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

LUNG CANCER

Cancer of the lung and bronchus, collectively referred to as lung cancer (and including cancer of the lining of the lung, or mesothelioma, and cancers metastatic to the lung), is the most common lethal malignancy in the USA and around the world. "Pleural mesothelioma", discussed in this review, occurs by malignant transformation of the cells that comprise the pleura, the lining of the lung and chest wall. These cells also surround the heart (pericardium) and abdominal cavity (peritoneum), the two other common sites for mesothelioma.

EPIDEMIOLOGY

Lung Cancer

Lung cancer, or bronchogenic carcinoma, is the most common visceral malignancy in the USA, with an estimated incidence of 170,000 in 1995. In North America, Europe, Australia and Japan lung cancer incidence is estimated at over 517,000 in 1995 (see Exhibit 1). Worldwide incidence is forecast to reach 2,000,000 in the year 2000. Lung cancer is now the number one cause of cancer death in the USA for both men and women, causing an estimated 157,400 deaths in 1995; the overall 5-year mortality is 90%. Incidence and mortality rates (per 100,000 population) vary significantly from country to country, ranging from a high of 135.9 and 128.2, respectively, among males in Belgium to 6.6 and 5.5 among females in Costa Rica (see Exhibit 2). Worldwide incidence rates have been calculated by assuming similar survival rates to those in the USA, in all other countries because such statistics are not readily available on a worldwide basis.

Lung cancer incidence and mortality rates have plateaued in the past several years in the USA but continued to climb abroad. Major contributors in the overall rise of incidence and deaths has been increasing longevity of the general population and a substantial climb in lung cancer among women. Actually, in the USA, lung cancer incidence rates declined among men in the 1985-1990 period but increased at an annual rate of over 2.2% among women. In the USA age adjusted lung cancer incidence and mortality rates in women rose steadily from around 18 and 13 in 1973 to 42 and 32 in 1995, respectively, more than doubling in a 22-year period. In Japan, between 1960 and 1992, the overall mortality rate increased almost 6-fold among both men and women, from 7.9 to 48.2 and 3.2 to 17.4, respectively.

Mesothelioma

Unlike lung cancer, mesothelioma is rare. Fewer than 2,000 new cases are diagnosed each year in the USA. Mesothelioma is epidemiologically linked to asbestos exposure, with a long latency period (up to 30 years) between exposure and disease. The incidence of mesothelioma has increased recently, three decades after a dramatic rise in the number of asbestos workers employed during and immediately after WWII, and some researchers fear that an epidemic of mesothelioma may occur within the next 10 years. Most, if not all, mesothelioma is associated with exposure to amphibole asbestos. There is a very high incidence of the disease among asbestos workers with long exposure and even wives of asbestos workers are at increased risk.

CLASSIFICATION

Histologic classification is important for prognosis and therapy of lung cancer (see Exhibits 3 and 6).

Small Cell Lung Cancer

Malignancies of the lung parenchyma are divided into histologic subtype; small cell lung carcinoma (sclc) is distinguished from all other types because of its different behavior, prognosis, and response to therapy. It is comprised of the "oat cell" or small cell type, the (slightly larger) intermediate type, and "mixed" type, containing both small cell carcinoma and another histologic subtype. Sclc is a subset of "neuroendocrine" carcinomas, which include bronchial carcinoids and well differentiated neuroendocrine carcinomas. Carcinoids are tumors of low metastatic potential which can occur in virtually any visceral organ, and can secrete neuroendocrine peptides which cause flushing, diarrhea and other symptoms in

Exhibit 1
Lung Cancer Incidence and Mortality in North America, Europe and Japan in 1995

	Death Rate				Incidence Rate			
Region	**Male**	**Female**	**Total**	**Total Deaths**	**Male**	**Female**	**Total**	**Total Incidence**
Europe*	85.3	18.9	51.3	258,815	90.4	22.6	51.7	281,144
EEC	89.1	20.1	53.8	187,699	94.4	24.1	58.4	203,975
Non-EEC Western	60.1	18.3	38.8	13,039	63.7	22.0	42.4	14,261
Non-EEC Eastern	81.4	15.5	47.8	58,077	86.2	18.6	51.7	62,908
North America	74.4	44.8	59.3	171,130	75.2	53.4	64.1	185,026
USA	74.1	46.0	59.8	157,400	74.6	54.8	64.6	169,900
Canada	77.2	31.9	54.2	13,730	81.8	38.3	59.8	15,127
Japan	49.0	17.2	32.8	40,563	51.9	20.6	36.0	44,511
Australia	60.3	19.5	39.8	6,212	63.9	23.4	43.6	6,798
				476,720				517,479

** Excludes the old USSR*
Source: Centers for Disease Control and Prevention, National Center for Health Statistics, Health and Welfare Statistics Association (Japan) and New Medicine

most patients. Well differentiated neuroendocrine carcinomas (also termed atypical or malignant carcinoid) appear to be of intermediate malignant potential. They occur primarily in cigarette smokers, but metastasize much less frequently, and the surgical cure rate approaches 50% in stage I patients.

Non Small Cell Lung Cancer

The remaining histologic types, primarily adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and several others, collectively termed "non-small cell" (nsclc), are grouped together because of their similar behavior, prognosis, and response to therapy. There is increasing evidence that the diverse histologic subtypes of bronchogenic carcinoma may all arise from the same epithelial cell lining the respiratory tract.

Mesothelioma

Three histologic subtypes of mesothelioma have been described: epithelial, sarcomatoid, and biphasic (having both epithelial and sarcomatoid features). Electron microscopy (EM) is often required to distinguish the ultrastructural detail of mesothelioma from adenocarcinoma, which can be difficult with light microscopy. But even with EM, pathologists will disagree on the diagnosis in up to 10% of cases. An entity termed "benign mesothelioma" has also been described. It is a rare, well encapsulated solitary fibrous tumor of the pleura, and is not associated with asbestos exposure. Surgical resection is curative, but if left untreated the tumor will extend locally and compress surrounding structures.

