietary adjuvant technologies	Research (o9/00)➢USA, Europe ❑ lung cancer
CytImmune Sciences ❑ EntreMed		Administration of Endostatin, via a colloidal gold delivery system ❑ injection	Preclin (o10/99)➢USA ❑ solid tumors
Cytoclonal Pharmaceutics (CPI) ❑ Wadley Institutes	LCG-MAb	MAb that recognize the LCG protein on the surface of some lung cancer cells; may have diagnostic and therapeutic applications	Phase I (o6/00)➢USA ❑ lung cancer
Cytoclonal Pharmaceutics (CPI) ❑ U Texas		Optimized antisense reagent from the Oasis library of gene regulators that inhibits the c-raf1 oncogene	Research (o4/00)➢USA ❑ lung cancer
Daiichi Pharmaceutical	Exatecan mesylate ❑ DX-8951f	Synthetic water soluble camptothecin analog; exhibits a more potent antitumor activity than other topoisomerase I inhibitors with a broader spectrum of activity ❑ IV	Phase II (o3/00)➢Europe ❑ previously untreated advanced (Stage IIIb/IV) nsclc
Daikin Industries	KIN-806	2-nitroimidazole derivative hypoxic cell radiosensitizer; immunopotentiator that activates macrophages and T lymphocytes ❑ IV	Preclin (o8/00)➢Japan ❑ solid tumors
Eli Lilly	Pemetrexed disodium, multitargeted antifolate (MTA) ❑ LY 231514 ❑ Alimta	Inhibits multiple enzymes involved in the purine and pyrimidine biosynthesis pathways; potently inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT), and other folate-dependent enzymes ❑ IV	Phase III (o3/00)➢USA, Australia ❑ nsclc
Eli Lilly ❑ Ilex Oncology	ILX-295501, LY295501	Diarysulfonylurea with antitumor activity ❑ PO	Phase II (o8/00)➢USA ❑ nsclc
EntreMed ❑ Bristol-Myers Squibb, Children's Hospital (Boston), Cell Genesys	Angiostatin	Recombinant angiostatin protein; blocks new blood vessels formation ❑ IV	Phase I (b3/00)➢USA; phase I (b7/00)➢USA (multimodality) ❑ solid tumors
EntreMed ❑ Children's Hospital (Boston), Harvard Medical School, NCI, Cell Genesys, Chiron	Endostatin	Recombinant form of Endostatin, a 20 kDa C-terminal fragment of collagen XVIII; an antiangiogenic protein that inhibits growth of blood vessels ❑ intramuscular	Phase I (b10/99, o7/00)➢USA ❑ advanced, refractory solid tumors
Enzon	PEG-[gamma]-camptothecin ❑ Prothecan	Polyethylene glycol-conjugated camptothecin-20-alanate, a water soluble prodrug of camptothecin ❑ IV	Phase I (o8/00)➢USA ❑ solid tumors
Fujisawa Pharmaceutical	FK-317	A benzmethoxy derivative of FK-973; a substituted dihydrobenzoxazine antitumor antibiotic that retains the antitumor activity of FK-973 without the side effect of vascular leak syndrome (VLS) ❑ injection	Phase II (o8/00)➢Japan; phase I (o8/00)➢USA ❑ solid tumors
Galderma Research & Development	CD437, AHPN	Synthetic retinoid that increases p53 expression and induces apoptosis	Research (o2/00)➢USA, Europe ❑ solid tumors

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GelTex Pharmaceuticals ❑ Parke-Davis (terminated 3/00), Nippon Kayaku, U Florida	Diethylnorspermine (DENSPM) ❑ CI-1006	Synthetic polyamine analog; depletes cancer cells of polyamines ❑ IV	Phase II (o3/00)➢USA ❑ nsclc
Genelabs Biotechnology (GBL)	GL331	Epipodophyllotoxin; etoposide analog in development against MDR cancers ❑ IV	Phase II (o8/00)➢USA ❑ sclc
Genentech	Herceptin	A recombinant DNA-derived humanized MAb (4D5) targeting the HER2 protein on tumor cells; an IgG1 k immunoglobulin ❑ IV	Phase II (o6/00)➢USA ❑ advanced (Stage IIIb or Stage IV), or recurrent nsclc
Genentech	rhuMAb-VEGF	MAb antagonist of VEGF; angiogenesis inhibitor ❑ IV	Phase II (c00)➢USA ❑ nsclc
GeneSense Technologies	GTI 2040	A fully phosphorothioated 20-mer oligonucleotide analog targeting R2, one of the components of ribonucleotide reductase ❑ injection	Phase I/II (b12/99)➢USA ❑ solid tumors
Genetix Pharmaceuticals ❑ Children's Hospital (Boston), Harvard U	Genostatin	Retroviral-mediated *in vivo* gene transfer of cDNAs encoding antiangiogenic proteins Angiostatin and Endostatin; demonstrated tumor growth inhibition when introduced in murine hematopoietic cells ❑ injection	Preclin (o5/99)➢USA ❑ solid tumors
Genta ❑ Johns Hopkins U, NCI	G3139 ❑ Genasense (Anticode)	An 18-mer fully phosphorothioated antisense oligonucleotide targeting the bcl-2 gene ❑ subcutaneous, IV	Phase I/II (o5/00)➢USA ❑ recurent sclc (combination)
Glaxo SmithKline	Edrecolomab ❑ 3622W94 ❑ Panorex	Humanized MAb that binds to EPG40 antigen (17-1A antigen) prevalent on most adenocarcinomas; humanized version of Panorex ❑ injection	Preclin (o3/00)➢Europe, USA ❑ nsclc
Hoffmann-La Roche	Arotinoid mofarotene ❑ Ro-8757	Third-generation synthetic retinoid analog containing a morpholine structure in the polar end group ❑ PO	Phase I (c99)➢Europe (combination) ❑ nsclc
Hyseq	EGFL6	Lung tumor marker; gene encodes a protein that exists outside the cell	Research➢USA (o3/00)
IBC Pharmaceuticals ❑ Immunomedics, Beckman Coulter	hMN-14 x 734 ❑ Pentacea	Second-generation radioimmunotherapeutic using the bispecific MAb technology platform Affinity Enhancement System (AES); one arm of the bispecific MAb targets CEA while the other is a receptor for diethylenetriamine pentaacetic acid (DTPA)-indium (In-DTPA) ❑ injection	Phase I/II (o5/00)➢France ❑ sclc
IGT Pharma ❑ U British Columbia, National Research Council	IGT-13 ❑ etoposide analog	A semisynthetic derivative of podophyllotoxin ❑ IV	Preclin (o6/00)➢Canada ❑ MDR solid tumors
IGT Pharma ❑ U British Columbia	Anhydrovinblastine (AVLB)	Semisyntheric derivative of vinblastine ❑ IV	Phase I (o8/00)➢USA ❑ refractory solid tumors
Ilex Oncology ❑ Burnham Institute	THP-Dox	Angiogenesis inhibitor; a peptide-doxorubicin conjugate ❑ injection	Preclin (o8/00)➢USA ❑ solid tumors
ImClone Systems ❑ Memorial Sloan-Kettering Cancer Center, Merck KGaA	Mitumomab ❑ EMD-60205 ❑ BEC2	Murine anti-idiotypic MAb which mimics GD3 ganglioside ❑ IV, intradermal	Phase III (o5/00)➢USA, Europe ❑ limited-disease sclc
ImClone Systems ❑ U California, San Diego, Aventis Pharmaceuticals, Merck KGaA	C225 ❑ IMC-C225 (formerly Cetuximab)	Chimerized MAb directed against EGFr ❑ IV	Phase I (c11/88)➢USA (indium-111 conjugate) ❑ squamous cell nsclc
ImmunoGen ❑ Takeda Chemical Industries, British Biotech	huN901-DM1	Anti-CD56 humanized MAb, huN901, conjugated to maytansinoid compound DM1 ❑ injection	Preclin (o5/00)➢USA ❑ sclc

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ImmunoGen ❑ Glaxo SmithKline, Pharmacia, Takeda Chemical Industries	huC242-DM1 ❑ SB-408075	Anti-mucin humanized MAb huC242 conjugated to maytansinoid compound DM1 ❑ injection	Phase I (o5/00)➢USA ❑ refractory nsclc
Incyte Genomics ❑ Roy Castle International Centre for Lung Cancer Research (RCIC)		Identification of genes implicated in lung cancer from patient samples using LifeSeq Gold gene sequence and LifeExpress gene expression databases	Research (o8/00)➢USA, UK ❑ lung cancer
Inex Pharmaceuticals	Onco TCS	Small lipid-based particulates carrying vincristine ❑ infusion	Phase II (b8/00)➢USA ❑ sclc
Institute of Cancer Research ❑ Leukaemia Research Fund, Kay Kendall Leukaemia Fund, Cancer Research Campaign	Bcl-10	A gene which is involved in the development of many tumors, including the most common cancers such as those of the lung, breast and colon	Research (o1/99)➢UK ❑ solid tumors
Introgen Therapeutics ❑ Aventis, NCI, U Texas M. D. Anderson Cancer Center, Sidney Kimmel Cancer Center	AD5CMV-P53 ❑ RPR/INGN-201	Adenoviral p53 gene therapy ❑ intraperitoneal, intralesional, intratumoral, IV, intra-arterial, bronchoalveolar lavage (BAL)	Phase II (o3/00)➢USA ❑ advanced, refractory nsclc (combination); phase II (o3/00)➢USA ❑ localized nsclc (cmbination); phase I (o5/00)➢USA ❑ bronchoalveolar carcinoma (BAC)
Introgen Therapeutics ❑ Aventis, U Texas M. D. Anderson Cancer Center, Sidney Kimmel Cancer Center	RV-p53 ❑ INGN-101	p53 gene transfer using a retroviral vector ❑ injection	Phase I/II (o8/00)➢USA ❑ nsclc
Isis Pharmaceuticals ❑ Novartis Pharmaceuticals (terminated 11/99)	ISIS-3521/ISI 641A	20-base antisense phosphorothioate oligonucleotide inhibitor of protein kinase C (PKC)-α expression ❑ IV	Phase II (o12/99)➢USA ❑ advanced, untreated nsclc
Janssen Pharmaceutica	R115777	Selective non-peptidomimetic farnesyl transferase inhibitor (FTI); inhibits the post-translational activation of ras ❑ PO	Phase II (p6/00)➢USA ❑ advanced (Stage IV), or recurrent nsclc; phase II (o8/00)➢USA ❑ relapsed sclc
Leo Pharmaceutical Products	CHS 828	Novel pyridyl cyanoguanidine antitumor agent ❑ PO	Phase I (o6/99)➢Europe ❑ solid tumors
Lexigen Pharmaceuticals ❑ Scripps Research Institute, U California, San Diego, Cancer Center	Hu14.18-IL2	Fusion protein consisting of humanized anti-ganglioside GD2 (14.18) MAb genetically linked to interleukin-2 (IL-2) ❑ IV	Phase I/Ib (o5/00)➢USA ❑ GD2-positive solid tumors
Magainin Pharmaceuticals	Squalamine ❑ MSI-1256F	Synthetic version of an aminosterol originally obtained form the dogfish shark *Squalus acanthias*; cationic steroid characterized by a condensation of an anionic bile salt intermediate with the polyamine, spermidine; angiogenesis inhibitor ❑ IV	Phase II (o2/00)➢USA (combination) ❑ nsclc
Magainin Pharmaceuticals	MSI-1596	Potent bactericidal cationic peptide; selectively permeabilizes cancer cells, including MDR lines, to conventional chemotherapeutic agents, while sparing normal cells ❑ injection	Preclin (o6/00)➢USA ❑ MDR tumors
Matrix Pharmaceutical ❑ Aventis, Kyowa Hakko Kogyo	FMdC ❑ MDL-101731, KW 2331 (Japan)	Nucleoside analog; novel inhibitor of ribonucleoside diphosphate reductase; antimetabolite ❑ PO, IV	Phase II (discontinued 10/99)➢USA ❑ nsclc; phase I (b3/00)➢USA (combination) ❑ solid tumors
Maxia Pharmaceuticals ❑ Sidney Kimmel Cancer Center, Galderma	MX335	Retinoid-related molecules (RRM) ❑ PO	Preclin (o8/00)➢USA ❑ nsclc

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Medarex ❑ Dartmouth Medical, Merck KGaA, Immuno-Designed Molecules (IDM)	MDX-447, H22 x H425, EMD 82633	Fully human, bispecific MAb directed against the CD64 receptor for IgG Fc, and EGFr ❑ IV	Phase II (o5/00)➢USA ❑ solid tumors
Memorial Sloan-Kettering Cancer Center ❑ Gem Pharmaceuticals (terminated 99)	GPX-330	A novel inhalation formulation of an anticancer drug for the prevention and treatment of lung cancer ❑ inhaled	Research (o7/00)➢USA ❑ nsclc
MGI Pharma ❑ Dainippon Pharmaceutical, NCI, U California	Irofulven [acylfulvene (6-HMAF)] ❑ MGI 114, NSC 683863	Semisynthetic analog of illudin S, a sesquiterpene isolated from the Jack o' lantern mushroom, *Omphalotus illudens* ❑ IV	Phase II (o6/99)➢USA ❑ nsclc
Myriad Genetics ❑ Schering-Plough	MKK3	A tumor suppressor gene thought to become mutated in lung cancer	Research (o1/00)➢USA ❑ lung cancer
National Cancer Institute (NCI)	2A11, NSC 377527	MAb which binds with high affinity to the bombesin-like peptide (BLP) gastrin-releasing peptide (GRP) ❑ IV	Phase II (c97)➢USA ❑ refractory sclc
Northwest Biotherapeutics		Dendritic cell-based immunotherapy ❑ IV	Preclin (04/00)➢USA ❑ solid tumors
Onyx Pharmaceuticals ❑ Pfizer	ONYX-015	Genetically engineered E1B-55kD gene-deleted group C adenovirus that replicates in and lyses cells lacking p53 activity ❑ intralesional, intraoperative, mouthwash	Phase I (o3/00)➢USA ❑ refractory solid tumors (phase III, b6/00 in the USA and Europe in head and neck cancer)
OSI Pharmaceuticals ❑ Pfizer (terminated 6/00)	CP-358,774, OSI-774	Small molecule that directly inhibits EGFr-TK; CP-373,420, a des-methyl metabolite of CP-358,774, is also a potent inhibitor of EGFr ❑ PO, IV	Phase II (o6/00)➢USA ❑ advanced, refractory nsclc
Otsuka Pharmaceutical	OPB-3206	MMPI ❑ PO	Preclin (o8/00)➢Japan ❑ lung metastases
Parke-Davis ❑ Southern Research Institute	CI-994, GOE 5549, PD 123 654	Novel substituted benzamide with cytotoxic and cytostatic activity ❑ PO	Phase III (o5/00)➢USA (combination) ❑ locally advanced, metastatic, recurrent, unresectable nsclc
Peptech ❑ Imperial Cancer Research Fund (ICRF), Imperial Cancer Research Technology (ICRT)	PTL-68300B ❑ Antagonist G, SPAG	A 6 amino acid modified synthetic peptide derived from the naturally occurring neurotransmitter, substance P ❑ infusion	Phase I (c97)➢UK ❑ sclc
Pharmacia ❑ NeoPharm, Georgetown U	Paclitaxel ❑ PNU-93914	Liposome encapsulated paclitaxel (LEP) based on cardiolipin, a lipid found in cardiac tissue ❑ IV	Phase I (b9/98; o3/00) ➢USA ❑ solid tumors
Pharmacyclics ❑ NCI, Nycomed Amersham, Hoechst Celanese	Lutetium-texaphyrin (Lu-Tex) ❑ Lutrin	Photosensitizer; belongs to a group of patented synthetic molecules called texaphyrins ❑ IV	Phase I (b00)➢USA ❑ lung cancer
Pharmacyclics ❑ NCI, U Texas, Hoechst Celanese, Abbott Laboratories	Motexafin gadolinium ❑ Xcytrin	Radiosensitizer; gadolinium texaphyrin (Gd-Tex) that selectively accumulates in cancer cells sensitizing them to radiation ❑ IV	Phase III (o8/00)➢USA, Canada, Europe ❑ brain metastases; phase I (b9/00) ➢USA ❑ Stage IIIa nsclc (combination)
PharmaMar	Ecteinascidin 743 ❑ ET-743, NSC 648766	A novel marine compound derived from the tunicate *Ecteinascidia turbinata*; a DNA minor groove, guanine-specific interacting agent that also targets topo I, inducing topo I-mediated protein-linked DNA break ❑ intermittent or continuous IV	Phase II (o6/00)➢USA, Europe ❑ advanced, refractory solid tumors
PharmaMar	Aplidine (dehydrodidemnin B)	Active didemnin isolated from the Caribbean tunicate *Aplidium albicans*; dehydroderivative of didemnin-B ❑ IV	Phase I (o3/00)➢Europe, Canada ❑ solid tumors