ETIOLOGY AND PATHOGENESIS

Lung Cancer

The median survival for patients with untreated lung cancer is 3-6 months from the time of diagnosis. Lung cancer metastasizes early, aided by the rich vascular and lymphatic supply in the lungs. The tumor spreads sequentially, first to regional lymph nodes, and then to distant sites. While chemotherapy and radiotherapy can improve survival by weeks or even months, they are extremely unlikely to cure; for early stage nsclc, complete surgical resection is the only potentially curative therapy available. Sclc, on the other hand, is almost always metastatic at the time of diagnosis and although not curable by surgical resection, it is more sensitive to chemotherapy than nsclc. In general, however, the result of therapy for lung cancer is poor; all patients with lung cancer should, therefore, be considered for studies evaluating new therapies or approaches to treatment.

Cigarette smoking. The overwhelming majority of lung cancer is linked to cigarette smoking. Tobacco smoke, even "second-hand" tobacco smoke, is classified as the most dangerous type of (Group A, proven human) carcinogen. It is the repeated stimulation of the lungs by the carcinogens in tobacco smoke that causes cancer. The risk of dying from lung cancer is 22 times higher among men who smoke and 12 times higher among women who smoke compared to those who never smoked. Cigarette smoking is directly responsible for 90% of deaths from lung cancer. However, a smoker has only a 7% lifetime risk of dying from lung cancer, largely

because smokers die at a younger age from heart disease and emphysema. There may also be a genetic predisposition affecting this risk. Also, according to Dr. Harvey Risch, an associate professor of epidemiology and public health at the Yale University School of Medicine, pack for pack, cigarettes may pose more of a lung cancer threat to women than to men. However, such conclusions based on isolated studies are questionable. Earlier research, in fact, showed that American men who smoke run a higher risk of dying from lung cancer than female smokers.

Other respiratory carcinogens. Other environmental toxins or noxious inhalants may increase the risk of contracting lung cancer. Exposure to radon, an inert gas produced by the radioactive decay of radium and uranium, has been consistently shown to be associated with an increased risk. Other respiratory carcinogens, such as asbestos, arsenic, mustard gas, chromium and nickel have also been causally implicated in lung cancer. Generally, air pollution is suspected as a cause in lung cancer and such a link may explain the steady increase of this cancer in the developing world where air pollution is often ignored in the effort to increase industrial output in an economically feasible manner.

Molecular factors. Despite extensive research into the biology of lung cancer, the basic molecular defect is not well understood. Numerous genetic changes have been observed in lung cancer cells as well as in lung cancer tissue *in vivo*, and carcinogenesis probably represents a multistep process involving several of these changes (see Exhibit 4). Deletions in chromosome 3p occur early, with chromosome 5q and 18q abnormalities noted during progression of the disease. Deletions of 13q (the retinoblastoma tumor suppressor gene locus) and 17p (the p53 gene locus) have also been noted.

The importance of the p53 gene in pathogenesis is underscored by the observation that mice genetically engineered to lack p53 expression develop sclc at a very high frequency. Abnormalities in the epidermal growth factor receptor (EGF-R), overexpression of the ras and myc family of oncogenes, and aberrant expression of the human papilloma virus (HPV) E6 and E7 genes have all been observed. The HPV E6 and E7 genes are implicated in the development of cervical carcinoma, where they are believed to target and inactivate both the p53 tumor suppressor gene product and the retinoblastoma gene product (pRB). pRB is a cell cycle regulatory molecule, whose function is to restrain the growth of cells. Recently, several studies have documented the loss of functional pRB in tumor cell lines and tissues from patients with nsclc. In addition, in tumors where pRB appears to be intact, there is loss of functional regulators of pRB such as p16INK4/MTS1/CDKN2, p15INK4b/MTS2, and possibly p18. Furthermore, it is possible to reintroduce pRB into tumor cells that lack functional pRB and inhibit tumor cell proliferation *in vitro* and *in vivo*. Current research suggests that inactivation of this pRB tumor suppressor pathway is the most common genetic change in nsclc.

Mesothelioma

Most, if not all mesothelioma is related to asbestos exposure. Amphibole asbestos is believed to be the causative agent, but recent studies suggest that the carcinogenic nature of asbestos may have more to do with the dimensions rather than the type of asbestos fiber. Long, thin fibers are better able to pass down the trachea and into the bronchial tree. The association of asbestos with mesothelioma is undisputed; whether any cases of mesothelioma occur in the absence of asbestos exposure remains unknown. Regardless, there is a very long latency period between exposure to asbestos and onset of mesothelioma, during which time asbestos fibers remain trapped in the lung and continue to irritate the mesothelium. It is this prolonged, chronic irritation which may be critical for tumorigenesis.

The molecular basis for the association with asbestos remains unclear. The neurofibromatosis type 2 gene (NF2) appears to be somatically mutated in a subset of mesothelioma tumors, but not in lung cancers. In one study, 12 of 14 mesotheliomas contained cytogenetic abnormalities near the NF2 locus, with 40% of those examined having mutations within the coding region of NF2. Transforming growth factor-α (TGF-α) may also play a role, as it is expressed only in asbestos-transformed cells (and not spontaneously transformed cells). Asbestos-transformed cells are stimulated to grow by exogenous TGF-α, and inhibited by neutralizing antibody against TGF-α. Aberrant expression of another oncogene, bcl-2, has been detected in malignant mesothelioma, but not in normal mesothelial cells. In contrast, aberrant expression of ras or c-erbB-2 has not been detected in mesothelioma, and no loss of the retinoblastoma protein has been noted (a common occurrence in nsclc).

There is evidence for an infectious element in the development of mesothelioma as well. Pericardial and pleural tumors develop in 100% of Syrian hamsters injected in the pleural space with wild type simian virus 40 (SV40). However, injection with SV40 containing a mutation in the small t antigen do not develop tumors, implicating this protein in tumorigenesis. SV40-like viral DNA sequences have been detected in 60% and the SV40 large T antigen viral oncoprotein has been detected in 85% of mesothelioma specimens studied, but in none of the asbestos laden matching lung tissue.

PRESENTATION, DIAGNOSIS AND STAGING

Although the outcome of patients with lung cancer is far more favorable when the disease is detected at an early stage no screening methodology has as yet demonstrated feasibility on a mass scale. The majority of patients present with symptoms such as cough, hemoptysis, dyspnea, or weight loss. Occasionally a routine chest x-ray will reveal an abnormality. Asymptomatic patients

Exhibit 2
Lung Cancer Incidence and Mortality by Gender in Selected Countries Worldwide in 1995

	Death Rate				Incidence Rate			
Country	**Male**	**Female**	**Total**	**Total Deaths**	**Male**	**Female**	**Total**	**Total Incidence**
Group 1								
UK	99.7	44.1	71.3	41,447	105.7	52.9	78.8	45,763
Germany	78.0	18.2	47.3	38,426	82.7	21.8	51.4	41,795
Italy	101.7	16.6	58.0	33,574	107.8	19.9	62.6	36,280
France	90.1	12.2	50.2	28,992	95.5	14.6	54.1	31,237
Spain	76.0	7.3	41.1	16,145	80.6	8.8	44.1	17,317
Holland	100.9	17.4	58.7	9,105	107.0	20.9	63.5	9,842
Belgium	128.2	15.6	70.8	7,099	135.9	18.7	76.1	7,637
Greece	88.1	14.7	50.8	5,212	93.4	17.6	54.9	5,632
Denmark	82.8	46.5	64.4	3,345	87.8	55.8	71.6	3,717
Portugal	47.2	9.9	27.9	2,759	50.0	11.9	30.3	2,995
Ireland	63.4	28.6	46.0	1,595	67.2	34.3	50.7	1,760
Subtotal	89.1	20.1	53.8	187,699	94.4	24.1	58.4	203,975
Group 2								
Austria	72.1	21.5	45.9	3,608	76.4	25.8	50.2	3,947
Sweden	45.9	21.3	33.5	2,937	48.7	25.6	37.0	3,246
Switzerland	71.6	13.8	42.2	2,933	75.9	16.6	45.7	3,178
Finland	64.5	14.9	39.0	1,970	68.4	17.9	42.4	2,142
Norway	53.2	20.2	36.5	1,591	56.4	24.2	40.2	1,749
Subtotal	60.1	18.3	38.8	13,039	63.7	22.0	42.4	14,261
Group 3								
Poland	90.3	16.8	52.6	20,387	95.7	20.2	57.0	22,078
Yugoslavia (old)	67.7	12.3	39.7	9,576	71.8	14.8	43.0	10,361
Czech Republic	100.1	15.8	56.9	9,032	106.1	19.0	61.4	9,753
Hungary	125.8	30.6	76.3	7,994	133.3	36.7	83.1	8,707
Romania	55.4	10.7	32.8	7,705	58.7	12.8	35.5	8,346
Bulgaria	64.6	12.5	38.1	3,382	68.5	15.0	41.2	3,665
Subtotal	81.4	15.5	47.8	58,077	86.2	18.6	51.7	62,908
Group 4								
Old USSR	65.4	7.2	34.7	99,147	69.3	8.6	37.3	106,619
Group 5								
USA	74.1	46.0	59.8	157,400	74.6	54.8	64.6	169,900
Group 6								
Japan	49.0	17.2	32.8	40,563	51.9	20.6	36.0	44,511
Canada	77.2	31.9	54.2	13,730	81.8	38.3	59.8	15,127
Argentina	46.9	8.3	27.2	8,871	49.7	10.0	29.4	9,596
Australia	60.3	19.5	39.8	6,212	63.9	23.4	43.6	6,798
Cuba	49.8	18.3	34.2	3,328	52.8	22.0	37.5	3,651
Hong Kong	62.1	31.6	47.1	2,603	65.8	37.9	52.1	2,879
Chile	17.6	6.5	12.0	1,582	18.7	7.8	13.1	1,738
New Zealand	57.6	25.1	41.2	1,362	61.1	30.1	45.4	1,503
Uruguay	83.8	7.3	44.6	1,317	88.8	8.8	47.8	1,411
Singapore	42.2	16.3	29.4	796	44.7	19.6	32.3	874
Israel	27.8	10.7	19.2	776	29.5	12.8	21.1	853
Costa Rica	11.1	5.5	8.3	201	11.8	6.6	9.2	222

Exhibit 3
Epidemiology of Lung Cancer in the USA by Type (1995)

	Incidence (#)	Mortality (#) and 5-year Survival (%)
All Types	169,900	157,400 (10-13)
By Sex		
Male	96,000	95,500 (12)
Female	73,900	62,000 (16)
By Type		
Nsclc (60%); squamous cell (30%; 80% proximal; 20% peripheral nodules) and adenocarcinoma and large cell lung cancer (30%); although histologically distinct, these three types of lung cancer are grouped together because all respond poorly to conventional chemotherapy but, in some cases, may be cured with surgery and radiotherapy	101,940	
Sclc (20%; 95% mediastinal or hilar, 5% peripheral); histologic subtypes include oat, hexagonal, lymphocytic, and spindle cell; natural histories of these subtypes are virtually identical	33,980	(5)
Mixed histology (20%; adenosquamous is most frequent mixed type, but other combinations can occur)	33,980	
Metasticized from other sites	150,000	
By Stage		
Nsclc (includes mixed histology lung cancers)		(16)
Stage I & II	23,000	(17-20)
Stage III	45,000	(10)
Stage IV	68,000	(0)
Sclc		
Limited sclc	10,000	(17)
Extensive sclc	23,980	(0)
By Treatment Modality		
Candidates for surgery alone or in combination with other therapies	33,000-45,000	
Candidates for radiotherapy alone or in combination with other therapies	100,000-146,980	
Candidates for chemotherapy, alone or in combination with other therapies	150,000-165,000	
Hospitalizations related to lung cancer (1993)	193,000	
Male	114,000	
Female	79,000	
Under 45 years of age	10,000	
Between 45 and 64-years of age	74,000	
Over 65	110,000	