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Progen Industries	Phosphomannopentaose sulfate ❑ PI-88	Oligosaccharide based compound which binds to the heparin binding site of angiogenesis-specific growth factors and prevents the heparin-dependent proliferation of endothelial cells; prevents metastasis ❑ IV	Phase I (b7/99)➢ Australia ❑ refractory solid tumors
Progenics Pharmaceuticals ❑ Memorial Sloan-Kettering Cancer Center, Aquila Biopharmaceuticals, U California, Bristol-Myers Squibb	Bivalent GM2/GD2 ganglioside conjugate vaccine ❑ MGV	MGV is composed of 2 ganglioside antigens, GD2 and GM2, conjugated to the immunogenic carrier protein, keyhole limpet hemocyanin (KLH), and combined with the QS-21 adjuvant ❑ subcutaneous	Phase II (o1/00)➢USA ❑ solid tumors
Protarga ❑ Abbott Laboratories, Bryn Mawr College, Martek Biosciences	DHA-paclitaxel ❑ Taxoprexin	Docosahexaenoic acid (DHA)-linked paclitaxel conjugate ❑ PO	Phase I (b5/99, o6/00)➢USA ❑ refractory solid tumors
Ribosepharm (Klinge Pharma)	Bendamustin(e), bendamustin HCl ❑ ZIMET 3393 ❑ Ribomustin, Cytostasan	Synthetic bifunctional alkylating agent ❑ IV	Phase II (o8/00)➢Germany ❑ sclc
Ribozyme Pharmaceuticals (RPI) ❑ Chiron, U Colorado	RPI.4610 ❑ Angiozyme	Chemically synthesized hammerhead ribozyme directed at VEGFr FLT-1 mRNA; antiangiogenic ❑ IV, subcutaneous	Phase I/II (o1/00)➢USA ❑ solid tumors
Sanofi-Synthelabo ❑ SRI International	Tirapazamine ❑ Tirazone	Bioreductive agent that is selectively activated to a reactive DNA-damaging species in hypoxic tumors ❑ IV	Phase III (b9/99)➢USA, Europe, Australia, Canada ❑ advanced, metastatic nsclc
Sanofi-Synthelabo	SR-49059	Vasopressin receptor type I-A antagonist ❑ PO	Phase IIa (o7/99)➢ Europe ❑ refractory sclc
Schering-Plough	SCH 66336	Small molecule tricyclic FTI ❑ PO	Phase II (o7/99)➢USA ❑ solid tumors
Scotia Pharmaceuticals ❑ Boehringer Ingelheim (terminated 11/98), Kyowa Hakko Kogyo	Temoporfin ❑ EF-9, KW-2345 ❑ Foscan	Second generation systemic photosensitizer; m-THPC-PDT ❑ IV	Phase I/II (c98)➢The Netherlands ❑ mesothelioma
Serono Laboratories	R-Frone, Rebif	Recombinant interferon-β1a (rIFNβ1a) ❑ subcutaneous	Phase III (o8/00)➢Europe ❑ nsclc
Servier Group	S-16020	Olivacine derivative; topoisomerase II inhibitor ❑ IV	Phase II (o1/00)➢France ❑ advanced solid tumors
Shionogi	254-S ❑ Nedaplatin	Second generation platinum complex with reduced nephrotoxicity ❑ IV	Phase I (o8/00)➢Japan ❑ lung cancer
SR Pharma ❑ U College London, Onyvax, Sakai Chemical Industry	SRL 172	Immunotherapeutic consisting of heat-killed *Mycobacterium vaccae*; Th1 adjuvant ❑ intradermal	Phase III (o8/00)➢Europe (combination) ❑ advanced nsclc; phase II (c00 ➢Europe ❑ sclc
Sugen ❑ Asta Medica	Pan-Her antagonist (formerly Her2 Antagonist)	Small molecule inhibitors of the HER receptor family which includes EGFr, HER2, and HER 4 ❑ IV	Preclin (o3/00)➢USA ❑ solid tumors
Sugen ❑ NCI, Esteve	Leflunomide ❑ SU101	Small synthetic molecule that inhibits the platelet-derived growth factor (PDGF)-TK signaling pathway; structurally similar to leflunomide❑ IV, subcutaneous	Phase II (c9/99)➢USA ❑ Stage IIIb/IV nsclc
Sugen ❑ Taiho Pharmaceutical, Esteve	Semoxind ❑ SU5416	Small molecule drug targeting the VEGF-mediated Flk-I/KDR TK pathway; inhibits VEGFr2 activation; blocks angiogenesis ❑ IV, PO	Phase I/II (o8/00)➢USA, Europe ❑ advanced solid tumors

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Sumitomo	Amrubicin ❑ SM-5887	Totally synthetic anthracycline; potent topoisomerase II inhibitor ❑ IV	Phase II (o1/99)➢Japan ❑ advanced sclc; phase II (o1/99)➢Japan ❑ advanced nsclc
SuperGen ❑ Stehlin Foundation for Cancer Research, Abbott Laboratories, Clayton Foundation for Reseaerch	9-nitro-20-(S)-camptothecin (9-NC) ❑ RFS 2000 ❑ Rubitecan	A third-generation topoisomerase I inhibitor; causes single-strand breaks in the DNA of rapidly dividing tumor cells; patented analog of camptothecin ❑ PO, inhaled	Phase II (b5/00)➢Europe ❑ advanced nsclc; phase I (o8/00)➢USA (inhaled) ❑ nsclc
SuperGen ❑ Immunex, Janssen Biotech, Cyclex	Etoposide ❑ Etoposide Extra	Reformulation of etoposide that increases stability and solubility ❑ injection	NDA filing pending (8/00) ➢USA ❑ solid tumors
SuperGen ❑ Janssen Biotech, Cyclex	Mitomycin C ❑ Mito Extra	Reformulation of mitomycin C that increases solubility and decreases hypersensitivity and other reactions seen with current formulation of mitomycin C ❑ injection	NDA (f1Q98)➢USA ❑ solid tumors
SuperGen ❑ Pharmachemie	Decitabine; dezocitidine ❑ NSC-127716, DAC	A hypomethylating deoxycytidine nucleoside analog ❑ infusion	Phase I/II (o3/00)➢ Canada ❑ Stage IV nsclc
Taiho Pharmaceutical ❑ Bristol-Myers Squibb	TAS-103	A novel quinoline derivative that targets topoisomerases I and II ❑ IV	Phase I (o5/99)➢USA ❑ refractory solid tumors
Therion Biologics ❑ NCI, Aventis Pasteur	ALVAC-CEA-B7.1	Avian pox (canarypox) virus vector, ALVAC (Avipox), expressing the CEA peptide antigen and the B7.1 costimulatory molecule ❑ intramuscular	Phase II (o8/00)➢USA ❑ CEA-expressing solid tumors
Therion Biologics ❑ NCI, Aventis Pasteur	rV-CEA ❑ TBC-CEA	Live recombinant vaccinia virus expressing the CEA peptide antigen ❑ intramuscular	Phase II (o5/00)➢USA ❑ CEA-expressing solid tumors
Therion Biologics ❑ NCI	rF-CEA	Live recombinant fowlpox virus expressing the CEA peptide antigen	Preclin (5/00)➢USA ❑ lung cancer
Therion Biologics ❑ NCI	rV-B7.1	Live recombinant vaccinia virus expressing the B7.1 peptide antigen	Preclin (5/00)➢USA ❑ CEA-expressing solid tumors
Titan Pharmaceuticals ❑ Ansan, Bar-Ilan Research and Development	AN9 ❑ Pivanex	Butyric acid synthetic analog that promotes cellular differentiation ❑ intraperitoneal, IV, intra-arterial, PO	Phase II (o11/99)➢USA ❑ nsclc
Titan Pharmaceuticals ❑ U Kentucky, Goodwin Biotechnology	Anti-1A7 antibody ❑ TriGem	DNA vaccine encoding 1A7; anti-idiotype MAb generated against the IgG1 anti-idiotype antibody 14G2A that binds the GD2 ganglioside ❑ IV	Phase II (o11/99)➢USA ❑ sclc
Titan Pharmaceuticals ❑ U of Kentucky Research Foundation, Goodwin Biotechnology	Anti-3H1 antibody ❑ CeaVac	Murine IgG1 anti-idiotype MAb generated against the 8019 IgG1 MAb that binds a CEA epitope; mimicks CEA ❑ intracutaneous, subcutaneous	Phase Ib/II (o3/99)➢USA ❑ nsclc
Transgene ❑ Imperial Cancer Research Fund (ICRF), Imperial Cancer Research Technology (ICRT)	VV-MUC-1-IL-2 ❑ TG1031	Attenuated recombinant vaccinia virus containing sequences coding for human MUC-1 and the costimulatory cytokine, IL-2 gene ❑ intratumoral	Phase I (o12/99)➢France ❑ nsclc
Tularik ❑ Princeton U, Eli Lilly	Lometrexol	An antifolate that is highly selective in inhibiting glycinamide ribonucleotide formyltransferase, the key enzyme of purine synthesis ❑ IV	Phase I (o12/99)➢USA ❑ solid tumors
Tularik	T67 (also known as T138067)	Pentafluorosulfonamidebenzene that binds specifically and irreversibly to β tubulin thereby disrupting the process of cell replication and causing tumor shrinkage; active against MDR tumors ❑ infusion	Phase I (b3/98; o5/00)➢USA ❑ solid tumors
Tularik	T607 (also known as T900607)	An analog of T67; targets tubulin and is active against MDR tumors ❑ bolus injection	Phase I (o5/00)➢USA, UK ❑ solid tumors

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U California, San Diego ❑ Triangle Pharmaceuticals (terminated 2/99)	L-alanosine	Toxic aspartate analog derived from *Streptomyces alanosinicus* ❑ continuous IV	Phase II (o3/99)➢USA ❑ Stage IIIb or Stage IV nsclc
U Texas M. D. Anderson Cancer Center	DP3-p53	Cationic liposome-p53 complex ❑ intratracheal, bronchial lavage	Preclin (o8/00)➢USA ❑ endobronchial lung cancer
Valentis ❑ Pfizer (terminated 12/97)	MB200 Series	Angiogenesis inhibitors ❑ IV	Preclin (o12/99)➢USA ❑ metastatic solid tumors
Vion Pharmaceuticals ❑ Yale U	VNP20009 ❑ Tumor Amplified Protein Expression Therapy (TAPET)	Live, genetically altered *Salmonella typhimurium* ❑ intratumoral, IV	Phase I (b8/99, o7/00) (intratumoral), (b3/00) (IV)➢USA, (b7/00) (IV)➢Europe ❑ advanced or metastatic solid tumors
Vion Pharmaceuticals ❑ Yale U	3-AP, OCX-191 ❑ Triapine	Ribonucleotide reductase inhibitor ❑ parenteral, IV	Phase I (o6/00)➢USA ❑ solid tumors
Vion Pharmaceuticals ❑ Yale U	3a-AP, 3b-AP	Ribonucleotide reductase inhibitor; prodrug ❑ parenteral, IV	Preclin (o7/00)➢USA ❑ solid tumors
Vion Pharmaceuticals ❑ Yale U	VNP40101M, 101M	Sulfonyl hydrazine prodrug ❑ IP, IV, PO	Preclin (o7/00)➢USA ❑ solid tumors
Viventia (was Novopharm Biotech)	NovoMAb-G2 scFV	Recombinant version of NovoMAb-G2, a single chain Fv (scFv) pancarcinoma specific MAb that recognizes an antigen widely present on lung cancer, among others tumors ❑ IV	Preclin (o12/99) ➢Canada ❑ solid tumors
Xenova Group ❑ Cancer Research Campaign, Auckland Cancer Research Laboratory	DACA ❑ XR5000	Novel synthetic anticancer; topoisomerase I and II inhibitor with activity in MDR cancer ❑ IV	Phase II (o6/00)➢Europe ❑ advanced nsclc
Xenova Group ❑ Auckland Cancer Research Laboratory	XR11576	A novel, next generation, topoisomerase I and II inhibitor ❑ PO	Preclin (o3/00)➢UK ❑ solid tumors
Xenova Group	XR5944	A novel bis-phenazine; an inhibitor of topoisomerase I and II with a preference for topoisomerase I ❑ IV	Preclin (o2/00)➢UK ❑ solid tumors
York Medical ❑ Centre of Molecular Immunology (CIM)	hu-EGF fused to TT or P64k	Vaccination with hEGF fused to either P64k or tetanic toxoid to stimulate the immune system to produce anti-EGF antibodies which target cancer cells ❑ intradermal	Phase II (o12/99)➢ Canada ❑ advanced nsclc

** Most of these agents are in different stages of clinical development for indications other than lung cancer. Subsribers to NEW MEDICINE's Oncology KnowledgeBASE (∩∩|OK) may interrogate this resource to establish the current status of these agents for any other indication for which they are being developed, including detailed results from reported clinical trials in terms of these agents' effectiveness, toxicity and clinical status.*

Source: NEW MEDICINE Oncology KnowledgeBASE (∩∩|OK), now on the Internet at oncologyknowledgebase.com, August 2000.

patients failed to demonstrate meaningful clinical activity with FMdC as a stand-alone therapy in this indication at the dose and regimen tested.

Subsequently, based on preclinical evaluations that showed that the combination of FMdC and cisplatin resulted in apparently synergistic antitumor activity that was significantly greater than the sum of the two agents used alone in human lung cancer models *in vitro* and in mice, the company initiated a phase I clinical trial of FMdC, in solid tumors, in combination with cisplatin.

Platinum-based Agents

Platinum-based chemotherapy has been shown effective in the treatment of lung cancer prompting the evaluation of novel agents from this group in this indication.

Nedaplatin (254-S), under development by Shionogi (Osaka, Japan), is a second-generation platinum analog with promising activity against a wide variety of solid tumors without renal toxicity. In a phase I clinical trial of nedaplatin in elderly patients (>70 years-of-age) with advanced nsclc, conducted at the National Cancer Center Hospital (Tokyo, Japan), DLT was thrombocytopenia, and the recommended dose was 100 mg/m^2, every 4 weeks. Because creatinine clearance (Ccr) is a predictive variable for thrombocytopenia, patients were stratified into two arms based on renal function. Initial doses of 254-S were 80 mg/m^2 and 60 mg/m^2 in arm-A (Ccr ≥60), and arm-B (Ccr <60), respectively, administered by 1-hour IV infusion. Doses were escalated in 20-mg/m^2 increments up to 100 mg/m^2, in successive cohorts of 3 to 6 patients, until

DLT. Among 36 (squamous=19 and non-squamous=17), chemotherapy-naive patients with advanced nsclc, treated with 72 cycles of chemotherapy (arm-A=22 and arm-B=14), there were no ≥Grade 3 toxicities. There were 2/7 PR and 4/15 PR at the 80 mg/m^2 and 100 mg/m^2, in arm-A, respectively, and 3/6 PR and 2/3 PR, in arm-B, respectively. DLT was determined as neutropenia and thrombocytopenia in arm-B at a dose of 100 mg/m^2; however, there was no severe nonhematologic toxicity observed in either arm. The recommended doses were 100 mg/m^2 in arm-A and 80 mg/m^2 in arm-B. PR was observed in 11/19 (58%) cases of squamous cell carcinoma and 1/17 (6%) cases of non-squamous cell carcinoma, for an ORR of 33% (Yamamoto N, etal, ASCO00, Abs. 792).

Oxaliplatin (Eloxatin; Sanofi-Synthelabo), a platinum-based drug approved in Europe as first-line therapy in advanced colorectal cancer, has also been evaluated in advanced nsclc, as monotherapy, and in various combinations. An NCI-sponsored multicenter phase II clinical trial (protocol IDs: UCCRC-10014, NCI-T99-0008) of oxaliplatin, in combination with paclitaxel, is ongoing in patients with advanced (Stage IIIb with pleural effusion or Stage IV), or recurrent nsclc. Approximately 17-37 patients will be accrued within 24 months. Objectives are to determine response, overall survival, time to tumor progression, and toxicities, particularly neurologic toxicity, and its correlation with creatinine clearance. Patients are treated with IV paclitaxel over 1 hour followed by IV oxaliplatin over 2 hours on day 1, repeated every 3 weeks in the absence of disease progression or unacceptable toxicity. Patients are followed for at least 2 years or until death. Study Chair is Ann M. Mauer at the University of Chicago Cancer Research Center.

A phase II clinical trial, was conducted at Centre Hospitalier Intercommunal (Creteil, France) in 33 patients with previously untreated unresectable advanced nsclc [either locoregional disease with PS 2 (n=19) or Stage IV disease (n=14)], enrolled between January 1992 and January 1994. Oxaliplatin (130 mg/m^2) was administered on an outpatient basis as a 2-hour infusion, every 21 days, without hydration. Response was assessed after every two courses. After 100 courses were administered, for a mean of 3 courses per patient (range=1-12), among 33 patients evaluable for response, there was 1 CR and 4 PR. The median response duration was 5.9 months. Based on 100 cycles evaluable for toxicity, transient, reversible, cold-related finger dysesthesias occurred in 29 patients, but were mild, and disappeared in most cases within a few days. There were brief episodes of pharyngolaryngeal discomfort in 8 patients (11 episodes) accompanied in 4 cases (3 patients) by transient episodes of inspiratory stridor, leading to treatment withdrawal in 2 patients (Monnet I, etal, Eur J Cancer, Jun 1998;34(7):1124-7).

Satraplatin (JM216), under development by Bristol-Myers Squibb under a license obtained from Johnson Matthey (Wayne, PA), is an orally available platinum drug. In a multicenter phase II clinical trial, conducted in Europe, chemotherapy-naive patients with limited-disease sclc, unfit for intensive chemotherapy, or those with extensive-disease, were treated with JM216 (120 mg/m^2), daily, for 5 consecutive days, every 3 weeks. Individual dose escalation to 140 mg/m^2 per day was allowed if toxicity was ≤Grade 2. After 88 cycles, among 27 patients assessable for toxicity, Grade 3 and 4 hematologic toxicities were neutropenia in 15.9% and 3.7%, lymphocytopenia in 47.6% and 17.1%, and thrombocytopenia in 19.5% and 10.3% of cycles, respectively. There was one incidence of neutropenic fever. Nausea, vomiting, and diarrhea were the most common nonhematologic toxicities. Except for Grade 4 diarrhea in 1 patient, no Grade 4 nonhematologic toxicity was observed. Among 26 patients evaluable for response, ORR was 38% (10/26), excluding 5 unconfirmed PR; there was no CR. Median overall time to progression was 110 days (range=5 to 624 days) and MST was 210 days (range=5 to 624 days) (Fokkema E, etal, J Clin Oncol, Dec 1999;17(12):3822-3827). In a phase II clinical trial, JM-216 did not appear to have significant antitumor activity as first-line treatment in nsclc, although in some patients it may have provided useful palliation (Judson I, etal, Ann Oncol, Jun 1997, 8(6):604-6).