Source: The Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute (NCI), the National Center for Health Statistics (NCHS), the American Cancer Society and New Medicine

can present with "paraneoplastic" symptoms caused by the cancer, but not directly due to the mass itself. Upon further investigation, a lung cancer is found. Clinically, sclc differs from nsclc in the high incidence of paraneoplastic syndromes. As a "neuroendocrine tumor," sclc often ectopically produces neuroendocrine or hormonal polypeptides. Ectopic production of ACTH, VIP, HGH, calcitonin or vasopressin, to name a few, can all cause symptoms. In addition, polymyositis, dermatomyositis, and a myasthenia gravis-like syndrome (Lambert-Eaton syndrome) and other phenomena can occur. Occasionally, paraneoplastic syndromes occur with nsclc as well, such as the hypercoagulability and migratory thrombophlebitis (Trousseau's syndrome) seen with adenocarcinoma.

After identifying an abnormality, a diagnosis is made by histologic identification of cancerous tissue. Sputum may contain malignant cells, which would provide such a histologic diagnosis. However, patients usually undergo bronchoscopy, bronchoalveolar lavage (if necessary), and mediastinoscopy to obtain tissue diagnosis and evaluate the presence of cancer spread to regional lymph nodes. If the suspected lesion is peripheral or otherwise inaccessible by bronchoscopy, a needle biopsy, open lung biopsy, or (increasingly) video-assisted thoracoscopic surgery (VATS), is used to obtain tissue diagnosis. If the primary lesion is small enough, it may be resected entirely via VATS with minimal morbidity. After a diagnosis of limited stage nsclc is made, other staging studies

Exhibit 4
Human Proto-oncogenes and Tumor Suppressor Genes Associated with Lung Cancer

Genetic Marker	Lung Cancer Involvement	Mechanism	Protein/Function of Protein Product
Proto-oncogenes			
c-erbAβ	Sclc	Deletion (may lead to dominant negative oncogene that inactivates a tumor suppressor gene)	Thyroid hormone receptor that binds tri-iodothyronine; transcription factor
Her-2/Neu (erbB-2)	Adenocarcinoma		p185, a membrane like receptor with intrinsic tyrosine kinase activity
c-raf-1	Sclc		p74; phosphoprotein with serine-threonine kinase activity
c-myc	Sclc	Amplification and overxpression	p64; sequence-specific DNA-binding protein
L-myc	Sclc		Sequence-specific DNA-binding protein?
N-myc	Sclc		Sequence-specific DNA-binding protein?
c-myb	Sclc	Amplification and over expression	p75
c-kit	Sclc; lower in nsclc		Transmembrane tyrosine kinase
c-jun	Sclc		Transcriptional activating factor AP1
c-src	Sclc		
Ras family	Nsclc, (20% of tumors and 30% of tumor cell lines); adenocarcinoma of the lung (30% of patients); squamous cell carcinoma (4%); large cell (10%); no mutations found in sclc	Normally prevents cell growth and division through cell transduction signals, guanosine triphosphatase activity and affinity for guanine nucleotides (GTP and GDP)	Ras proteins (188-189 amino acids, MW=21,000)
H-ras-1	Nsclc	Point mutations	p21/ membrane-associated guanosine triphosphate (GTP)-binding; GTPase
K-ras-2	Nsclc; 90% of adenocarcinoma (in 1/3 of cases activation occurs in codon 12 of exon 1)	Point mutations	p21/membrane-associated GTP-binding; GTPase; present in squamous cell cancer and adenocarcinomas; 5-year survival rates were 12% when strongly expressed and 64% when negative
N-ras	Nsclc	Point mutations	p21/ membrane-associated GTP-binding; GTPase
Tumor Suppressor Genes			
p53	Mutations in p53 are present in over 50% of lung cancer; mutations are present in 74% of established tumor cell lines and 49% of tumor specimens in nsclc and in 100% of established cell lines and 77% of tumor specimens in sclc	Mutation in lung cancer attributed to smoking is usually a G to T transversion; radon appears to mutate p53 differently (in a study of under ground miners with lung cancer, none of the p53 mutations found in 37%, were of the G to T transversion type)	See FO, V1 #1, p 24
MTS-1 (multiple tumor suppressor gene)	Homozygous p16 deletions were found in 25% of cell lines derived from lung tumors; p16 was missing in 36% of nsclc tumors according to researchers at the U California at San Diego (Tsutomu Nobori, Nature, April 21, 1994)	p16 inactivation may stimulate cancerous growth in some, but not most, human tumors; mechanism of tumorigenesis remains unclear	Encodes the cell cycle regulator protein p16
Rb (retinoblastoma)	Rb mutations are detected in about 60% of sclc and 20-30% of nsclc; inactivation of the pRB tumor suppressor pathway is the most common genetic change in nsclc	It is possible to reintroduce pRB into tumor cells that lack functional pRB and inhibit tumor cell proliferation *in vitro* and *in vivo.*	pRB; tumor cell lines and tissues from patients with nsclc did not contain functional pRB
Cyclin-dependent kinase 4 (CDK4)-inhibitor gene on chromosomes 9q21	CDK4-inhibitor gene is frequently deleted or rearranged in melanomas, gliomas, lung cancers and leukemias	CDK4-inhibitor gene is thought to be a physiological suppressor of proliferation; cells unable to produce the inhibitor may be prone to neoplastic transformation (Nature Vol 368, April 21, 1994)	

Source: New Medicine

such as bone scan and head CT are usually undertaken to evaluate any other suspicious lesions and document the absence of distant metastases. Staging of nsclc was more accurate using metabolic PET scanning rather than CT, as was differentiation of operable from inoperable disease (Valk, PE, etal, ASCO95, Abs. 1060). Magnetic resonance imaging (MRI) because of its higher contrast resolution, is potentially capable of detecting chest wall invasion not detected by CT. Sonography has demonstrated a 100% sensitivity and 98% specificity in detecting chest wall invasion.