Other Agents

Bendamustin (Ribomustin), a water-soluble membrane-stabilizing benzimidazol nitrogen mustard derivative, under development by Ribosepharm (Munich Germany), a unit of Klinge Pharma (Munich, Germany), is in a phase II clinical trial in sclc. Although this agent did not demonstrate any activity in nsclc, among 22 patients with extensive-disease sclc, IV bendamustin (70 mg/m^2), administered on days 1 to 4, every 28 days, resulted in 9 PR for an ORR of 40.9%. Hematologic toxicity was mild while nonhematologic toxicity, consisting of nausea/vomiting, diarrhea, fever and alopecia, was tolerable. This drug's activity in sclc is comparable to that of other established agents. Also, combination regimens with this agent appear feasible because of its acceptable toxicity profile (Reck M, etal, Pneumologie, Oct 1998;52(10):570-3).

CHS 828, a novel pyridyl cyanoguanidine with potent antitumor activity *in vitro* and *in vivo* in human breast and lung cancer cell lines (Hjarnaa PJ, Cancer Res 15 Nov 1999;59(22):5751-7), under development by Leo Pharmaceutical Products (Ballerup, Denmark), is in a multicenter phase I clinical trial (protocol ID: EORTC-16985), initiated in Europe in April 1999, being conducted under the sponsorship of the EORTC Early Clinical Studies Group, with Thomas Cerny as Chair. Patients with solid tumors are treated with oral CHS 828 every 3 weeks. Treatment continues for at least 2 courses in the absence of disease progression or unacceptable toxicity. Cohorts of 3-6 patients are administered escalating doses of CHS 828 until MTD is reached. Patients are followed for up to 4 weeks. A total of 30 patients will be accrued for this study.

CI-994, under development by Parke-Davis, is a novel oral agent with a mechanism of action possibly involving modulation of histone deacetylation. A randomized, double blind, placebo-controlled, multicenter, phase III clinical trial (protocol IDs: PD-994-013, ILEX-994-013) of gemcitabine with or without CI-994, is ongoing to determine the efficacy and safety of this combination in the treatment of recurrent, locally advanced, or metastatic, unresectable nsclc that failed or relapsed after one prior first-line platinum-containing therapy. Patients are stratified according to performance status and are randomized to one of two treatment groups, one administered oral CI-994 (6 mg/m^2), daily, on days 1 to 21, and IV gemcitabine over 30 minutes on days 1, 8, and 15, and the other gemcitabine and placebo capsules instead of CI-994. Treatment repeats every 28 days in the absence of disease progression or unacceptable toxicity (Orr DW, etal, ASCO00, Abs. 763). A total of 176 patients will be accrued for this study.

Irofulven (MGI 114), under development by MGI Pharma (Minnetonka, MN), is a semisynthetic analog of a natural product that, upon entering tumor cells, covalently binds to DNA, inhibiting DNA synthesis, and inducing apoptosis. Under an agreement with MGI, the NCI initiated two clinical trials in nsclc in 1999.

Temozolomide (Temodal; Schering-Plough), a novel alkylating agent, is an imidazotetrazine derivative, and a prodrug of mitozolomide that converts spontaneously to monomethyl triazenoimidazole carboxamide (MITC), a cytotoxic agent. *In vivo*, the ring structure of temozolomide opens to form a cytotoxic agent which mainly acts by alkylating guanine residues in DNA. Schering-Plough obtained exclusive worldwide rights in 1992 to market temozolomide through a licensing agreement with Cancer Research Campaign Technology.

In August 1999, the FDA granted accelerated approval to Temodal in capsule form (5 mg, 20 mg, 100 mg, 250 mg) for the treatment of adult patients with refractory anaplastic astrocytoma, at first relapse, whose disease progressed on a nitrosourea- and procarbazine-containing drug regimen. However, in January 1999, ODAC voted against approval of Temodal for the indication of glioblastoma multiforme that progressed or recurred after standard therapy. Temodal has been approved in Europe for both these indications.

In clinical studies, the side effects of temozolomide therapy, most commonly nausea, vomiting, headache and fatigue, were generally mild to moderate and self-limiting. Each of these side effects was severe in ≤10% of cases, with nausea and vomiting readily controlled with standard antiemetic therapy. Hospitalization, blood transfusion and discontinuation of therapy because of myelosuppression occurred in less than 10% of cases. Myelosuppression usually occurred within the first few cycles of therapy, was not cumulative and was resolved within 14 days.

A multicenter phase II clinical trial (protocol ID: EORTC-08965), to enroll up to 70 patients with advanced nsclc with/without brain metastases, untreated by chemotherapy for metastatic disease, was initiated in July 1997 by the EORTC Lung Cancer Cooperative Group with Giuseppe Giaccone, MD, as Chair. Temozolomide is administered PO in equally fractionated doses over 5 days, repeated every 4 weeks. In patients with brain metastases treatment is discontinued if disease progresses in the brain and nonbrain sites, or progresses in the brain lesion but stabilizes in the other target lesions. Those with progression in target lesions in the brain but with contemporary evidence of response in the other target lesions may be further treated with temozolomide, in addition to nonchemotherapy medical treatment of the brain metastases (steroids, mannitol, etc.). Patients with the reverse response may also remain on temozolomide therapy, in addition to specific local radiotherapy of nonbrain lesions. Treatment is discontinued in patients without brain metastases if there is clear cut progression before the first disease evaluation which is undertaken 8 weeks after initiation of treatment. Patients with stable disease are treated for a minimum of 8 weeks and evaluated thereafter. In most cases, treatment consists of a minimum of 2 cycles, and may continue for a maximum of 6 cycles, in the absence of disease progression or unacceptable toxicity. All patients are followed every 6 weeks for survival. Study objectives include assessment of the therapeutic activity of temozolomide in this setting and duration of response, and characterization of the drug's acute side effect profile.

Tirapazamine (Tirazone), under development by Sanofi-Synthelabo (Paris, France), is a chemosensitizer, and potential radiosensitizer, that acts by undergoing one electron reduction in hypoxic conditions forming cytotoxic free radicals that produce DNA strand breaks, causing cell death. The drug entered an international multicenter phase III clinical trial in September 1999, in combination with other chemotherapeutics, among them cisplatin. Phase III clinical data from CATAPULT I trials, reported in June 1998, demonstrated that tirapazamine, in combination with cisplatin, significantly increased MST in Stage IIIb and IV nsclc, when compared with cisplatin alone. CATAPULT I began in 1995 at 40 centers in Australia, Canada, Scandinavia, Germany, Belgium, the UK and the USA. Both treatments were administered on an outpatient basis, once every three weeks. The primary study endpoint was duration of survival. The tirapazamine-plus-cisplatin regimen was associated with mild to moderate adverse events, including acute, reversible hearing loss, reversible, intermittent muscle cramping, diarrhea, skin rash, nausea, and vomiting. There were no incremental increases in myelo-suppression, peripheral neuropathy, or renal, hepatic, or cardiac toxicity, and there were no deaths related to tirapazamine. MST was significantly longer (34.6 versus 27.7 weeks) and the response rate was significantly greater (27.5% versus 13.7%) for patients treated with tira-

pazamine plus cisplatin (n=218) than for those treated with cisplatin alone (n=219). In conclusion, the CATAPULT I study shows that tirapazamine enhances the activity of cisplatin in patients with advanced nsclc and confirms that hypoxia is an exploitable therapeutic target in human malignancies (Von Pawel J, etal, J Clin Oncol, March 2000;18(6):1351-9).

Another ongoing clinical trial, known as CATAPULT II, is designed to compare the tirapazamine/cisplatin combination to the etoposide (VP 16)/cisplatin combination. Further studies are using bi- and tri- therapy in nsclc. For instance, tirapazamine is being evaluated as induction chemotherapy, in combination with cisplatin and vinorelbine, and subsequently, as a radiosensitizer in combination with RT, in an NCI-sponsored phase I clinical trial (RTOG-9810) in unresected locally advanced nsclc without evidence of hematogenous metastases (Stage II, IIIa, or IIIb). 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 establish 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 IV 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 maximum of 36 patients will be accrued for this study.

NOVEL FORMULATIONS AND DRUG DELIVERY APPROACHES

Numerous formulations of existing drugs are in development mostly to mitigate the side effects of these drugs and/or improve their delivery and, in many cases, also enhance their activity. Among drugs most actively targeted for improved delivery is paclitaxel with a number of novel formulations in development. A thorough review of such approaches is beyond the scope of this report.

Lipid Formulations

Onco TCS is based on a proprietary lipid envelope-based drug delivery system, Transmembrane Carrier System (TCS), under development by Inex Pharmaceuticals (Vancouver, Canada), that optimizes the delivery of IV drugs by providing prolonged blood circulation, tumor accumulation, and extended drug release at the tumor site. The key component of TCS is PEG-ceramide, a fusion regulator and exchangeable polymer that consists of ceramide lipids, derived from sphingomyelin and cholesterol, linked to a 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). In Onco TCS, the lipid envelope encapsulates a high concentration of vincristine. Onco TCS is in clinical trials for various cancer indications including sclc. Onco TCS is currently being investigated in a pivotal phase II/III trial in relapsed non-Hodgkin's lymphoma (NHL), at 20 medical centers in Canada and the USA. In August 2000, Inex initiated a phase II clinical trial with Onco TCS in sclc patients who relapsed after first-line treatment with a combination of etoposide and cisplatin, as well as those who cannot tolerate etoposide and cisplatin, to be conducted at the Arizona Cancer Center and the Southern Arizona VA HealthCare System (Tucson, AZ).

Liposome-encapsulated paclitaxel (LEP), based on cardiolipin, a lipid found in cardiac tissue, is under development by NeoPharm (Bannockburn, IL), in collaboration with Pharmacia. In a phase I clinical trial, conducted at Fox Chase-Temple University Cancer Center (Philadelphia, PA), LEP was administered IV over 45 minutes, every 3 weeks, using standard IV tubing. No antiemetics were administered. Among 26 patients [Stage IV nsclc=21, sclc=1 breast cancer=2, nasopharyngeal cancer=1, and unknown primary=1; prior chemotherapy=10 (prior paclitaxel=3), and 5 chemotherapy-naive patients treated with prior radiation], treated in cohorts of 3 with escalating dose levels, from 90 mg/m^2 to 300 mg/m^2, a total of 105 cycles were administered. No neuropathies or myalgias were observed at any dose level, and no alopecia was seen at doses ≤175 mg/m^2. Dose-limiting toxicity was seen in 2 patients at 300 mg/m^2 (mucositis), 2 at 250 mg/m^2 (neutropenic sepsis, anaphylaxis), and 1 at 175 mg/m^2 (anaphylaxis). Hematologic toxicities included Grade 4 neutropenia and leukopenia and Grade 3 thrombocytopenia and anemia, starting at 175 mg/m^2. Non-hematologic toxicities included Grade 3-4 mucositis and Grade 3 diarrhea at doses ≥250 mg/m^2. Routine premedication with diphenhydramine and hydrocortisone mostly eliminated liposome infusion reactions that included transient back pain and flushing in 5 patients and rigors in 1 patient. One patient treated at the 300 mg/m^2 dose level died from complications of severe mucositis, and one, at 250 mg/m^2, died from complications of the primary tumor and neutropenic sepsis. There were 2 PR (breast cancer and nsclc) and 3 minor responses (1 breast cancer and 2 nsclc). LEP is easily administered and well tolerated at doses up to 175 mg/m^2 without apparent alopecia, myalgia, or neurotoxicity. Patient accrual continues with dose escalation to 200 mg/m^2 (Joseph Treat, ASCO00, Abs. 881).

Aerosol Delivery

Theoretically, anticancer agents in aerosol formulation may be delivered locally to the lungs to treat various stages of lung cancer, and also act as preventatives in those with precancerous lesions, or in populations at risk because of

exposure to carcinogens and/or hereditary/familial factors. In very early, localized disease, aerosol therapy could also offer an alternative to resection. Such an approach may prove a practical, nontraumatic and cost-effective means of treating lung cancer without subjecting patients to resection and/or systemically delivered toxic chemotherapy.

Aerosol doxorubicin, under development by Batelle Pulmonary Therapeutics (Columbus, OH), has been entered in a phase I clinical trial (protocol #00-C-0088), being conducted at Arthur G. James Cancer Hospital & Richard J. Solove Research Institute (Columbus, OH), the National Cancer Institute, and Memorial Sloan-Kettering Cancer Center (NY, NY). In order to qualify for the study, patients must have either clinical evidence of primary lung or tracheal cancer, or cancer metastatic to the lung with a life expectancy >3 months. Study participants are treated with one dose of doxorubicin, every 3 weeks, for a total of 3 doses in 9 weeks. The drug is administered by inhalation through a mouthpiece on a special machine on an inpatient basis.

Aerosol retinoid therapy, represents one approach that may be significantly enhance the use of retinoids by delivering them directly to the lung because, although retinoids were shown effective against lung cancer, their side effects when administered systemically, renders them inappropriate as chemopreventives. However, local delivery may allow administration of larger doses of the active agent, up to 100 times higher than possible via the oral route while minimizing systemic exposure to the drug by an order of magnitude, resulting in a 1000-fold aggregate advantage over oral delivery. Potentially, an aerosol epithelial delivery system could treat the 100 square meters of the typical tracheal-bronchial tree with medication in much the same way that cigarette smoke infuses this area with carcinogens.

Currently, James Mulshine, Section Head at the NCI, and his team, are conducting a double-blind, phase IIb clinical trial of a retinoid mouthwash, involving 57 patients suffering from leukoplakia, a premalignant cancer of the buccal cavity. Although the efficacy of this approach has not been assessed as yet, the gastrointestinal bleeding characteristic of the agent has not been observed in any of these patients. Once this trial is unblinded, the researchers will begin testing a retinoid aerosol in very early lung cancer, in a clinical trial involving up to 20 patients.

Aerosolized GM-CSF was evaluated at Mayo Clinic (Rochester, NY) in a phase I clinical trial in cancer metastasized to the lung. GM-CSF was administered at 3 dose levels (60 mg, 120 mg, and 240 mg), twice daily, for 7 days. If no toxicity was encountered, patients rested for 7 days, and then were treated and monitored at the next dose level. Six patients were treated at all three dose levels. There was no incidence of pulmonary toxicity, bone pain, fevers, or malaise. Of these 6 patients, 2 with measurable lung metastases from renal cell carcinoma, and melanoma, progressed. Among the other 4 patients treated with an additional 2–5 months of intermittent aerosol GM-CSF at 240 mg without toxicity, 2 with leiomyosarcoma and osteosarcoma, remained without lung metastases, disease stabilized in 1 patient with Ewing's sarcoma, and 1 patient with melanoma was responding at the time of this report. Aerosol delivery of GM-CSF appears to achieve effective immunologic activation without significant toxicity (Anderson PM, etal, ASCO99, Abs. 1734:449a, and Clin Cancer Res, Sep 1999;5(9):2316-23).

Inhaled RFS 2000 (Rubitecan), a camptothecin under development by SuperGen, is in a phase I clinical trial for the treatment of primary lung cancer, and pulmonary metastatic disease, at M. D. Anderson Cancer Center (MDACC), and Baylor College of Medicine (Houston, TX). In addition, a multicenter, open-label, phase II clinical trial (protocol ID: EORTC 16996SL) of oral Rubitecan in advanced sclc was initiated in May 2000, in 12 centers in Europe, under the auspices of the EORTC Early Clinical Studies Group. RFS 2000 is administered PO, as a "5 days on-2 days off" treatment. The trial, to be completed in August 2001, will recruit 50 patients.

ANGIOGENESIS INHIBITORS

Although there is clear proof of principle linking angiogenesis with tumor growth, and the establishment of metastasis, effective inhibition of angiogenesis in the clinic has proven elusive. Some of the early problems stem from inappropriate treatment strategies that employed antiangiogenesis as monotherapy in advanced disease where the treatment proved too little too late. However, these early studies helped to demonstrate the relative safety of many antiangiogenesis agents in current use, paving the way in their deployment as adjuncts in chemotherapy/multimodality treatments in both advanced and early disease. If they prove active in this setting these agents may be used as a chronic anticancer treatment to prevent metastases and recurrence, thus transforming cancer from an acute life-threatening disease to a chronic condition like diabetes or arthritis.

Matrix Metalloproteinase Inhibitors (MMPI)

Matrix metalloproteinases (MMP) are a family of enzymes secreted or expressed on the surface of tumor and surrounding stromal cells, that degrade components of the extracellular matrix. MMPIs were one of the first antiangiogenesis agents to enter clinical trials, and advance to phase III status. However, recently, their clinical development has hit a number of snags, stemming both from a lackluster effectiveness, and a troublesome toxicity profile. Key among the toxicity problems of MMPIs are musculoskeletal complications attributed to inhibition of collagenase I by these agents. For instance, development of an oral MMPI, Bayer's BAY 12-9566, a biphenyl MMP-2 and MMP-9 inhibitor, was discontinued in September 1999 while in phase III clinical trials in both sclc and nsclc.

BMS-275291 (D-2163), under development by Bristol-Myers Squibb based on an exclusive worldwide license from Celltech (Slough, UK), is an orally available MMPI selective against specific MMP enzymes. BMS-275291 does not appear to affect TNF or IL-1 release, believed to play a key role in the inflammation process that may lead to side-effects. The drug is in phase III clinical trials in the USA and Europe in advanced nsclc, in combination with paclitaxel and carboplatin.

Marimastat, under development by British Biotech (Oxford, UK), has reached phase III development in many solid tumors, including nsclc. A phase III randomized, double-blind clinical trial (protocol IDs: ILEX-C03-IVB/173, NCI-V96-1113, BB-C03-IVB/173), comparing the effect of marimastat versus placebo on overall survival in patients with Stage IIIa/b nsclc with minimal residual disease following chemotherapy, radiotherapy, and/or surgery, was ongoing as of May 1999. The study is assessing the effect of marimastat on time to disease progression and safety and tolerability in these patients. Patients are randomized not <2 and not >8 weeks after treatment with the last prior modality, and stratified by participating institution. Patients are randomly assigned to either oral marimastat or oral placebo, administered twice daily. Treatment begins within 5 days of minimization, and continues for up to 18 months after the last patient is enrolled, unless disease progression, or unacceptable toxicity intervenes. Patients deriving benefit at the end of the study may continue treatment, if desired. Patients are followed every 3 months. A total of 504 patients will be entered over 30 months at approximately 60 centers. Kathleen Heck of Ilex Oncology Services (San Antonio, TX) is Chair.

A pilot pharmacokinetic study of marimastat, in combination with carboplatin and paclitaxel, was conducted in 22 chemotherapy-naive patients with metastatic, or locally advanced, inoperable, nsclc (Stage IIIb=23% and Stage IV= 77%). Treatment consisted of marimastat (10 mg or 20 mg), *bid*, in combination with IV paclitaxel (175 mg/m^2 or 200 mg/m^2), over 3 hours, and IV carboplatin (AUC=7) over 1-2 hours. Treatment completion was defined as 4 21-day cycles of chemotherapy; 17/22 patients completed 4 chemotherapy cycles (total cycles=82). The combination was well tolerated at low- and high-dose levels with 17% and 20% Grade 2 musculoskeletal toxicities reported, respectively. No unexpected or cumulative toxicities were observed. Preliminary findings suggest that concurrent administration of marimastat did not influence the pharmacokinetics of the other drugs. Among 22 evaluable patients there were 11 (50%) PR, and disease stabilized in 4 (18%) and progressed in 6 (27%) (Anderson I, etal, ASCO99, Abs 719:187a).

Step 1 of a randomized, double blind, multicenter, placebo-controlled, phase III clinical trial (Protocol IDs: EORTC-08962, EORTC-08962B, CAN-NCIC-BR12), conducted to determine whether treatment with marimastat prolongs overall survival and time to progression in patients with sclc who have achieved CR or PR after first-line chemotherapy, with or without radiotherapy, initiated in March 1997, was closed in December 1999, while step 2 was ongoing as of March 2000. The study will also determine the tolerability, toxicity, and QoL of prolonged administration of marimastat. Patients are randomized into two groups with half administered PO marimastat, twice daily (breakfast and evening meal), and the other half a placebo. Treatment continues for 2 years, or until documented disease recurrence, or progression. All patients are followed every 6 months until death. Projected accrual is 360, with an equal number of patients in both arms. The study is being conducted under the auspices of the EORTC Lung Cancer Cooperative Group, with Giuseppe Giaccone of the Academisch Ziekenhuis der Vrije Universiteit (Amsterdam, the Netherlands) as coordinator of EORTC- 08962, Christian Manegold as Chair of EORTC-08962B, and by the National Cancer Institute of Canada (NCIC) Clinical Trials Group with Frances A. Shepherd, Chair of study CAN-NCIC-BR12.

Neovastat (AE-941), under development by Aeterna Laboratories (Quebec City, Canada), under an NCI Clinical Trials Agreement, is an MMPI undergoing phase III clinical trials in a variety of solid tumors, including nsclc. Neovastat is a shark cartilage liquid extract with a dual antiangiogenic action, acting as an MMPI, and interacting with the VEGF receptor. In December 1999, an IND was filed in Canada, and the USA for a phase III clinical trial which was initiated in May 2000. This randomized, placebo-controlled, double-blind, phase III clinical trial will involve approximately 70 sites across North America, and will evaluate the efficacy of Neovastat as an adjunctive treatment to induction platinum-based chemotherapy, followed by concurrent chemoradiotherapy. Over 750 chemonaive patients are to be recruited into this study. Dr. William K. Evans, Professor of Medicine at the University of Ottawa, in Canada, and Dr. Roy Herbst, at MDACC, are co-PIs of the trial.

Neovastat (500 mg/kg) was additive to cisplatin (3 mg/kg) in reducing the number of lung metastasis (83% reduction with the combination compared to 54% with cisplatin alone). No mortality and no loss of body weight were observed at 500 mg/kg, the highest dose administered. During a phase I/II open-ended trial, 80 lung cancer patients (64% with distant metastases) were treated with daily PO Neovastat monotherapy (5 to 95 mg/kg). An incidence of 7% of non-serious adverse events was observed, that most commonly involved the gastrointestinal system (nausea, vomiting). Neovastat at 120 and 240 ml/day resulted in clinical improvements in analgesics consumption, weight loss and disease progression compared to lower doses administered during the first 12 weeks. In another study, 126 patients with solid tumors (lung cancer=42) were administered Neovastat alone (n=72), or combined with chemotherapy (n=39), or radiotherapy (n=15). In all clinical studies involving >540 patients (>177

treated for >3 months), no serious clinical toxicity, or laboratory abnormalities related to AE-941 were reported (Evans WK, etal, ASCO99, Abs. 1938:502a).

Prinomastat (AG3340), under development by Agouron Pharmaceuticals (La Jolla, CA), is a synthetic selective inhibitor of certain MMP enzymes such as gelatinase A (MMP-2) and gelatinase B (MMP-9), stromelysin-1 (MMP-3), membrane type 1-matrix metalloproteinase MT1-MMP (MMP-14), and collagenase-3 (MMP-13), associated with growing tumors, but is less potent against MMP-1, associated with normal maintenance of collagen in the joints. AG3340 was designed on the basis of the x-ray crystal structure of recombinant human MMPs. The most common toxicities of prinomastat have been observed in the joints, and include joint pain, stiffness and swelling, and in a few patients, some limits in the mobility of certain joints, most often in the shoulders and hands. All of these effects were reversible and were effectively managed by treatment rest and dose reductions.

In July 2000, Pfizer announced it would discontinue the two ongoing phase III clinical trials of prinomastat in combination with cytotoxic chemotherapy in advanced nsclc. A phase III clinical trial of Prinomastat, initiated in August 1999, had been designed to evaluate the safety and efficacy of this agent as part of a first-line therapy, in combination with chemotherapy. In this study, that was being conducted at sites in North America, Europe, and Australia, patients were being randomized to either treatment with oral Prinomastat or placebo, in combination with gemcitabine and cisplatin.

In another phase II/III randomized double-blind, placebo-controlled clinical trial, that was to enroll 500 patients, that began in May 1998 in sites throughout North America, oral AG3340 was being administered in tablet form in combination with paclitaxel and carboplatin. The primary objective of this study was to compare time to progression between patients treated with AG3340, or placebo, in combination with paclitaxel and carboplatin. Secondary endpoints included response rates, survival, and QoL measurements. The study was conducted at Toronto General Hospital, in Canada, and the University of Arizona Cancer Center.

Treatment consisted of two doses of AG3340, used in two contrasting tumor-stromal settings, one known to be associated with no joint effects, and the other with a moderate incidence of joint effects; the latter dose chosen as pharmacologic evidence of MMP enzyme inhibition. Treatment is continued until disease progression. Because reduced rate of growth associated with MMP inhibition may extend beyond the time of progression, treatment with placebo, or AG3340, may continue in a blinded manner during second-and third-line therapies. Among 250 patients with nsclc, enrolled as of November 1998, in addition to front-line chemotherapy, 28 were treated with AG3340, or placebo, in combination with regimens including vinorelbine (n=7), cisplatin n=6), gemcitabine (n=4), etoposide (n=2), taxotere (n=2), mitomycin (n=1), vinblastine (n=1), estramustine (n=2), and radiation to metastatic sites (n=11). Other than standard toxicities attributable to chemotherapy, toxicities of AG3340 had been minimal (Collier M, etal, ASCO99, Abs. 1861:482a).

Angiostatin and Endostatin

Phase I clinical trials with both Angiostatin and Endostatin, under development by EntreMed (Rockville, MD), are currently ongoing. These agents are being evaluated as monotherapy in refractory solid tumors to establish phase II dose, and assess any toxicities. Angiostatin is also being evaluated in conjunction with radiation therapy in the treatment of solid tumors.

Squalamine

Squalamine (MSI-1256F), a synthetic aminosterol originally derived from the dogfish shark, under development by Magainin Pharmaceuticals (Plymouth Meeting, PA), was shown in preclinical evaluations to be an angiogenesis inhibitor. A phase II clinical trial in nsclc commenced in June 1999 at the University of Wisconsin Comprehensive Cancer Center (Madison, WI), under the direction of Dr. Joan Schiller. A second site for the study is planned at MDACC, under the direction of Dr. Roy Herbst. These trials will test the safety and efficacy of squalamine in combination with paclitaxel and carboplatin. Squalamine is being administered IV with each 3-week cycle of chemotherapy. It is anticipated that approximately 35 patients will be enrolled in the study. Efficacy will be assessed by the number of patients whose tumors stop growing, along with number of individuals who experience tumor shrinkage. In preclinical studies, the combination of squalamine and a platinum analog demonstrated significant antitumor activity against human lung cancer (Schiller JH and Bittner G, Clin Cancer Res, Dec 1999;5(12):4287-94).

VEGF Antagonists

Over 22 different antagonists of VEGF and its receptor, Flt-1, are in development with several having entered clinical trials, for a variety of indications.

Angiozyme, under development by Ribozyme Pharmaceuticals (Boulder, CO), is a hammerhead ribozyme that blocks angiogenesis by inhibiting production of VEGFr. A multidose phase I/II was initiated at the Cleveland Clinic Foundation (Cleveland, OH) in November 1999, to enroll 15-25 cancer patients, to examine the safety, pharmacokinetics and effect on biologic markers of subcutaneous doses of daily Angiozyme, administered for 28 days. According to completed phase Ia (Study 9801) and phase Ib (Study 9901) clinical trials, no adverse effects were noted when single escalated doses of Angiozyme were administered either IV or subcutaneously to healthy volunteers or cancer patients. The absolute bio-

availability following subcutaneous administration was estimated to be 74%-90% (Parker VP, etal, ASCO00, Abs. 703).

rhuMAb-VEGF, under development by Genentech (South San Francisco, CA), is one of a few VEGF antagonists in late stages of clinical development in a variety of solid tumors. In a multicenter randomized phase II clinical trial, performed at Vanderbilt University (Nashville, TN), Kaiser Permanente (Vallejo, CA), MDACC, Fox Chase Cancer Center (Philadelphia, PA), University of Colorado (Denver, CO) and UCLA (Los Angeles, CA), 99 chemotherapy naive patients (adenocarcinoma=61%, squamous cell carcinoma=19%, and other=20%) with advanced (Stage IIIb=16%, or Stage IV=66%), or recurrent (18%) nsclc, were treated either by a combination of carboplatin (AUC=6) and paclitaxel (200 mg/m^2), alone, every 3 weeks, for 6 cycles (group A=32 patients), or with these same drugs along with low-dose rhuMAB VEGF (7.5 mg/kg) (group B=32), or high-dose rhuMAB VEGF (15 mg/kg) (group C=35), every 3 weeks, until progressive disease. Patients in group A whose disease progresses could cross over to single-agent rhuMAb VEGF treatment. The most serious side effect was sudden and life-threatening hemoptysis of unknown origin, which occurred in 6 rhuMAb VEGF-treated subjects, and was fatal in 4; 4/6 occurred in patients with squamous cell carcinoma (DeVore RF, etal, ASCO 2000, Abs. 1896). As reported in May 2000, ORR was 40% in group C, compared with 31% in group A, and 22% in group B. Time to relapse was 7 months in group C, compared to 6 months for group A and 4 months for group B. Although the data provide preliminary evidence that rhuMAb VEGF, at a dose of 15 mg/kg, and in combination with carboplatin/paclitaxel chemotherapy, may increase response rates, and prolong time to disease progression in this setting when compared with carboplatin/paclitaxel chemotherapy alone, it now seems unlikely that patients with squamous cell lung cancer in the large airways would be treated with this drug in the future because of the adverse side effects.

Semoxind (SU5416), under development by Sugen (South San Francisco, CA), prevents angiogenesis by blocking VEGFr2 (flt-1/KDR) phosphorylation (Mendel DB, etal, AACR00, Abs. 2842). The drug is being evaluated for various indications, having reached phase III clinical trials in colorectal cancer. In June 1999, the FDA approved Sugen's proposed design for a phase III clinical trial to evaluate SU5416 against standard chemotherapy regimens in chemonaive patients with nsclc. The primary endpoint is survival, with secondary endpoints of time-to-disease progression and objective response rate. This proposed trial reflects Sugen's development strategy for SU5416, which is to rapidly move into phase III testing based on the cumulative results of over 20 phase I and phase II clinical trials involving more than 135 patients with nsclc and other solid tumors.

Other Agents

BN-50730, under development by Beaufour Ipsen (Paris, France), significantly inhibits growth of orthotopic lung tumor and subcutaneous prostatic carcinoma xenografts in athymic nude mice. BN-50730 has an antiproliferative effect on human umbilical vein endothelial cells (HUVEC) *in vitro*, yet has little effect on *in vitro* tumor cell proliferation, suggesting that it is antiangiogenic. Inhibition of basic fibroblast growth factor (bFGF)-induced HUVEC proliferation by BN-50730 indicates antagonism via the angiogenic bFGF pathway. Tumor cells used in this study produced bFGF. Although bFGF is known to be a strong promoter of angiogenesis, little is known about the intracellular signaling pathways. Interestingly, BN-50730 has been shown to antagonize platelet-activating factor (PAF), suggesting that PAF is an important intracellular messenger in the bFGF signal transduction cascade (Hunt JD, etal, AACR00, Abs. 4099:645).

REGULATION

Most new approaches for the treatment of cancer center on attempts to interfere in pathways involved in the regulation of certain activities that play a role in dysregulation leading to malignancy. Although older cytotoxic drugs also exhibit such regulatory activities as enhancement of apoptosis, inhibition of angiogenesis, cell cycle disruption, etc., their main action is broadly cytotoxic and not selective enough to prevent the demise of healthy cells, ergo the undesirable toxicities of most standard chemotherapy. In theory, highly targeted regulation of only certain aberrant activity would result in effective means of combating cancer with minimal toxicity.

Cell Cycle Regulation

The cell cycle is the target of various agents in development for a variety of indications (see FO, pp 590-600). However, to date, cell cycle regulating drugs remain in the very early stages of development, with most undergoing preclinical testing. One suggestion regarding the application of cell cycle regulators in the treatment of cancer, is that it may be necessary to ascertain the molecular profile of cell cycle regulating genes in individual tumors in order to predict responsiveness and optimize the use of these agents. For instance, *in vitro* evaluations found that UCN-01-induced G1 arrest can occur in cells null for p53 and p16CDKN2, and that Rb status influences the ability of UCN-01 to induce a G1 arrest (Mack PC, etal, Clin Cancer Res, Sep 1999;5(9):2596-604).

Flavopiridol, under development by Aventis, is a semisynthetic derivative of a tree bark compound that is a potent CDK1 inhibitor, arresting cell cycle progression in either G1 or G2. In *in vitro* studies, flavopiridol demonstrated activity against nsclc (Shapiro GI, etal, Clin Cancer Res, Oct 1999;5(10):2925-38). Keith C. Bible, MD, PhD, at the Mayo Clinic Foundation (Rochester, MN) has been

awarded a 3-year grant (July 1, 1999 to June 30, 2002) to attempt to improve understanding of how flavopiridol kills cancer cells, how cancer cells can become resistant to the toxic effects of flavopiridol, and how to predict which cancer patients are most likely to benefit from treatment with this agent.

A phase II clinical trial of single-agent flavopiridol in previously untreated Stage IV nsclc (protocol ID: T97-0057, Dana-Farber #97-128), was conducted at Dana-Farber Cancer Institute (Boston, MA), under PI Geoffrey Shapiro, MD. Patients were treated with flavopiridol (50 mg/m^2/day and a concentration of 0.1-0.2 mg/ml), as a 72-hour continuous infusion, delivered via a port-a-cath, every 14 days. Dose escalation to 60 mg/m^2/day was permitted if there was no significant toxicity. Among 18 treated patients (adenocarcinoma=17, bronchoalveolar carcinoma=1, squamous cell carcinoma=1), 16 were evaluable for response. Of these, treatment was escalated to 60 mg/m^2/day in 5 patients and was reduced to 40 mg/m^2/day in 3. There were no responses. Disease stabilized in 5 patients for at least 3 months; in 4/5 patients disease progression was documented at 3, 3.5, 4 and 5 months, respectively, and, in one patient, it continued for 9+ months while on treatment. Toxicities included Grade 2 diar-rhea (44%), fatigue (11%), tumor pain (6%), orthostatic hypotension (6%), nausea (6%), and increased pleural effusion (11%) not clearly related to disease. Thrombotic events occurred in 6 patients (33%) with 3 occurring at the port-a-cath site. At the doses and schedule used in this study, flavopiridol did not exhibit cytotoxic activity in nsclc, although protracted periods of disease stability was achieved with acceptable toxicity (Shapiro, G, etal, ASCO99, Abs. 2013:522a). Final results of this trial are to be published in late 2000. Because of these results, flavopiridol as monotherapy does not appear effective in metastatic nsclc. A new clinical trial in nsclc, to be initiated at Dana-Farber, will investigate flavopiridol in combination with paclitaxel. Prolonged administration of flavopiridol causes diarrhea which may prove the DLT compromising its effectiveness by limiting the dose necessary for maximum effectiveness.