In sclc, staging studies have limited impact on treatment and survival, but are used more often to follow disease and response to therapy. Because of the high likelihood of metastatic disease at the time of diagnosis, most patients with sclc undergo bone scan, head CT, and occasionally bone marrow biopsy and aspiration. These tests detect new occult metastases in up to 45% of patients not suspected of having metastatic disease.

Patients with mesothelioma will present with a variety of symptoms directly attributable to tumor, including dyspnea, cough, weight loss, chest pain and, occasionally, fever. Asymptomatic patients may be identified by routine chest x-ray. Almost all patients will develop a pleural effusion at some point, leading to further symptoms. Neither thoracentesis of pleural fluid nor needle biopsy of a suspected pleural mass yield malignant tissue in most cases, causing a delay in diagnosis. Because of this difficulty in diagnosis and the need for a relatively large amount of tissue, an open pleural biopsy is usually performed.

Mesothelioma spreads by direct extension, and rarely metastasizes to distant sites. The only radiographic studies that are routinely obtained are chest CT (to evaluate the extent of local disease) and chest X-ray (to follow disease). If there is concern about the tumor compromising local structures, then additional studies are performed. For prognosis and for clinical trials, the staging system consists of stage I, disease within the pleural capsule; stage II, direct local extension, including the mediastinum; stage III, extension into hemithorax or peritoneum; and stage IV, distant metastases.

Biomarkers

Numerous neuroendocrine factors are associated with lung cancer (see Exhibit 5) but no biomarkers have demonstrated sufficient sensitivity and specificity for routine screening of asymptomatic populations with lung cancer. An ELISA test (DR-70) based on an affinity purified polyclonal antibody is under development by AMDL (Tustin, CA) as a diagnostic test for lung cancer irrespective of histology. The test measures serum levels of a circulating extracellular matrix complex (CEMC) which has not been completely characterized but is postulated to result from degradation of the extracellular matrix during cancer invasion and metastasis. A clinical evaluation of the test (Fields, etal, 12th Annual International Conference on Human Tumor Markers, NYC, June 1995) found that mean levels of CEMC were higher in cancer patients than in controls and in those with advanced disease.

Another sensitive test that may diagnose lung cancer at an early stage is based on detecting K-ras codon 12 mutations in bronchoalveolar lavage fluid. Specimens from patients who had undergone diagnostic bronchoscopy for suspected lung cancer were assayed with a highly sensitive polymerase chain reaction-primer-introduced restriction with enrichment for mutant alleles (PCR-PIREMA) method. K-ras codon 12 genotypes detected in tumor specimens were identical to those found in corresponding lavage fluid (Mills, etal, J Natl Cancer Inst, 87:1056, 1995).

In nsclc, serum levels of carcinoembryonic antigen (CEA), tumor-associated glycoprotein 72 (TAG-72), squamous cell antigen, and tissue polypeptide antigen have all been proposed as markers of disease progression and response to therapy, but it is unclear if they offer an advantage over standard chest x-ray. MAbs to CEA and TAG-72 (b72.3 and CC-49) may have utility in nsclc. Anti-TAG-7 and CEA MAb mixtures may be even more effective in detecting squamous cell carcinomas.

Several of the newer assays, such as Cyfra 21.1 and CK18, measure the serum level of cytokeratin fragments (the structural components of nsclc tumor cells). A large multicenter trial, the Cyfra 21-1 Multicenter Study Group, recently found that this marker is highly specific, and may be more sensitive for the squamous-cell subset of nsclc (Rastel D, etal, Eur J Cancer 1994;30A(5):601-6). Cyfra 21.1 was also a useful marker in differentiating malignant from benign pleural effusions (Saka H, etal, ASCO95, Abs. 32). A test to monitor lung cancer using Cyfra 21.1 developed by Centocor (Malvern, PA) is sold in Europe by CIS bio international (Gif sur Yvette, France).

One recent study has suggested that detection of sclc can be improved by the concurrent use of four different biomarkers, but this remains unconfirmed. Biomarkers of sclc which include hormones such as ACTH and ADH, and enzymes such as neuron-specific enolase and creatine kinase, have been shown to correlate with the extent of disease and response to therapy in individual cases. CEA is not a useful diagnostic marker in sclc because a majority of patients have normal CEA; however, elevated CEA is associated with distant metastases. In general, the spectrum of biomarker expression differs from tumor to tumor, and no single marker for all sclc has yet been identified. In December 1994 Boehringer Mannheim (Mannheim, Germany) said it was granted a USA patent for a diagnostic test for sclc based on a MAb to synaptophysin, a neuroendocrine marker. Another biomarker with may be useful in the detection of primary or secondary sclc and in staging of the disease, is the delta-like (dlk) gene and its corresponding protein which contains epidermal growth factor (EGF)-like repeats and appears to be a member of the family of EGF-like neurogenic genes first identified in *Drosophila.* In addition, dlk may play a role in hematopoiesis. ImClone Systems (New York, NY)