UCN-01, under development by Kyowa Hakko Kogyo (Tokyo, Japan), is a staurosporine analog that is a protein kinase C inhibitor that may block G2 arrest of the cell cycle following DNA damage. It also acts on cell cycle-dependent mechanisms, such as induction of expression of p21 protein, and inhibition of cyclin-dependent Rb kinases. UCN-01 induces a p53-independent/rb-dependent G1 arrest. Combination with cisplatin may be particularly effective in nsclc, as adding UCN-01 to this regimen may potentiate the DNA damaging effects of cisplatin by abrogating the G2 checkpoint arrest. To prove this premise, a phase I clinical trial of this combination has been initiated at the University of California Davis Cancer Center (Sacramento, CA), and the VA Northern CA Health Care System (Martinez, CA). The protocol involves sequential administration of cisplatin and UCN-01 with correlative molecular studies of serial patient tumor biopsies (Gumerlock PH, etal, ASCO00, Abs. 1942).

Approaches Targeting the Epidermal Growth Factor Receptor (EGFr)

The epidermal growth factor receptor (EGFr) is a very important target for the development of drugs against many solid tumors, including lung cancer. It has been demonstrated that cancer cells can become dependent on growth signals mediated through the EGFr for their survival. Over 300,000 cancer patients in the USA undergo treatment every year for tumors that overexpress EGFr. For example, an estimated 70% of lung cancer, and 80% of prostate cancer tumors overexpress EGFr.

ABX-EGF, under development by Abgenix (Fremont, CA), in collaboration with Immunex (Seattle, WA), is a fully human IgG_2 MAb generated by Abgenix using XenoMouse technology. ABX-EGF binds EGFr with high affinity, blocking the binding of both EGF and TGF-α to various EGFr-expressing human carcinoma cell lines, and abolishing EGF-dependent tumor-cell activation, and proliferation. Upon binding to the receptor on tumor cells, ABX-EGF is internalized but not degraded, suggesting that it may be recycled to the cell surface. ABX-EGF also inhibits *in vitro* the spontaneous production of angiogenic factors such as VEGF and interleukin 8 (IL-8) from tumor cells by 75% and 85%, respectively (Yang X-D, etal, ASCO00, Abs. 183).

Under a joint development and commercialization agreement, entered in July 2000, Immunex will pay Abgenix an initial license fee, with a second license fee payable upon commencement of phase II clinical trials. Both development costs and any potential profits from sales of a targeted product will be shared equally. Immunex and Abgenix will share responsibility for product development with Abgenix responsible for completing the phase I trial, and both companies will share efforts in the execution of phase II clinical trials for a variety of cancer indications. Immunex has primary responsibility for phase III clinical trials, and would market any potential product, while Abgenix has retained co-promotion rights.

An IND was filed in July 1999, to initiate a phase I clinical trial of ABX-EGF in the treatment of patients with renal, prostate, pancreatic, or esophageal cancer, or nsclc. This multicenter dose-escalation, clinical trial (protocol IDs: UCLA-9906078, NCI-G00-1673, ABX-EG-9901) will be conducted under the direction of the Jonsson Comprehensive Cancer Center's (Los Angeles, CA) Arie Belldegrun, MD, as Study Chair, and is expected to accrue a total of 31 patients over approximately 14 months; as of 1 June 2000, this study was not yet open for patient recruitment.

Trastuzumab (Herceptin; Genentech), is a recombinant DNA-derived humanized MAb (4D5) targeting the HER2 protein on tumor cells. HER-2/neu (HER2) is a 185-

kDa glycoprotein related to the EGFr that is overexpressed in nsclc (Klapper LN, etal, PNAS USA, 27 Apr 1999;96(9):4995-5000 and Scheurle D, etal, ASCO00, Abs. 2012). Herceptin, already on the market for the treatment of advanced HER-2-expressing breast cancer, is also being evaluated in a variety of solid tumors, including nsclc. However, the significance of HER2 overexpression in nclc has not been demonstrated. Problems also arise from the reliability of current detection of HER2 expression, as it appears that different methodologies produce different results (Hirsch F, etal, ASCO00, Abs. 1900). Furthermore, presence of overexpression did not impact the outcome of Stage IIIa/b nsclc patients being treated by neoadjuvant chemotherapy (Tafur I, etal, ASCO00, Abs. 2078).

ZD 1839 (Iressa), under development by AstraZeneca, is in phase II clinical trials in advanced solid tumors. According to combined results from two phase I clinical trials, this orally administered drug exhibited activity as monotherapy in nsclc. Among 50 patients with nsclc, there was 1 PR lasting 9+ months, while reduction of measurable disease was observed in 2 patients (Baselga, J, etal, ASCO00, Abs. 686). Similar observations were reported from another phase I clinical trial. Among 16 nsclc patients, there were 2 PR, one at the 300 mg dose level, lasting 9+ months, and one at the 525 mg dose level, lasting 6+ months; disease regressed significantly in 2 more nsclc patients, one at the 400 mg dose level for 2 months, and the other at the 700 mg level for 6+ months, and disease stabilized in 2 patients, one at the 225 mg level for 5 months and the other at the 525 mg level for 5+ months (Ferry D, etal, ASCO00, Abs. 5E).

Farnesyl Tranferase Inhibitors (FTI)

Farnesyl transferase inhibitors (FTI) are a new class of drugs that inhibit post-translational C-terminal modification of many essential proteins including ras, rac, rho and most cellular G-proteins.

R115777, an FTI under development by Johnson & Johnson, is being evaluated in numerous tumor types, including lung cancer. R115777 is a methyl-quinolone derivative that is a potent, selective non-peptidomimetic inhibitor of the farnesyl transferase enzyme required in the post-translational activation of ras. An NCI-sponsored phase II multicenter clinical trial (protocol IDs: MAYO-982401; NCI-T99-0072) to study the effectiveness of R115777 in treating recurrent or metastatic nsclc (Stage IV), was being planned as of July 2000. Patients are to be treated with oral R115777 twice daily, until disease progression, or unacceptable toxicity. The study will assess the effectiveness, overall survival time, and time to disease progression of this approach, determine its toxicities in this setting, evaluate the inhibition of protein farnesylation *in vivo*, and correlate such inhibition to plasma levels of R115777, and the occurrence of CYP450 polymorphisms, and relate these to drug toxicity, pharmacokinetics, and response to treatment. Patients are to be followed every 3 months for 5 years. A total of 50 chemotherapy-naive (except low-dose cisplatin as a radiosensitizer) patients will be accrued for this study over 12 months. Alex A. Adjei, MD, of Mayo Clinic Cancer Center is Study Chair.

An NCI-sponsored multicenter phase II clinical trial to study the effectiveness of R115777 in treating relapsed, extensive-disease sclc, began in September 1999. Study objectives are to determine R115777 treatment effectiveness, duration of response, time to disease progression, survival, and QoL in sclc patients who experienced at least a PR that lasted for at least 3 months, with one prior chemotherapy regimen. The study will also assess the safety of R115777, and the presence of ras mutations in relapsed patients. Patients are treated with oral R115777, every 12 hours, for 14 consecutive days, followed by 7 days of rest. Treatment continues in the absence of unacceptable toxicity or disease progression. QoL is assessed at baseline, on day 15 of each course, and at the end of the study. A total of 27-40 patients will be accrued for this study whose chair is Abraham Chachoua, MD, at Kaplan Cancer Center (New York, NY).

SCH 66336, under development by Schering-Plough, is a potent, orally bioavailable FTI with *in vivo* and *in vitro* activity against a wide variety of human and murine tumor cell lines and xenografts. In a phase I clinical trial, a combination of SCH 66336 and gemcitabine demonstrated significant activity in advanced solid tumors, including nsclc and mesothelioma (Hurwitz HI, etal, ASCO00, Abs. 717).

Approaches Targeting p53

rAd/p53, under development by Canji (San Diego, CA), is a viral vector carrying wild-type p53. The basis of this treatment approach is evidence linking p53 mutations with nsclc. It, therefore, appears reasonable that replacement of mutated/missing p53 would restore tumor suppressor function in cancer cells. In nsclc, gene transfer with this construct is being carried out by various administration routes, including intratumoral injection, and bronchoalveolar lavage (BAL).

A phase I clinical trial (protocol IDs: 199/13942, E-6597) of rAd/p53, administered by BAL, was started in November 1998 in patients with unresectable nsclc. Patients are being assessed for expression of the p53 gene, and subsequent induction of apoptosis in tumor and normal tissues exposed to rAd/p53. This trial is being conducted by the Eastern Cooperative Oncology Group with David P. Carbone, MD, as Study Chair. In a phase I clinical trial, conducted at MDACC, up to six intratumoral injections of rAd/p53, administered to 21 patients with advanced nsclc at monthly intervals, were well-tolerated. Expression of the p53 transgene was evident, along with potentially useful clinical responses. Time to disease progression in the indicator lesion treated with rAd/p53, appeared enhanced by higher doses of vector, concomitant cisplatin therapy, and evidence of apoptosis on tumor

biopsy specimens (Roth JA, etal, Semin Oncol, Jun 1998;25(3 Suppl 8):33-7).

Another multicenter phase I clinical trial of rAd/p53, in combination with RT, in patients with nsclc, was initiated in January 2000 (protocol IDs: 199/14657, E-8597). Patients are being administered rAd/p53 by direct injection into an endobronchial lesion via bronchoscopy, or into locoregional tumors via multiple percutaneous punctures under fluoroscopic, ultrasonic, or CT scan guidance on days 1, 3, and 8, and also undergo RT from day 2 through 11. Patients will be assessed for any vector incorporation, antitumor response, local control, viral dissemination, and development of adenovirus antibodies. Joan Hoff Schiller, MD, of the Eastern Cooperative Oncology Group, is the Study Chair.

RPR/INGN 201, under development by Introgen Therapeutics (Austin, TX), involves an intratumoral administration of an adenovirus vector containing wild-type p53 complementary DNA. In a phase II clinical trial, conducted at MDACC, 16 patients with localized nsclc who were not candidates for surgery or chemoradiation, were treated with 3 intratumoral injections of RPR/INGN 201 on days 1, 18 and 32, in conjunction with radiation therapy (60 Gy). RPR/INGN 201 doses were escalated from 3 x 10^{11} to 3 x 10^{12} viral particles (vp), and were injected directly into the primary tumor by bronchoscopy (n=3), or computed tomographic (CT) guidance (n=13); 13 patients underwent 61 CT-guided biopsies or injections with 13 pneumothoraces that were managed with observation (n=8) or percutaneous pleural catheter (n=5).

Grade 3 or 4 toxicity occurred in 3/16 (19%) patients, and there were no treatment-related deaths. Tumor response was assessed by a 3-month tumor biopsy and CT evaluation. Pathologic negative biopsies were noted in 8 out of 11 (62%) patients. Among 13 evaluable patients, there were 5 CR (39%), 2 PR (15%), and disease stabilized in 1 (8%) patient and progressed in 5 (39%). Median follow-up of all 16 patients was 7.2 months with a 1-year survival rate of 65%. Progression-free survival rate was 45.5% (median=8.0 months) at one year with all failure attributable to metastatic progression (n=5) rather than local failure. These results suggest that adenoviral-mediated p53 gene therapy can be safely accomplished in conjunction with RT. Compared to a previously reported 3-month pathologic control rate of 15% to 17% with chemoradiation or RT alone, the combination of RPR/INGN 201 and RT warrants further evaluation (Swisher S, etal, ASCO00, Abs. 1807).

A pilot phase I clinical trial (ECOG 6597) of RPR/INGN 201, delivered via bronchoalveolar lavage (BAL) to involved lobes of the lung in patients with bronchoalveolar carcinoma (BAC), was undertaken primarily to evaluate the safety of RPR/INGN 201 delivery by BAL, and also to determine expression of the p53 gene, induction of apoptosis in tumor cells, and clinical evidence of response. Initially, two treatments, at the same dose level, were administered two weeks apart, to a single involved lobe. If this was tolerated, and there was perceived benefit, additional treatments to all involved lobes were allowed. The initial dose level was 2 x 10^9 vp per dose, escalated by ten-fold increments with each patient treated only at a given dose level.

As of November 1999, among 14 patients enrolled in the trial, after two treatment cycles, pathologic response was observed on biopsy in 2 patients, 4/9 evaluable patients experienced an improved corrected carbon monoxide (CO) diffusing capacity (DLCO) of 20% or more, and 4/11 patients reported symptomatic improvement. Grade 4 pulmonary toxicity was noted in one patient at the 2 x 10^{10} vp dose level, but 2 other patients added at this level did not show any further dose-limiting toxicity (DLT), and treatment is ongoing at the 2 x 10^{12} vp dose level (Kubba S, etal, ASCO00, Abs. 1904).

ONYX-015, under development by Onyx Pharmaceuticals (Richmond, CA), is an E1B gene-attenuated adenovirus (mutant virus) which lyses p53 deficient cells selectively. Loss of heterozygosity (LOH) and p53 mutations have been detected in more than 50% of lung cancers. The agent is in phase I clinical trials in refractory solid tumors. *In vitro*, ONYX-015 effectively lyses nsclc cell lines (NCI-H522 and NCI-H1703) that lack functional p53 gene, but not cells with normally expressed p53. In combination with standard chemotherapy, synergistic effects were also clearly seen in these cell lines when ONYX-015 was combined with cisplatin and paclitaxel while no lysis was observed when the cells were treated with the chemotherapeutic agents alone. When combined with a low-dose chemotherapy combination, the cytolysis effect of ONYX-015 was increased by a factor of 10. In addition, the virus (with or without chemotherapy) can lyse fresh human lung cancer cells without affecting normal lung single-cell suspensions. Based on these and subsequent preclinical studies, ONYX-015 is entering phase I clinical trials for the treatment of patients with advanced lung cancer (You L, etal, ASCO99, Abs. 1768:458a).

Agents Targeting Other Markers

G3139 (Genasense), under development by Genta (Lexington, MA), is an antisense construct targeting bcl-2. The drug is in clinical trials, in combination regimens with various chemotherapeutics, in many cancer types, including sclc. Genta's strategy is to proceed to phase III clinical trials with this construct in selected indications in combination with prevailing standard therapies.

In an NCI-sponsored ongoing phase I/II clinical trial (protocol IDs: UCCRC-10017, NCI-T98-0091), G3139 is being evaluated in combination with paclitaxel in recurrent sclc at the University of Chicago Cancer Research Center under PI Charles M. Rudin, MD. The study is to enroll 19 to 33 patients whose disease recurred after prior treatment, to be stratified according to whether they were

previously exposed to taxanes. Treatment consists of continuously administered IV G3139 for 1 week followed by 2 weeks of rest, with IV paclitaxel administered over 3 hours on day 6 of each course. Treatment lasts for a minimum of 2 courses in the absence of disease progression, or unacceptable toxicity. Intrapatient dose escalation is allowed. Trial objectives include assessment of feasibility of paclitaxel administration during continuous intravenous delivery of G3139 and toxicity, as well as evaluation of any correlation between bcl-2 expression and treatment efficacy. Patients are followed until death.

ISIS 3521, an antisense inhibitor of PKC-α expression, under development by Isis Pharmaceuticals (Carlsbad, CA), is expected to enter a phase III clinical trial in 2000. In a clinical trial, comprising a phase I portion involving 18 patients (nsclc=12 and other tumors=6), and a phase II expansion, limited to patients with nsclc, being conducted at Stanford University (Stanford, CA), patients were treated with ISIS 3521 in combination with standard chemotherapy. In the phase I portion, patients were treated with carboplatin (AUC=5 or 6) and paclitaxel (175 mg/m^2) alone, on cycle 1 while with cycle 2 and beyond, escalating doses of ISIS 3521 (1.0-2.0 mg/kg/day), administered as a continuous IV infusion on days 1 to14, were added to the regimen, with carboplatin and paclitaxel on day 4. In the ongoing phase II clinical trial, all patients were treated with carboplatin (AUC=6) and paclitaxel (175 mg/m^2) with ISIS 3521 (2.0 mg/kg/day) starting on cycle 1. Treatment was repeated every 21 days until maximum benefit.

Final results of the phase I study showed that toxicity between cycles 1 and 2 (without and with ISIS 3521) did not differ. No DLT was seen at maximum doses of carboplatin (AUC=6), paclitaxel (175 mg/m^2) on day 4, and ISIS 3521 (2.0 mg/kg/day for 14 days), and there was no evidence of any pharmacokinetic interactions between ISIS 3521, and either chemotherapy agent. In both phases, 72 cycles were administered to 18 nsclc patients. Toxicity consisted of Grade 3 (5 patients, 20 cycles) and Grade 4 (4 patients, 8 cycles) neutropenia and Grade 3 (2 patients, 2 cycles), and Grade 4 (1 patient, 2 cycles) thrombocytopenia. Among 15 evaluable nsclc patients, PR was noted in 53%, a minor response in 13%, and disease stabilized in 20%. Median time to progression was 6.5 months with a 90% overall survival at a median follow up of 8 months (Yuen A, etal, ASCO00, Abs. 1802).

According to interim results the overall response rate among 13 patients with nsclc treated in both phases of this study was 62% (Yuen A, etal, AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Suppl Clin Cancer Res, Vol 5, Nov 1999, Abs. 580). Survival results show that 7/15 (47%) patients lived at least 1 year or more with the longest survival at 21 months following study entry.

IMMUNOTHERAPY/VACCINES

There is a pressing need for immunotherapy approaches to treat lung cancer, prevent disease recurrence and, potentially, immunize high-risk populations, such as smokers, the elderly, those exposed to occupational hazards, etc. However, at this point immunotherapy in these settings remains an investigational technique in very early stages of development.

Cytokine-producing Tumor Vaccines

Cytokines may be effective in the treatment of lung cancer (see FO 1166-1167), and also enhance the immunogenicity of lung cancer vaccines.

Adoptive immunotherapy (AI), based upon the injection of autologous lymphocytes, manipulated *in vitro* to express various cytokines, is a promising experimental technique in the treatment of solid tumors. Investigators at the Istituto Nazionale per la Ricerca sul Cancro (Genova, Italy) report enhanced survival, and long lasting disease-free periods, in a significant number of 296 patients with solid tumors (melanoma, kidney cancer, nsclc, mesothelioma, neoplastic pleural effusion, and liver cancer) who entered clinical trials in early 1990, involving treatment with either locoregional or systemic AI, using both LAK and TIL cells, in combination with subcutaneous rIL-2. AI appeared efficacious in the treatment of melanoma, and lung and hepatic cancers (Semino C, etal, Anticancer Res, Nov-Dec 1999;19(6C):5645-9).

Vaccination with autologous tumor cells expressing interleukin (IL)-2, interferon γ (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF), in combination with local RT, was also more effective than either approach alone in treating lung metastases of murine renal cell carcinoma using the mouse Renca pulmonary metastasis model. Neither local RT alone, nor the combination of RT and multiple vaccination with irradiated wild-type Renca, significantly reduced the number of lung tumors. In contrast, the combination of RT and multiple vaccinations with cytokine-producing Renca cells significantly reduced the number of lung tumors. This regimen was more effective than multiple vaccinations with cytokine-producing Renca cells alone (Nishisaka N, etal, J Immunother, Jul 1999;22(4):308-14).

SRL 172

SRL172, under development by SR Pharma (London, UK), is a suspension of killed *Mycobacterium vaccae* (strain NCTC 11659) that functions as an immunomodulator by acting as an immune switch, triggering development of Th1 lymphocytes in preference to Th2 cells. In human trials, improvements in clinical symptoms have been accompanied by changes in immune mediators indicative of a switch to Th1 cell production. In October 1998, a randomized, multicenter, phase III clinical trial was initiated to recruit more than 400 patients at 30 centers across Europe, including sites in the UK, Austria, Germany, Poland

and Hungary. Enrollment was completed as of September 1999, and results should be available during the first half of 2001.

In phase II lung cancer trials, a combination of SRL172 and standard chemotherapy was shown to extend survival in comparison to chemotherapy alone. Interim results from a 28-patient phase II trial in nsclc, conducted at the Royal Marsden Hospital (Sutton, UK) and the Kent Cancer Centre (Kent, UK), indicated that treatment with SRL172, in addition to chemotherapy, resulted in a 61% survival benefit compared with chemotherapy alone (13.8 months versus 8.5 months).

Vaccines Against CEA-expressing Tumors

Carcinoembryonic antigen (CEA) is a 180-kDa oncofetal glycoprotein overexpressed by a wide range of malignant tumors, including approximately 70% of nsclc. In general, CEA-expressing tumor cells are only weakly recognized by the immune system. However, the high level of expression of the CEA gene in many different human tumors supports the use of CEA as a target for vaccine development, and several different approaches are being studied for CEA-specific immunotherapy. These include use of antibodies directed against CEA, as well as strategies that target CEA-reactive T cells, including the use of specific HLA-restricted peptides derived from CEA, insertion of the CEA gene into recombinant viral and bacterial vectors, and pulsing of CEA onto dendritic cells. CEA vaccines may also be combined with cytokines or costimulatory molecules to increase vaccine effectiveness.

One of the challenges in CEA vaccine development is assessing the biological relevance to humans of animal studies of CEA-targeted immunotherapy. Much of the current understanding of CEA vaccine therapy derives from studies using immune-competent mice transplanted with human CEA-gene-transfected murine tumors. However, such models are inadequate when addressing such issues as pre-existing tolerance to self-tumor antigens, or the potential for autoimmunity after CEA vaccination. Transgenic mice that express the human CEA gene represent a potentially useful preclinical model for evaluating vaccines that are based on CTL effector mechanisms directed at CEA. Dr. F.J. Primus and associates, at Vanderbilt University Medical Center, have used a 32.6-kb fragment containing the complete human CEA gene and flanking sequences, isolated from a genomic cosmid clone, to produce transgenic C57BL/6 mice (C57BL/6J-TgN(CEAGe)18FJP) capable of inducing CTL recognizing CEA-specific MHC class I epitopes on CEA-expressing human tumor cells. These mice have demonstrated a faster tumor growth rate and inability to generate anti-CEA antibodies when transplanted with a murine tumor expressing human CEA, as compared with non-transgenic mice bearing CEA-expressing tumors (Mizobata S, etal, Cancer Immunol Immunother, Aug 2000;49(6):285-95, and Clarke P, etal, Cancer Res, 1 Apr 1998;58(7):1469-77).

Anti-CEA antibodies, used routinely to detect CEA-expressing tumor cells, may also play a role in immune-mediated tumor rejection. Presence of bound antibody may initiate both complement-mediated cytotoxicity, and antibody-directed cellular cytotoxicity (ADCC). However, these cytotoxic effects require adequate surface localization of CEA on the targeted tumor cells, and the heterogeneous nature of CEA makes complete eradication of cells within a tumor mass difficult. Also, inadequate blood supply to solid tumor masses prevent efficient penetration of solid tumors by antibodies. Furthermore, because many MAbs developed for in vivo clinical use are derived from mice, HAMA reactions typically preclude their repeated use in patients. Researchers at KS Biomedix (Guildford, Surrey, UK) have created anti-CEA MAbs using lymphocytes from immunized sheep, having affinities several orders of magnitude higher than murine MAbs. One of these sheep MAbs (SMA) has a dissociation t(1/2) of 8 days, thus providing a longer therapeutic window than is available with murine MAbs, reducing the need for reapplication and the potential for human anti-SMA reactions (Osborne J, etal, Hybridoma, Apr 1999;18(2):183-91).

Researchers at Vanderbilt University are using transgenic mice to study the targeting and treatment of CEA-expressing tumors with a bivalent, single-chain anti-CEA antibody and IL-2 fusion protein derivative. In this approach, the variable domains of a high affinity anti-CEA antibody, T84.66, are used to form a single-chain variable fragment joined to the crystallizable fragment, Fc (scFvFc); murine IL-2 is fused to the COOH-terminal end of the scFvFc to form the fusion protein, scFvFc.IL-2, which exhibits tumor localization properties similar to intact MAb in CEA-transgenic mice bearing CEA-positive murine tumors, without significant antigen-specific targeting to CEA-positive normal tissues. The growth of CEA-expressing, but not antigen-irrelevant, syngeneic tumor cells was inhibited after treatment of transgenic mice with scFvFc.IL-2, suggesting the utility of anti-CEA antibody-directed cytokine targeting in the treatment of CEA-expressing carcinomas (Xu X, etal, Cancer Res, 15 Aug 2000;60(16):4475-84).

Recombinant viruses expressing CEA protein or peptides represent the best-studied CEA vaccine strategy. This approach makes use of the fact that CEA peptides can activate CTL response through HLA-restricted epitopes within the CEA protein. Several CTL epitopes restricted by HLA-A2, the most common human histocompatibility molecule, have been reported (Tsang KY, etal, J Natl Cancer Inst, 5 Jul 1995;87(13):982-90), and scientists at Takara Shuzo's Biotechnology Research Laboratories (Otsu, Shiga, Japan) have described both HLA-A3- and HLA-A24-restricted CTL epitopes from CEA. A peptide from CEA (CEA[9(61)]: HLFGYSWYK) was shown to induce CTL capable of killing a tumor cell line expressing HLA-A3, and the corresponding tumor-associated antigen. Additional MHC binding studies with the most common HLA

molecules, belonging to the HLA-A3 superfamily, demonstrated that CEA[9(61)] binds five of five A3 supertype molecules with high affinity, indicating that this new CTL epitope should be immunogenic in individuals expressing either HLA-A3, or other members of the HLA-A3 superfamily (Kawashima I, etal, Cancer Res, 15 Jan 1999;59(2):431-5). Two peptides, QYSWFVNGTF and TYACFVSNL, were found to be capable of eliciting CTL lines that lysed tumor cells expressing HLA-A24, the most frequent allele among Japanese, and CEA. The cytotoxicity to tumor cells by the CTL lines was antigen-specific since it was inhibited by peptide-pulsed cold target cells as well as by anti-class I MHC and anti-CD3 MAbs. Identification of novel CEA epitopes for CTL offers the opportunity to design and develop epitope-based immunotherapeutic approaches for treating HLA-A24+ patients with tumors that express CEA (Nukaya I, etal, Int J Cancer, 5 Jan 1999;80(1):92-7).

Various approaches are employed to introduce CEA into tumor cells. The most well characterized viral vectors are the poxviruses, particularly vaccinia virus. Recombinant vaccinia virus can incorporate long segments of genetic information without seriously compromising the virus' capacity to replicate accurately, is easily engineered, stimulates strong immune responses, and has the longest record of successful use as a live-attenuated virus vaccine in the human population to prevent smallpox. Methods for constructing recombinant vaccinia viruses have been extensively described, and several different tumor antigens have been incorporated into these viruses, including CEA; a CEA-expressing vaccinia vector (rV-CEA) has proven effective in treating established colorectal tumors in mice (Kaufman H, etal, Int J Cancer, 30 Jul 1991;48(6):900-7, and McLaughlin JP, etal, Cancer Research, 1996 May 15, 56 (10):2361-7).

In early clinical trials in patients with advanced CEA-expressing tumors, vaccination with rV-CEA proved safe even when high titers of virus were administered (McAneny D, etal, Ann Surg Oncol, Sep 1996;3(5):495-500). In an NCI-sponsored phase I clinical trial, conducted in collaboration with Therion Biologics (Cambridge, MA), completed in 1998, CEA-specific T-cell growth and cytotoxicity, as well as enhancement of antibody-mediated immune responses, were seen in patients with breast, lung, and gastrointestinal tract adenocarcinomas, treated with 3 doses of rV-CEA (Schlom J, etal, Breast Cancer Research and Treatment, 1996, 38(1):27-39).

To avoid the neutralizing antibody responses induced by vaccinia virus, attention has been directed to the use of non-replicating poxviruses, such as the avipoxviruses, as vectors. Avipoxviruses, which include fowlpox and canarypox virus, are pathogenic in birds, but are incapable of replicating in mammalian cells. Yet, they elicit strong CTL responses in both rodent models and humans, without the induction of strong neutralizing antibodies (Paoletti E, Proc Natl Acad Sci USA, 15 Oct 1996;93(21): 11349-53).

A canarypox virus vector, ALVAC (Avipox), developed by Virogenetics, now merged with Aventis Pasteur (Lyon, France and Toronto, Ontario, Canada), was combined with Therion's CEA gene to form ALVAC-CEA. The CEA gene was modified prior to vector insertion to ensure that it is transported to the surface of the infected cell following vaccination to enhance antigen recognition by immune cells. ALVAC-CEA, evaluated in a phase I clinical trial (protocol IDs: GUMC-95026, NCI-T94-0154D), conducted at Georgetown University's Vincent T. Lombardi Cancer Research Center (Washington, DC), was found to be safe and immunogenic in patients with advanced CEA-expressing cancers.

Vaccines such as rV-CEA and ALVAC-CEA may be administered independently, or as part of a "prime-boost" immune-conditioning regimen in which an antigen-expressing poxvirus vector first primes the immune system, and is then followed by either an immunologically unrelated poxvirus expressing the same antigen, or the same poxvirus vector expressing a different tumor-associated antigen and/or cytokines or T-cell costimulatory factors, to boost the immune response. The most commonly used approaches for improving the clinical effectiveness of these vaccines involved use of cytokines IL-2 and/or GM-CSF, and the costimulatory molecule B7.1. IL-2, an immune regulatory protein broadly involved in cell growth and differentiation, may augment the antitumor response to rV-CEA or ALVAC-CEA through expansion of tumor-specific T cells; GM-CSF has been shown to promote growth and activation of dendritic cells, thus improving the antigen presentation 'arm' of the immune system. The B7 costimulatory molecules are homodimeric members of the immunoglobulin supergene family; activation of T-cells requires two signals via molecules on antigen-presenting cells (APC), the first delivered to the T-cell receptor upon recognition of the peptide/MHC complex, and the second delivered by CD28 molecules expressed on T cells after the engagement of the B7 costimulatory molecule, expressed by activated APC (Bretscher P, Immunol Today, Feb 1992;13(2):74-6).

NCI-sponsored phase I studies of ALVAC-CEA-B7.1 vaccine, expressing the CEA gene and the B7.1 costimulatory molecule, in patients with advanced CEA-expressing adenocarcinomas were completed in 1999. A clinical trial (protocol IDs: AECM-97107, NCI-T97-0084) of the vaccine alone was conducted at the Albert Einstein Cancer Research Center (Bronx, NY) and, in combination with the adjuvant GM-CSF (protocol IDs: FCCC-97010, NCI-T97-0044), at the Fox Chase Cancer Center, under PI Margaret von Mehren, MD. In this latter trial, 30 patients with advanced CEA-expressing cancers (colorectal=22, lung=4, and 1 each with cancer of the pancreas, gallbladder, jejunum and esophagus) were immunized with 4.5 x 10^8 pfu, intradermally, every other week, for 4 courses, in combination with subcutaneous GM-CSF (250 µg) injected in the immunization site for 5 days, beginning two days prior

to vaccination. Patients with stable or responding disease were administered monthly boosts until progression. All patients developed erythema and swelling at vaccine sites, with some having reactions at the site of GM-CSF injections as well. Grade 3-4 toxicities included elevations in liver function tests in patients with known liver metastases, electrolyte abnormalities, pain and anemia, none of which were clearly related to therapy. Vaccine site biopsies, done 48 hours post injection, uniformly exhibited leukocytic infiltration and CEA staining. Disease stabilized in 10 (37%) of 27 evaluable patients after 4 vaccinations in combination with GM-CSF, who were also administered 1-4 monthly booster injections. In contrast, disease stabilized in 6 (26%) of 23 patients who were treated with the vaccine alone (von Mehren M, etal, ASCO00, Abs. 1883).

An NCI-sponsored phase II clinical trial (protocol IDs: GUMC-97118, NCI-T97-0033) is presently underway at Georgetown University under the direction of John L. Marshall, MD, Study Chair, to assess the safety and effectiveness of a prime-boost vaccination regimen involving sequentially administered rV-CEA and ALVAC-CEA, in combination with GM-CSF, with and without IL-2, in patients with advanced CEA-expressing tumors. A minimum of 24 patients will be accrued into this study. Clinical trials with ALVAC-CEA are being conducted under NCI-sponsorship pursuant to five-year CRADAs with Therion, entered into in November 1994 and October 1995, and renewed in February 2000.

Dendritic cells expressing CEA represent a new approach to cancer immunotherapy. Dendritic cells (DC) are phenotypically-distinct, professional APC found in lymphoid organs, skin and mucosa, and the bone-marrow. Their function is to internalize, process, and present antigen via the MHC class I and MHC class II pathways to naive T-lymphocytes with high efficiency, playing a central role in the regulation of T- and B-lymphocyte activation *in vivo*. DC expressing tumor antigens are capable of stimulating antigen-specific CTL to destroy cancer cells without harming normal tissue. The use of DC that have been exposed for a short time to high concentrations of specific antigen (i.e., pulsed) has been proposed as a means of generating more effective antigen-specific T-cell responses (Banchereau J and Steinman RM, Nature, 19 May 1998;392(6673):245-52). Scientists at Duke University Medical Center (Durham, NC) have shown that DC, generated from peripheral blood mononuclear cells (PBMC) of healthy individuals, or from cancer patients, and pulsed with CEA peptides or mRNA, are capable of stimulating a potent CD8+ CTL response *in vitro* (Nair SK, etal, Nat Biotechnol, Apr 1998;16(4):364-9). Early clinical trials of DC vaccines are being conducted using re-administered autologous DC that have been expanded *ex vivo* and pulsed with CEA.

In a pilot phase I study at the Duke University Comprehensive Cancer Center, autologous DC were generated *in vitro* from the PBMCs of HLA-A2-positive patients with metastatic malignancies expressing CEA. These DC were then expanded in serum-free media supplemented with GM-CSF and IL-4, loaded with the HLA-A2-restricted CEA peptide CAP-1, and then administered as 4 weekly or biweekly IV infusions to groups of three to six patients in escalating dose levels of 1 x 10^7, 3 x 10^7, and 1 x 10^8 cells/dose; a subset of the patients in the last group were also treated with intradermal injections of 1 x 10^6 DC. There were no toxicities directly attributable to the treatment. In terms of response, 1 patient had a minor response, and disease stabilized in another. Skin punch biopsy at DC injection sites demonstrated pleomorphic infiltrates in the 3 patients evaluated (Morse MA, etal, Clin Cancer Res, Jun 1999;5(6):1331-8).