Exhibit 5
Neuroendocrine Markers Associated with Lung Cancer

Neuroendocrine Markers	Comments
Cytoplasmic secretory granules	Characteristic of sclc
L-dopa decarboxylase	Sclc
Neurone specific enolase (NSE)	Nsclc, sclc; tumors expressing NSE seem to behave more aggressively and respond better to chemotherapy; in one series, 70% of nsclc tumors were positive for NSE; in another series NSE values correlated with overall survival (Shaw E, etal, ASCO95, Abs. 29)
Creatine kinase-BB	Sclc
Gastrin-releasing peptide (GRP)	Sclc; GRP is the mammalian equivalent of bombesin, a neuropeptide found in amphibian skin; a family of bombesin-like peptides (autocrine growth factors for sclc) has been identified, including GRP and neuromedin B, which bind to specific cell-surface receptors that belong to the class of G-protein coupled, calcium-mobilizing receptors comprising seven transmembrane helices clustered to form a ligand-binding pocket; among strategies to inhibit GRP are MAbs, synthetic antagonists and drugs interfering with second messenger pathways; however, because only about 1/3 of sclc express bombesin, it is unlikely that specific bombesin antagonists will prove practical in the clinic
Ranatensins (Neuromedin B, Neuromedin C, Litorin)	Sclc; neuromedin B and its receptor which share significant homology with GRP and its receptor, is also expressed in many sclc cell lines; they may bind to each other's receptor at different affinities; therefore, despite successful inhibition of GRP receptors, sclc growth may still be stimulated by neuromedin B
Transferrin	Sclc
Insulin-like growth factor I (IGF-I)	Sclc; IGF-I is a polypeptide that is mitogenic for a variety of cell types secreted by both sclc and nsclc; binding sites for IGF-I have been demonstrated on sclc cells and exogenous IGF I stimulates the growth of these cells; this effect can be blocked by an antibody to the IGF-I receptor, implicating IGF-I as an autocrine growth factor for sclc; the IGF-I peptide and its RNA transcribed from the IGF-I gene, IGF-binding proteins (IGF-BP), IGF-I receptor (IGF-I-R) and its mRNA are possible targets for anti-neoplastic drugs, antibodies or growth-factor analogs as potential new approaches to therapy (Favoni RE, etal, International Journal of Cancer, 1994 Mar 15, 56(6):858-66)
Bradykinin	Sclc
Neurotensin	Sclc
Cholecystokinin	Sclc
Vasoactive intestinal peptide (VIP)	Sclc; the gene encoding the human type I VIP receptor (HVR1), also termed the type II PACAP receptor, was cloned, characterized, and localized to the short arm of human chromosome 3 (3p22), in a region associated with sclc; HVR1 is expressed selectively in human tissues with a relative prevalence of lung > prostate > peripheral blood leukocytes, liver, brain, small intestine > colon, heart, spleen > placenta, kidney, thymus, testis (Sreedharan SP, etal, PNAS of the USA, 1995 Mar 28, 92(7):2939-43)
Vasopressin	Sclc
Serotonin	Sclc
Galanin	Sclc; acts as a direct growth factor in sclc
Acetylcholine	Sclc
Calcitonin	Sclc
Adrenocorticotrophic hormone (ACTH)	Sclc
Tachykinins (Neurokinin A, Substance P)	Sclc; substance P antagonists are broad-spectrum antagonists that appear theoretically attractive but may prove inapplicable *in vivo*
Opioid	Sclc
Somatostatin (somatotropin release inhibiting factor, SRIF)	Sclc; SRIF are potent inhibitors of certain sclc cell lines *in vitro* and in animals
Epidermal growth factor (EGF)	Nsclc
Transforming growth factor-a	Nsclc
Platelet derived growth factor (PDGF)	Nsclc
Leu-7	Nsclc
Synaptophysin	Nsclc; in one series 11.2% of nsclc tumors were positive for this marker
Chromogranin A	Nsclc, sclc; tumors expressing these markers seem to behave more aggressively and respond better to chemotherapy

is considering acquiring an exclusive worldwide patent of this technology from the NIH which holds patent rights.

Radioconjugates

Imaging studies utilizing radiolabeled conjugates are actively under investigation for both nsclc and sclc.

OncoTrac, a Fab' fragment of MAb NR-LU-10 linked to technetium-99, in development for both sclc and nsclc, has been shown as sensitive and specific as CT scanning, and has a positive predictive value of 95% in the detection of sclc. NeoRx (Seattle, WA) developed OncoTrac in collaboration with Boehringer Ingelheim (BI; Ingelheim am Rhein, Germany) which filed a PLA with the FDA in March 1994. BI's subsidiary, Dr. Karl Thomae (Biberach an der Riss) will manufacture the product for worldwide use. DuPont Merck (Wilmington, DE) will market OncoTrac in the USA. OncoTrac is intended for staging of sclc prior to therapy. (Editor's note: Inadvertently this agent was omitted in Exhibit 4, pp 66-67 of FO, V1, #2/3).

CEA-Scan (was Immun-4; ImmuRAID-CEA-Tc-99m) under development by Immunomedics (Morris Plains, NJ) in collaboration with Pharmacia (Stockholm, Sweden) is in phase III clinical trials in nsclc. Anti-CEA Fab' IMMU-4, conjugated to technetium 99m was able to detect 72% of known lesions by SPECT imaging, although a persistent blood pool of radiolabel complicated the image interpretation (Kramer EL, etal, Cancer 1994 Feb 1;73(3 Suppl):890-5).

^{131}I anti-CEA-anti-carbohydrate 19-9 (CA 19-9) MAb immunoscintigraphy to detect mediastinal lymph node metastases, one of the most important prognostic variables of in lung cancer, did not prove superior to CT. Among 14 evaluable patients, sensitivity and specificity were 0.83 and 0.12 for immunoscintigraphy, and 0.66 and 0.50 for CT, respectively. Although one patient had pathologically confirmed metastasis detected by immunoscintigraphy but not by CT, results with the former were hampered by a very high level of false positives. Also, there was no relationship between positive immunoscintigraphy and a high serum CEA level. ^{131}I anti-CEA-anti-CA 19-9 did not add value to non-invasive mediastinal staging of lung cancer because of lack of specificity and insufficient sensitivity (Boilleau G, etal, Lung Cancer, 1994 Sep, 11(3-4):209-19).

Radiolabeled somatostatin. A majority of sclc tumors express the receptor for somatostatin, not normally found in lung tissue. In several different studies, the radiolabeled somatostatin analog ^{111}In-pentetreotide (OctreoScan; Mallinckrodt Medical, St. Louis, MO) detects tumors in 92-100% of patients tested, and shows promise as a more sensitive tool to follow disease prior to and after chemotherapy. OctreoScan obtained regulatory clearance June, 1994 based on a PLA filed in November 1992 and was launched in October 1994. OctreoScan is also approved in the Netherlands and received approval from the European Committee for Proprietary Medicinal Products in December 1994. Mallinckrodt has filed for approval in Canada. OctreoScan is used to detect sclc and abdominal and thyroid tumors in conjunction with gamma scintigraphy, including single photon emission computed tomography (SPECT). Pentetreotide imaging may also be used to detect nsclc (Kirsch CM, etal, Eur J Nucl Med 1994 Dec; 21(12):1318-25). The pentetreotide used in OctreoScan is a modified version of octreotide (Sandostatin; Sandoz). In the USA OctreoScan costs $800 per procedure.

PROGNOSIS

Although 5-year survival rates associated with lung cancer in the USA have been dismal, ranging between 10% and 13%, great improvements have been made in 1-, 2- and 3-year overall survival rates of localized nsclc, estimated at 81%, 66% and 58%, respectively. Improved short term survival is probably attributable to aggressive combination chemotherapy and multimodality therapy that are currently offered to most patients with lung cancer, other than stage I nsclc. In spite of the lethality of lung cancer average years of life lost from this cancer in the USA, estimated at 14.9, are fewer than the average for all cancers (15.3), mainly because lung cancer occurs later in life.

Non Small Cell Lung Cancer

The prognosis of patients with nsclc depends on extent of disease spread. Patients with surgically resectable tumors have the best prognosis (stages I & II, disease limited to the lungs and local lymph nodes), with a 30-75% 5-year survival. Patients with locally or regionally advanced lung cancers (stage III, tumors extending locally into surrounding structures or involving distant lymph nodes) have a worse prognosis, which has improved in recent years because of aggressive multimodality therapy. Patients with stage III nsclc may be further divided into "more-favorable" (IIIA, involvement of ipsilateral mediastinal lymph nodes) and "less favorable" (IIIB, involvement of contralateral mediastinal or distant lymph nodes) groups. Distant metastases or involvement of the great structures in the mediastinum, such as the heart, great vessels, and trachea (stage IV) are ominous; median survival for these patients is less than 24 weeks.

Other factors that affect prognosis within each stage have also been identified. These include tumor collagen content, evidence of mucin expression, degree of cellular differentiation and DNA content (ploidy), tumor bulk (tumor size for early stage disease, and number of distant metastases for stage IV disease), and evidence of blood vessel microinvasion by tumor. In addition, patients with good performance status and women appear to have a better prognosis. Patients who survive lung cancer, however, are at significantly increased risk for second cancers of the aerodigestive tract.

Exhibit 6
Treatment Protocols for Lung Cancer by Type and Stage

Stage	Primary Therapy	Chemotherapy Regimens	Other Options and Goals
NSCLC			
Stage I and II	Surgery	Adjuvant, investigational	Prevention of secondary tumors
Stage IIIa	Surgery; adjuvant or neoadjuvant chemotherapy and radiation therapy	Cisplatin-based	
Stage IIIb	Chemotherapy and radiotherapy (surgery is experimental)	Cisplatin-based	Paclitaxel, if no response to cisplatin
Stage IV	Chemotherapy and radiotherapy	Cisplatin-based, vinorelbine	Paclitaxel, if no response to cisplatin
SCLC			
Limited	Chemotherapy and radiation therapy; occasionally surgery	Combination chemotherapy with either cisplatin or cyclophosphamide	Consider PCI
Extensive	Chemotherapy and radiation therapy	As above	Consider PCI

Small Cell Lung Cancer

Sclc, if untreated, is the most aggressive of any malignancy, with a median survival of 2-4 months. Unlike nsclc, sclc almost always presents with metastatic spread (often with occult metastases), and is much more sensitive to chemotherapy. But as for nsclc, prognosis depends primarily on the extent of disease spread. One third of patients will have "limited" disease - confined to one hemithorax, the mediastinum, or ipsilateral supraclavicular lymph nodes - at diagnosis, with median survival of 10-16 months. At 2 years, 10-25% of these patients will still be alive, with half of them surviving beyond 5 years. These long-term survivors die more often from concurrent disease and second cancers as from lung cancer recurrence. Patients with "extensive" disease (spread beyond the above areas) have a worse prognosis, with median survival of 9-12 months and 0-2% survival beyond 2 years.

Prognosis is adversely affected by co-morbid diseases (such as lung disease and heart disease) that may affect a patient's ability to tolerate therapy. In addition, for unclear reasons, men fare worse than women, and patients with elevated serum levels of NSE and alkaline phosphatase, and low levels of albumin, have a poorer prognosis.

Mesothelioma

The median survival of patients with mesothelioma is 10 months. Histologic subtype is a significant prognostic factor, with median survival for epithelial, biphasic, and sarcomatoid histology, at 12, 7, and 4 months, respectively. Early stage and younger and healthier patients all have a better prognosis, and lymph node involvement is associated with a worse prognosis among clinical stage I and stage II patients. Unfortunately, little improvement in survival has occurred in the past 15 years.

PREVENTION

Lung cancer is refractory to most currently available treatment options. Although prevention would be an appropriate intervention for this type of cancer, few approaches have been shown to have any impact at all. Among strategies found to have a protective effect against lung cancer is consumption of fresh fruits and vegetables and intake of vitamins A, C and E and selenium and other micronutrients. Recently, aspirin has also been shown to prevent tumor multiplication in mice with lung cancer induced by carcinogens found in cigarette smoke. In a study conducted by Andre Castonguay at Laval University (Quebec City, Canada) aspirin inhibited tumor multiplication in 60% of the animals treated. Aspirin was also found to prevent production of prostaglandins that promote cell proliferation in nsclc both *in vitro* and in mice.