Ongoing NCI-sponsored clinical trials of DC CEA vaccines in the treatment of metastatic cancers at Duke University Comprehensive Cancer Center are using autologous DC pulsed with RNA derived from CEA-expressing tumor cells (Nair SK, etal, Int J Cancer, 2 Jul 1999;82(1):121-4). The advantage of this approach is that CEA-specific RNA encodes multiple CEA epitopes for various HLA types, allowing patients to be immunized without the prior determination of their HLA type, or use of HLA-specific CEA epitope(s). A phase I clinical (protocol IDs: DUMC-96098, NCI-G97-1272, DUMC-1817-99-10R3) of an autologous CEA RNA-pulsed DC vaccine in treating metastatic cancer that has not responded to previous treatment, including metastatic lung cancer, was started in June 1997; a maximum of 18 patients will be accrued for this study. The Study Chair is Herbert Kim Lyerly, MD. To date, no toxicity has been observed in treated patients. Published results of an animal study using the RNA vaccine showed that it dramatically reduced the spread of lung cancer in mice, and protected them from developing new tumors (Boczkowski D, etal, J Exp Med, 1 Aug 1996;184(2):465-72).

Vaccines Against Ganglioside-expressing Tumors

Cell surface gangliosides, which are released by tumor cells, block antigen presentation by human monocytes, and inhibit antitumor cellular immune response *in vivo*. Several gangliosides such as GM2, GD2, and GD3 have been thought of as target molecules for active or passive immunotherapy because of their dominant expression on the tumor cell surface, especially in tumors of neuroectodermal origin, including sclc. When expression of three gangliosides, FucGM1, GM2 and GD3, recognized as tumor-associated antigens, was evaluated in sclc tissue specimens collected at autopsy, expression of FucGM1, GD3 and GM2 was observed in 70%, 60% and 40%, respectively, of the tumor cells in all lesions from the same patient (5 of 8 cases), indicating that FucGM1 is a relevant ganglioside antigen in sclc. Therefore, specific immunotherapy involving more than one ganglioside antigen in sclc should at least include FucGM1, which is present on most sclc but on few normal tissues, and GD3, a glycolipid epitope expressed on the surface of certain cancer cells, including

those of melanoma and sclc (Brezicka T, etal, Lung Cancer, Apr 2000;28(1):29-36).

Fucosyl-GM1-keyhole limpet hemocyanin (KLH) conjugate vaccine is being evaluated at Memorial Sloan-Kettering Cancer Center and Cornell University Medical College (New York, NY) in patients with sclc. In the present trial, fucosyl-α1-2Galβ1-3GalNAcβ1-4(NeuAcα2-3)Galβ1-4Glcβ1-1Cer (Fuc-GM1), a ganglioside expressed on the cell surface of sclc, was selected as a target for AI. Patients who experienced a major response to initial therapy were vaccinated subcutaneously, on weeks 1, 2, 3, 4, 8, and 16, with Fuc-GM1 (30 μ), conjugated to the carrier protein KLH, and mixed with the adjuvant QS-21, licensed from Aquila Biopharmaceuticals (Framingham, MA). All 10 patients evaluable for response who were vaccinated at least five times, demonstrated a serological response, with induction of both IgM and IgG antibodies against Fuc-GM1, despite prior treatment with chemotherapy with or without radiation. Post-treatment flow cytometry demonstrated binding of antibodies from patients' sera to tumor cells expressing Fuc-GM1. In the majority of cases, sera were also capable of complement-mediated cytotoxicity. Mild transient erythema and induration at injection sites were the only consistent toxicities (Dickler MN, Clin Cancer Res, Oct 1999;5(10):2773-9). Ganglioside vaccines combining other gangliosides with KLH and QS-21 are under evaluation at Memorial Sloan-Kettering Cancer Center, in collaboration with Progenics Pharmaceuticals (Tarrytown, NY), against various solid tumors.

Mitumomab (EMD-60205, BEC-2), under development by ImClone (New York, NY), in collaboration with Merck KGaA (Darmstadt, Germany), is a murine anti-idiotypic MAb which, by mimicking the GD3 ganglioside, induces an anti-anti-idiotypic antibody, and an anti-GD3 antibody T-cell-mediated response directed against GD3-expressing tumor cells. BEC2 may be administered together with Bacillus Calmette Guerin (BCG) as an immune stimulant adjunct. Research with other murine MAbs has shown that immune system binding of such complexes may be significantly enhanced by the human-anti-mouse-antibody (HAMA) response, induced by the murine nature of the MAb, improving cytotoxic T-cell response (Qi W, etal, AACR99, Abs. 2351:355).

A randomized, multinational, phase III clinical trial (protocol IDs: EORTC-08971, EORTC-08971B, UCLA-9902001), initiated in May 1998, is being conducted by the EORTC Lung Cancer Cooperative Group (Giuseppe Giaccone, Chair) to determine safety and survival impact of BEC2 and BCG vaccination in patients with limited-stage sclc who completed a regimen of first-line combined modality therapy, involving RT, either concurrently or sequentially, with induction chemotherapy. Responders (either CR or PR) to therapy are randomized to one of two treatment arms, either standard care alone, or standard care plus BEC2/BCG vaccination, consisting of five intradermal injections of BEC2/BCG over a period of 10 to 12 weeks unless unacceptable toxic effects arise, or disease progresses. QoL is assessed prior to vaccination, at weeks 6, 12, and 24, and every 6 months thereafter; patients are followed every 3 months until death. Approximately 820 patients will be accrued.

In a phase II study, conducted at Memorial Sloan-Kettering Cancer Center (New York, NY), and Weill Medical College (New York, NY) of Cornell University (Ithaca, NY), 15 patients who had completed standard induction chemotherapy (with and without RT) for sclc, were administered 5 intradermal injections of BEC2 plus BCG, over a 10-week period. All patients developed anti-BEC2 antibodies, with anti-GD3 antibodies observed in 5 patients, including those with the longest relapse-free survival (RFS). The median RFS for patients with extensive disease was 11 months, and, at over 47 months, it had not been reached for patients with limited disease; only 1/7 patients relapsed after a median follow-up of 47 months. Immunized patients demonstrated a statistically significant prolonged survival rate compared to a contemporary group of nonimmunized patients (Grant SC, etal, Clin Cancer Res, Jun 1999;5(6):1319-23).

In a phase I clinical study involving 15 patients with sclc, immunized with BEC2 plus BCG over a 10-week period, following completion of standard therapy, all patients developed anti-BEC2 antibodies, with one patient developing anti-GD3 antibodies; median survival was 20.5 months (Grant SC, etal, ASCO97, Abs. 1630:454a).

Vaccines Against MUC-1-expressing Tumors

MUC-1 is a cell surface mucin that is upregulated and aberrantly glycosylated in epithelial cancers, including lung adenocarcinoma. As a result, MUC-1 is a target for tumor immunotherapy in lung cancer.

BLP-25 vaccine, under development by Biomira (Edmonton, Canada), incorporates a synthetic 25-amino acid sequence of the MUC-1 cancer mucin, encapsulated in a synthetic liposomal delivery system. The liposome enhances recognition of the cancer antigen by the immune system, and improves delivery. BLP25 vaccine is a therapeutic vaccine designed to induce an immune response to cancer cells.

In August 2000, Biomira initiated a multicenter randomized, controlled, phase IIb clinical trial of BLP25 vaccine in advanced nsclc (Stage IIIb or IV) to enroll 166 evaluable patients, 83 patients per study arm, at approximately 10 Canadian sites. Patients who responded, or whose disease stabilized, after first-line standard chemotherapy, are to be randomized to either BLP25 vaccine, plus best supportive care or to best supportive care alone. Best supportive care can include local radiotherapy and second line chemotherapy, according to current standard clinical practice. Objectives of the trial are to measure safety, and possible survival benefit, of BLP25 in this setting. Secondary endpoints of the trial are QoL and immune

response. The overall purpose of this trial is to determine whether demonstrated immune response against the vaccine translates to clinical benefit. Trial enrollment is estimated to take approximately 12 months, with completion estimated in 24 months.

The second stage of the phase II clinical trial program with BLP25 commenced in January 2000. The overall purpose of the phase II trial program is to determine how to optimize an immune response in patients with nsclc; this stage will study whether the effect of BLP25 is enhanced by the addition of liposomal IL-2 (L-IL-2), while preserving a satisfactory safety profile. This second trial stage will involve 14-20 patients.

In August 1999, a phase II clinical trial was initiated to determine whether a higher dose (1000 µg) and more frequent administration of BLP25 vaccine would enhance its effect in patients with advanced nsclc; enrollment was completed in December 1999. Conducted at the Cross Cancer Institute (Edmonton, AB, Canada), the trial's higher vaccine dose was found to induce strong MUC-1 specific T-cell proliferation response in 6 of 8 evaluable patients.

A phase I clinical trial, conducted at the Cross Cancer Institute, began in the third quarter of 1998, with patient enrollment completed in March 1999. Sixteen highly selected nsclc patients were randomized to treatment with either 20 µg or 200 µg doses of BLP25 vaccine; median survival time ranged from 5.4 months (low dose) to 14.7 months (high dose). Class I restricted cytotoxic T-lymphocyte responses to cells displaying the MUC-1 antigen developed in 5 of 12 evaluable patients (Palmer MC, etal, ASCO00, Abs. 1824).

Vaccines Against Tumors Expressing HER2

HER2/neu gene amplification and protein overexpression occurs in 20-40% of invasive cancers of the breast, and in a substantial percentage of ovarian, lung, prostate, colon, uterine and stomach carcinomas. Best studied in breast cancer, HER2/neu overexpression is associated with poor prognosis; the presence of HER2/neu protein in breast cancer correlates with aggressive disease, and is associated with resistance to conventional-dose chemotherapy. HER2 is also overexpressed in nsclc, and is the target of immunotherapy in this setting. Scientists at Takara Shuzo's Biotechnology Research Laboratories have identified an HLA-A3-restricted CTL epitope from HER2/neu. This peptide (HER2[9(754)]: VLRENTSPK) was shown to induce CTL that was capable of killing a tumor cell line expressing HLA-A3 and HER2. Additional MHC binding studies with the most common HLA molecules, belonging to the HLA-A3 superfamily, demonstrated that the HER2[9(754)] epitope was able to bind to four of five alleles that were the same with those that bind to a CEA epitope (Kawashima I, etal, *ibid*).

HER2 peptide vaccine, a microsphere-encapsulated, multivalent formulation of HER2/neu peptides, under development by Corixa (Seattle, WA), in collaboration with Glaxo SmithKline, is being evaluated in several phase I clinical trials. In this construct, the HER2/neu peptides are attached to the polymer microsphere component through a covalent bond to form particulate protein antigen complexes that are administered to the patient in conjunction with a pharmaceutically acceptable excipient, in an amount sufficient to induce MHC class I-restricted cytotoxic T-lymphocyte responses. Bioresorbable microspheres, having an average diameter ranging in size from about 0.5 micron to about 6 microns, are produced from a synthetic copolymer, poly(lactic-co-glycolic acid), or PLGA, approved by the FDA for use in sutures, and certain controlled-release drug delivery products. In microsphere-mediated antigen presentation for augmenting immune responses, microspheres of a particular size range are used that are taken up by APC. This differs from other approaches which circumvent the normal antigen presentation pathways, including various gene therapies as well as liposome or recombinant-protein lipid formulations, where significant amounts of the delivered product may be taken up by non-APC, or lost in the blood stream, or elsewhere in the body.

In March 1999, Corixa initiated an open-label, non-randomized phase I clinical trial (protocol ID: UWASH-103; NCI-V99-1574) of a multivalent HER2/neu TAA vaccine using microsphere-encapsulation in HLA-A2-positive patients with primary or metastatic adenocarcinoma of the breast, ovary, or lung, in either patients with previously treated Stage III cancer, or those in Stage IV in CR or with stable disease not undergoing concurrent chemotherapy. This trial, being conducted at the University of Washington (Seattle, WA) under the direction of Dr. Mary L. Disis, and at Fred Hutchinson Cancer Research Center (Seattle, WA), is investigating the vaccine formulation's safety as well as its utility in enhancing immune responses to HER2/neu TAA. According to this phase I protocol, patients undergo leukapheresis prior to the initiation of treatment, and after the final vaccination. Patients are entered sequentially into one of three treatment arms to be administered HER2- derived p369-377 peptide incorporated into PLGA microspheres, and GM-CSF, either intradermally (arm I), or subcutaneously, in two different dose levels (arms II and III). Treatment is repeated every 4 weeks, for up to 6 courses, in the absence of unacceptable toxicity. Objectives of this trial are to determine the safety of serial intradermal or subcutaneous vaccinations in this setting, whether CTL specific for the HER2 protein can be elicited in patients with HLA-A2 by immunization with this regimen, which route of immunization, intradermal or subcutaneous, is more effective in generating HER2-specific CTL, and the extent to which escalated dose of this agent affects the immune response. A total of 15 patients (5 per treatment arm) are to be accrued for this study.

An earlier phase I clinical trial, initiated in September 1996 at the University of Washington, and completed in 1999, evaluated the effects of a multivalent approach to

HER2/neu-based vaccines by using 3 vaccine formulations, each composed of 3 short peptides from the extracellular or intracellular domains of HER2/neu, admixed with the adjuvant GM-CSF; 64 patients with Stage III or IV HER2 expressing breast (n=53), ovarian (n=9), or non-small cell lung (n=2) cancer were enrolled and immunized by intradermal injection once a month for a total of 6 immunizations with 1 of the 3 vaccine formulations; 38 patients completed all 6 vaccines, and median for the study population as a whole was 3 vaccines. There was no significant toxicity associated with the immunizations, or with the generation of a HER2/neu-specific immune response. Overall, 50 (78%) immunized patients developed significant T-cell immunity to HER2/neu peptides, while 40 (62%) developed significant HER2/neu protein-specific T-cell responses, an *in vitro* surrogate of potential tumor response; there was no difference in the immunogenicity of the 3 vaccine formulations tested.

The phenomenon of epitope spreading was observed in 42 (76%) patients, providing additional confirmation that vaccination provoked a significant patient immune response to HER2/neu in patients administered peptides derived from the extracellular domain portion of the protein. Development of epitope spreading significantly correlated with the generation of a HER2/neu protein-specific T-cell response. Immune T-cells elicited by vaccination were also shown to migrate outside the peripheral circulation indicating potential ability to traffic to the tumor site.

Peptide-based vaccines were less effective at generating HER2/neu antibody immunity, with 55% (n=35) of patients developing HER2/neu peptide-specific antibodies, but only 20% (n=13) of patients generating HER2/neu protein-specific antibody; the HER2/neu protein-specific antibodies were IgG, with a predominant IgG1 component. Analysis of longitudinal responses in patients completing immunization for a median of 11 months (range 9-28 months) demonstrates that HER2/neu-specific immunity persists and continues to evolve and augment after immunizations have been completed (Disis M, etal, ASCO00, Abs. 1857A, Goodell VJ, etal, ASCO00, Abs. 1826, Disis ML, etal, Clin Cancer Res, Jun 1999;5:1289-97, and Disis ML, etal, ASCO98, Abs. 375).

RADIATION THERAPY

Radioimmunoconjugates

Pantacea, a second-generation radioimmunotherapeutic, under development by IBC Pharmaceuticals, a subsidiary of Immunomedics (Morris Plains, NJ and Hillegom, The Netherlands), uses the bispecific MAb technology platform Affinity Enhancement System (AES), developed by Immunotech (Marseilles, France), a subsidiary of Beckman Coulter (Fullerton, CA). In this approach, one arm of a bispecific MAb targets CEA TAA, and the other is a receptor for diethylenetriamine pentaacetic acid (DTPA)-indium (In-DTPA).

Radiosensitizers

Because blood circulation often is unable to meet the oxygen demand of rapidly growing tumors, one common hallmark of a tumor's microenvironment is oxygen starvation, or cell hypoxia. Hypoxic cells are inherently resistant to both radiotherapy, and many types of cytotoxic chemotherapy. Because tumor hypoxia is considered a limiting factor in the curability of many cancers, including nsclc, there is considerable effort to identify agents and/or combinations that would selectively kill hypoxic cells. Among structurally different classes of drugs with selective toxicity towards hypoxic cells are 2-nitroimidazoles, mitomycins, and benzotriazine dioxides such as tirapazamine. These drugs are selectively activated in the absence of oxygen to reactive intermediates that can damage DNA. Radiosensitizers are drugs that enhance the efficacy of ionizing radiation in the treatment of solid tumors. Radiosensitizers act as oxygen mimics and/or can be bioreductively activated to selectively enhance the toxicity of RT towards hypoxic cells while sparing aerobic cells.

KIN-806, under development by Daikin Industries (Kyoto, Japan), is a bifunctional 2-nitroimidazole derivative hypoxic cell radiosensitizer that demonstrated tumor growth control and suppression of lung metastasis *in vitro* and *in vivo*. KIN-806 showed an excellent effect as a radiosensitizer, and also suppressed lung metastasis regardless of RT modality. Also, control of the metastatic lung nodules did not depend on the irradiation dose but rather on the KIN-806 dose (Inomata T, etal, Int J Mol Med, Sep 1999;4(3):257-60).

Motexafin gadolinium (Xcytrin), a gadolinium texaphyrin (Gd-Tex) radiosensitizer, under development by Pharmacyclics (Sunnyvale, CA), selectively accumulates in tumor cells and, when activated by X-rays, increases tumor cell damage. Xcytrin also increases the activity of certain chemotherapy agents in tumors. This effect is believed to be related to gadolinium texaphyrin's ability to stabilize cytotoxic free radicals produced by certain chemotherapy agents, such as bleomycin and doxorubicin. Xcytrin's selective uptake in tumors potentiates the activity of cancer chemotherapy agents in tumor cells but not in normal tissues, thereby increasing the therapeutic margin.

Xcytrin is in development for various indications. It is in a pivotal phase III clinical trial in the treatment of brain metastases in combination with RT. This phase III clinical trial which is being conducted at more than 60 cancer centers in the USA, Canada and Europe, is expected to complete its target 425-patient enrollment by the end of 2000. As of May 2000 enrollment was about two-thirds complete. The coprimary efficacy endpoints of this trial are improvement in either survival, or time to neurologic progression. According to a report from the open-label, lead-in phase of the trial that treated 25 patients with brain metastases to validate the design of the phase III clinical trial, Xcytrin appeared to improve local tumor control in the brain, with

few patients experiencing tumor progression, neurocognitive deterioration, or death attributable to tumor progression.

Xcytrin is also in an NCI-sponsored phase I clinical trial (protocol IDs: OSU-T99-0073, NCI-T99-0073) of induction chemotherapy with carboplatin and paclitaxel, preoperative RT, and surgical resection, in Stage IIIa nsclc. Trial objectives are to determine and compare the frequency and grade of toxicities with the use of gadolinium texaphyrin as a radiosensitizer at two dose levels during preoperative RT, measure the tumor, involved lymph nodes, and normal lung concentrations of gadolinium and compare to the image pixel intensity obtained by the 1.5 Tesla MRI. In this dose escalation study, patients are treated with IV paclitaxel over 3 hours, followed by IV carboplatin over 1-2 hours, every 3 weeks, for 3 courses. Three weeks after completion of induction chemotherapy, patients are treated with IV Gd-Tex, over 30 minutes, twice weekly, for 10 doses during preoperative RT which is administered daily, 5 days a week, for 5 weeks. Approximately 3.5 weeks after completion of preoperative RT, patients undergo complete surgical resection. Three hours prior to surgery, patients are administered an eleventh dose of Gd-Tex if they do not develop Grade 3 or 4 toxicity with the tenth dose. An MRI, without contrast, is also performed prior to surgery. If the tumor is found to be unresectable, patients may be treated with additional courses of RT and/or chemotherapy. Cohorts of 3-6 patients are treated with escalating doses of Gd-Tex until MTD is determined. Patients are followed at 1 month, and then every 4 months for 5 years. A total of 3-12 patients will be accrued for this study within 1 year. John C. Grecula, MD, at Arthur G. James Cancer Hospital at Ohio State University (Columbus, Ohio) is the PI.

RSR-13, under development by Allos Therapeutics (Denver, CO), is a synthetic small molecule that increases the release of oxygen from hemoglobin. RSR-13 allosterically stabilizes deoxyhemogloblin through noncovalent binding to hemoglobin, thereby reducing the affinity of hemoglobin for oxygen, resulting in a right shift in the oxygen dissociation curve. Oxygen release to tissue is thus increased (without elevations in blood flow or blood pressure), improving tumor oxygenation, and enhancing radiation-induced cell killing. To date, more than 275 patients have been treated with RSR-13. In lung cancer, RSR-13 is being evaluated in advanced nsclc, and in brain metastases resulting from various primary tumors including nsclc, but excluding sclc.

An open-label, multicenter phase II clinical trial (protocol IDs: ALLOS-RSR13RT-010, VU-VCC-THO-9828), was initiated in October 1998, to study the effectiveness and safety of induction chemotherapy with paclitaxel, and carboplatin, followed by fractionated RT plus IV RSR-13, in locally advanced (Stage IIIa or IIIb), unresectable nsclc of any histology. Enrollment in the study was completed in August 2000 after 50 patients were entered. The PI is Hak Choy, MD, at Vanderbilt University Medical Center. The pri-mary efficacy endpoint of the trial is response rate of the primary tumor in the chest, assessed at two months after the course of RT combined with RSR13. Secondary endpoints include overall survival, progression-free interval in the chest, and time to development of progressive disease outside the chest (radiation portal).

A phase III randomized, open-label, multicenter clinical trial, being conducted by the NABTT (New Approaches to Brain Tumor Therapy) Consortium, is to enroll up to 408 patients with brain metastases from a confirmed primary malignancy (excluding sclc, germ cell tumors, and lymphomas).

Proton Beam Therapy

In August 2000, the FDA awarded 510K clearance to Optivus' (San Bernardino, CA) Conforma 3000 technology for delivering protons to tumors. The unique properties of protons provide a distinct physical advantage over X-ray beams, because unlike traditional RT, protons are very specific to their target, sparing normal tissue and reducing side effects, while delivering higher radiation to the tumor. Protons also deliver homogeneous radiation to irregular three-dimensional volumes such as those seen in various cancers. The only operational hospital-based Optivus proton treatment facility in the world, having treated more than 5,000 patients to date, was installed in 1990 at Loma Linda University Medical Center (LLUMC; Loma Linda, CA). Although there are about 40 proton treatment protocols, the facility development costs, ranging between $50 and $100 million, render this a very high investment for most healthcare facilities.

Proton beam therapy is a viable option to patients ineligible for surgery. In a prospective study, undertaken to assess the efficacy and toxicity of conformal proton-beam RT, 37 patients with early-stage, medically inoperable (Stage I=27, Stage II=2, Stage IIIa=8) nsclc were enrolled between July 1994 and March 1998. Patients with good cardiopulmonary function (n=18) were treated with 45 Gy to the mediastinum and gross tumor volume with photons with a concurrent proton boost to the gross tumor volume of an additional 28.8 cobalt gray equivalents (CGE) for a total tumor dose of 73.8 CGE administered over 5 weeks. Patients with poor cardiopulmonary function (n=19) were treated with proton-beam RT to the gross tumor volume only, with 51 CGE administered in 10 fractions over a 2-week period. Follow-up of evaluable patients ranged from 3 to 45 months, with a median of 14 months. No significant toxicities were encountered, except that 2 patients in the proton and photon arm developed pneumonitis that resolved with oral steroids. The actuarial disease-free survival at 2 years was 86% for Stage I patients, and 63% the entire group. Local disease control was 87% (Bush DA, etal, Chest 1999 Nov;116(5):1313-9), compared with an average of 50% using traditional RT.

CHEMOPREVENTION

Chemoprevention in lung cancer encompasses a variety of objectives, including:

- prevention of lung cancer recurrence after aggressive treatment to affect a cure
- prevention of development of secondary lung cancers, a risk that is higher among smokers than former smokers who survive lung cancer (risk is estimated at 5% per year, with a 30-50% actuarial risk at 10-12 years after treatment, and not only involves new lung cancer but otheraerodigestive cancers such as head and neck cancer, or esophageal cancer, or acute leukemia)
- prevention of malignancy in those exposed to known risk factors
- prevention of precancerous lung conditions from evolving into bona fide malignancy

Vitamins

Vitamin intake, a low-cost chemoprevention strategy in lung cancer, remains controversial. Although vitamins, particularly the antioxidants beta carotene, an analog of vitamin A, and vitamin E, were found to be inversely related to the risk of lung cancer in many prospective epidemiological studies, findings from a large randomized primary chemoprevention trial of adult smokers showed that therapy with beta-carotene was associated with an 18% increased risk of developing lung cancer. No role for vitamin E or vitamin C has been established in lung cancer. Therefore, supplementation with antioxidant vitamins cannot be recommended for the prevention of lung cancer. However, vitamin intake may be beneficial in patients with lung cancer. In a cross-sectional study of 36 postoperative nsclc patients, that examined possible effects of vitamin intake and folate status on disease-free survival, 19/36 patients (53%) who reported vitamin supplementation, experienced longer median censored survival compared with nonusers (41 months versus 11 months). Also, with adjustment for cancer stage, the association between RBC folate and censored survival ($r = 0.35$), and between serum folate and censored survival ($r = 0.32$), approached statistical significance, indicating that a similar trend toward long-term survival exists in patients with higher circulating folate concentrations (Jatoi A, etal, J Surg Oncol, Aug 1998;68(4):231-6).

Vitamin A was also shown beneficial in a clinical trial of chemoprevention of second cancers in lung cancer survivors. Among 307 patients with surgically resected Stage I nsclc, treated with retinyl palmitate (derived from vitamin A), there was a 50% reduction in the number of second lung cancers. In this trial, after curative surgery, patients were randomly assigned to either oral retinyl palmitate (300,000 IU), daily, for 12 months, or no treatment. After a median follow-up of 46 months, 56 (37%) patients in the treated arm, and 75 (48%) in the control arm developed a recurrence, or new primary tumors; 18 patients in the treated group, and 29 patients in the control group, developed second primary tumors (Pastorino U, etal, J Clin Oncol, Jul 1993;11(7):1216-22).

However, results from a large multicenter randomized clinical trial, EUROSCAN (European Study on Chemoprevention with Vitamin A and N-Acetylcysteine) that enrolled, between June 1988 and July 1994, 2,592 patients (93.5% were current or former smokers) with either head and neck (60%) or lung (40%) cancer, failed to show any benefit from either agent alone, or when used in combination. No statistically significant difference was observed in overall survival or event-free survival between patients administered retinyl palmitate or N-acetylcysteine and controls (van Zandwijk N, etal, JNCI, 21 Jun 2000, 92(12):977-86). Discrepancies between all these results remain unresolved, underscoring the complexity of lung cancer chemoprevention.

Nonsteroidal Anti-inflammatory (NSAI) Drugs/Derivatives

Celecoxib (Celebrex; Pharmacia) belongs to a new family of NSAI drugs that are specific inhibitors of cyclooxygenase enzyme 2 (COX-2), unlike traditional NSAIs that inhibit both COX-1 and COX-2, or only inhibit COX-2 preferentially over COX-1. Celecoxib and rofecoxib (Vioxx; Merck), another COX-2 inhibitor, were recently commercialized in the USA, primarily for the treatment of pain caused by all types of arthritis (osteoarthritis and rheumatoid arthritis). In this setting, these drugs appear to be as effective as standard NSAIs but have a more favorable side effects profile, causing fewer GI complications.

Preclinical studies show that COX-2 is overexpressed in a number of human tumors, including lung cancer. In animal studies, celecoxib inhibits the growth of tumors and acts as an anti-angiogenic. In December 1999, the FDA approved Celebrex as an adjunctive treatment for patients with familial adenomatous polyposis (FAP), at the recommended daily dose of 400 mg *bid*. The drug is currently being evaluated in clinical trials as a chemopreventive in bladder and colon cancer, and may also be applicable to lung cancer.

Exisulind (Aptosyn), under development by Cell Pathways (Horsham, PA), is the sulfone metabolite of the NSAI sulindac, and a member of the class of pro-apoptotic drugs termed selective apoptotic antineoplastic drugs (SAAND). SAAND compounds act by correcting a defect within a fundamental apoptosis pathway. SAANDs such as Aptosyn induce apoptosis in neoplastic cells by inhibiting guanosine 3',5'-cyclic monophosphate (cGMP) phosphodiesterase (PDE) isoforms of the PDE5 and PDE2 gene families; cGMP PDE is an enzyme overexpressed in precancerous and cancerous cells, and is responsible for the breakdown of cGMP. Inhibition of cGMP PDE results in an increase in cellular cGMP, and this messenger molecule induces apoptosis through a series of steps involving the activation of protein kinase G and caspases, as well as attenuation of the cellular expression of β-catenin (Thompson

WJ, etal, AACR99, Abs. 26:4, Li H, etal, AACR00, Abs. 1100:172, Chang W-C L, etal, AACR00, Abs. 3149:494, Rice PL, etal, AACR00, Abs. 5435:855, Liu L, etal, AACR00, Abs. 374:59, and Thompson WJ, etal, Cancer Res, 1 Jul 2000;60(13):3338-42). Preclinical research has confirmed that regulation by Aptosyn is independent of other well-known apoptosis protein regulators, including p53, bcl-2 and bax. In addition, despite being a NSAI derivative, Aptosyn lacks COX inhibitory activity (Piazza GA, etal, Cancer Res, 15 Jun 1997; 57(12):2452-9). Using a patented (USA patent #5,858,694) screening process, the company has created a library of over 500 SAANDs, including more than 200 that display significantly greater *in vitro* apoptotic potency than Aptosyn.

Because angiogenesis may be related to apoptosis, it is also possible that inhibition of angiogenesis may contribute to Aptosyn's antineoplastic properties. When testing this hypothesis, Aptosyn statistically inhibited angiogenesis in several different types of human lung tumor xenografts in Balb/c mice (Skopinska-Rozewska E, etal, Int J Tissue React 1998;20(3):85-9). According to published data and company reports, Aptosyn has also demonstrated synergistic or additive activity *in vitro,* and in animal experiments, when administered in combination with such chemotherapeutics as cisplatin, docetaxel, doxorubicin, gemcitabine, paclitaxel, and vinorelbine, the MAb trastuzumab, and such potentially chemopreventive agents as *cis*-retinoic acid and nordihydroguaiaretic acid. Used in combination with cisplatin and paclitaxel, Aptosyn exhibited strong synergistic activity at concentrations that were subtherapeutic for each drug alone (Chan D, etal, ASCO99, Abs. 1884:488a, and Soriano AF, etal, Cancer Res, 15 Dec 1999;59(24):6178-84).

A pilot study is ongoing to evaluate exisulind in the prevention of recurrence of lung cancer. Also, as of June 1999, a single center study was enrolling patients with advanced lung cancer, in an open-label safety clinical trial to evaluate the safety of higher doses of exisulind as well as preliminary efficacy (based on disease progression) in advanced disease states. Also, in September 1999, Cell Pathways entered into a collaboration with Aventis to investigate the therapeutic potential of exisulind, in combination with docetaxel (Taxotere), in previously untreated nsclc. The two companies will jointly share the cost of this effort with each retaining all marketing rights to its respective products. The initial phase I trial will evaluate escalating doses of exisulind, in combination with a standard regimen of Taxotere and carboplatin, to determine safety and dosing. Upon successful completion, this trial will be immediately followed by a phase II open-label efficacy study of the 3-drug combination regimen, designed to support future studies, and potential product registration. Additional trials will investigate exisulind and docetaxel combinations in breast, prostate, and pancreatic cancers, as well as previously treated nsclc. Phase I clinical trials to evaluate escalating doses of exisulind in combination with a standard regimen of gemcitabine (Gemzar; Eli Lilly) for the treatment of pancreatic and bladder cancer, and nsclc, are also being planned.

Retinoids

The beneficial effects of retinoids on epithelial cells have been shown in numerous studies. For instance, early work in head and neck cancer confirmed the ability of retinoids to interrupt carcinogenesis by reversing premalignant lesions, and decreasing the incidence of second primary tumors. Retinoids were also shown to control multiplication and differentiation of epithelial bronchial cells, and may prevent precancerous lung cells from becoming malignant. However, none of the currently available retinoids, including all-*trans*-retinoic acid (ATRA), 13-*cis*-retinoic acid (13cRA), 9-*cis*-retinoic acid, and 4-hydroxyphenyl retinamide, demonstrated chemopreventive effects in lung cancer. One possible explanation is that the effects of retinoids depend on the status of various nuclear retinoid receptors, whose dysfunction may lead to carcinogenesis. The effects of retinoids are mediated by the nuclear retinoic acid receptors (RARα, RARβ, and RARγ), and the retinoid X receptors (RXRα, RXRβ, and RXRγ). Although expression of RARα and RXRα is either normal or elevated in nsclc, in contrast, a large percent of lung tumors show a significant decrease in the expression of RARβ, RARγ, and RXRβ, as well as a high frequency of LOH at 3p24, which was also observed in non-neoplastic lesions, suggesting that altered retinoid receptor expression may play a role in lung carcinogenesis (Picard E, etal, JNCI, 16 Jun 1999;91(12):1059-66). In addition, basal or treatment-induced levels of RARβ may represent an intermediate endpoint and/or independent prognostic factor in lung cancer. Future research with retinoids in lung cancer should be focused on the investigation of new generation compounds with a specificity for individual retinoid nuclear receptors (Toma S, etal, Ann Oncol 1999;10 Suppl 5:S95-102).

Retinoids such as 13cRA and ATRA, have also demonstrated moderate activity in treating lung cancer as single agents, or in a more promising approach, combined with biological therapy, chemotherapy, or RT. A phase I clinical trial, conducted at Rotterdam Cancer Institute and University Hospital, in the Netherlands, assessed the feasibility of combining cisplatin and etoposide (VP-16) with the arotinoid mofarotene (Ro 40-8757) and determined the DLT of this agent, in this combination, in patients with nsclc. Treatment consisted of oral Ro 40-8757, escalated from 84 mg/m^2, once daily, to 42 mg/m^2, thrice daily, on days 1 to 21, IV cisplatin (100 mg/m^2) on day 2, and IV VP-16 (100 mg/m^2) on days 2 to 4, repeated every 3 weeks. DLT, consisting of delayed nausea/vomiting, was reached at 42 mg/m^2 thrice daily, and MDT was set at 28 mg/m^2 thrice daily. Skin toxicity occurred but was manageable. Among 18 patients evaluable for toxicity and response, ORR was 50%, at the upper rate of what can be expected with the

cisplatin and VP-16 combination alone (van Zuylen L, etal, Anticancer Drugs, Apr 1999;10(4):361-8).

Thymalfasin

Thymalfasin (thymosin α1; Zadaxin), under development by SciClone Pharmaceuticals (San Mateo, CA), is an immunostimulatory peptide that has been approved outside the USA for the treatment of hepatitis B and C. Recent studies have shown that thymalfasin may also prevent lung tumor formation. Daily administration of subcutaneous thymalfasin (0.4 mg/kg) in the urethane injection carcinogenesis A/J mouse model, reduced lung adenoma multiplicity by approximately 45%, 40%, and 17%, 2.5, 3, and 4 months after urethane injection, respectively. Animals treated with thymalfasin had a significantly greater white cell density than controls, and endogenous thymalfasin-like peptides were detected in the mouse lung. These results indicate that exogenous thymalfasin prevents lung carcinogenesis in A/J mice (Moody TW, etal, Cancer Lett, 31 Jul 2000;155(2):121-7).

INDEX OF COMPANIES & INSTITUTIONS

— continued on back page

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