Retinoids

Various retinoids, natural or synthetic derivatives of vitamin A, such as retinol, the retinoids 13-cis retinoic acid (marketed for acne treatment as Accutane by Hoffmann-La Roche), all-trans-retinoic acid and 4-hydroxyphenyl retinamide, are in phase III clinical trials for chemoprevention of second primary tumors following lung cancer. Because one of the many actions of retinoids is the induction of epidermal differentiation, clinical trials with this class of agents have largely been conducted in epithelial or squamous cell tumor types. Intensive clinical research has focused on the role of retinoids in preventing second primary tumors following head and neck or lung cancer. Phase III studies with positive results were those that targeted reversal of pre-malignant lesions or the prevention of second primary tumors rather than those that targeted cells that had already undergone malignant transformation. It appears that chemoprevention using retinoids may reverse the pre-malignant process rather than suppress malignant growth (Alberts DS and Garcia DJ, Journal of Nutrition, 1995 Mar, 125(3 Suppl):692S-697S).

In Europe, a large chemoprevention study, EUROSCAN (EUROpean Study on Chemoprevention with vitamin A and N-acetylcysteine), was undertaken to evaluate the efficacy of vitamin A, as retinol palmitate, and N-acetylcysteine in the prevention of second primary tumors in patients treated for lung, larynx and oral cancer. More than 50 European medical centers are participating in this study that is coordinated by the European Organization for Research and Treatment of Cancer (EORTC). Another study, the beta-carotene and retinol efficacy trial, CARET, is a multicenter, two-armed, double-masked randomized chemoprevention trial designed to test whether oral administration of beta-carotene (30 mg/day) plus retinol palmitate (25,000 IU/day) decreases the incidence of lung cancer in high risk populations, namely, heavy smokers and asbestos-exposed workers. This intervention combines the antioxidant action of beta-carotene and the tumor suppressor mechanism of vitamin A. Involving 14,420 smokers and 4,010 asbestos-exposed participants (114,100 person-years through February 1998), CARET is expected to detect a 23% reduction in lung cancer incidence in the two populations combined and 27%, 49%, 32%, and 35% reductions in the smokers, female smokers, male smokers, and asbestos-exposed subgroups, respectively. CARET is highly complementary to the Finnish alpha-tocopherol-beta-carotene study and the Harvard Physicians Health Study (beta-carotene alone) in the NCI portfolio of major cancer chemoprevention trials (Omenn GS, etal, Cancer Research, 1994 Apr 1, 54(7 Suppl):2038s-2043s).

CURRENT THERAPY

The choice of therapy depends on the histologic subtype, location, and stage of disease, and its symptoms (such as hypercalcemia or vascular obstruction). In addition, a patient's functional status and concurrent diseases are considered prior to deciding therapy. Most approaches involve multimodality treatments and combination chemotherapy (see Exhibit 7). However, lung cancer responds poorly to chemotherapy. No single mechanistic explanation for lung cancer's chemoresistance has been elucidated (Mulshine JL, etal, Lung Cancer, 1994 Mar, 10 Suppl 1:S73-81).

Stage I and II nsclc

Surgical resection is the only curative therapy for nsclc, and only patients with early stage (stage I, II, and selected stage III) nsclc are candidates for surgery. Many of these patients also have concurrent emphysema and heart disease from cigarette smoking, so careful preoperative evaluation of pulmonary and cardiac function is essential to evaluate the potential benefit of surgery. The operative mortality is less than 5% for lobectomy, but it is age-related and increases with underlying heart disease. If a patient has such poor pulmonary reserve that he or she cannot tolerate loss of one entire lung, then a limited (lobar or wedge) resection is considered. A limited

Exhibit 7
Representative Combination Chemotherapy and Multimodality Approaches for the Treatment of Lung Cancer

NSCLC
COMBINATION CHEMOTHERAPY
Cisplatin Combinations
Vinorelbine (VNR) (standard therapy)
Carboplatin (phase II; Ardizzoni A, etal, British J of Cancer, 1995 Jan, 71(1):115-9)
VNR + ifosfamide (IFX) + G-CSA (phase II; ASCO95, Abs. 1125 and 1135)
Amofistine + vinblastine (phase II; ASCO95, Abs. 1084)
Simultaneous IP cisplatin + etoposide (VP-16) (phase II; ASCO95, Abs. 1104)
Paclitaxel + VP-16 + G-CSF (phase I; ASCO95, Abs. 1076)
Paclitaxel (escalating doses) (phase I/II; ASCO95, Abs. 1058)
Paclitaxel + IFX (phase I/II; ASCO95, Abs. 1067)
Docetaxel (phase I/II; ASCO95, Abs. 1059, 1062 & 1087)
Gemcitabine (GEM) (phase I/II; ASCO95, Abs. 1064, 1066 & 1089)
Epirubicin (phase III; ASCO95, Abs. 1054)
Teniposide (phase II; ASCO95, Abs. 1082)
Mitomycin C (MMC, Mutamycin; Bistol-Myers Squibb) + vindesine (phase III, ASCO95, Abs. 1102 and 1107)
MMC + IFX + IFN-α 2b (phase II; Ardizzoni A, etal, British J of Cancer, 1995 Jan, 71(1):115-9)
Irinotecan (CPT-11) + vindesine (phase I; Shinkai T, etal, Cancer Res, 1994 May 15, 54(10):2636-42)
CPT-11 + G-CSF (phase I; Masuda N, etal, J Clin Onc, 1994 Jan, 12(1):90-6 & Phase II; ASCO95, Abs. 1108)
Fotemustine (phase II; Riviere A, etal, European J Cancer, 1994, 30A(5):587-90)
Tirapazamine (phase I; ASCO95, Abs.1540)
Recombinant IFN-α (phase II; Kataja V and Yap A, European J Cancer, 1995, 31A(1):35-40)
Carboplatin Combinations
Paclitaxel + IFX (phase I/II; ASCO95, Abs. 1067)
IFX + VP-16 + GM-CSF (phase I; Krigel RL, etal, J Clin Onc, 1994 Jun, 12(6):1251-8)
GEM (phase I/II; ASCO95, Abs. 1063)
Paclitaxel (phase II; ASCO95, Abs. 1103)
High dose paclitaxel + peripheral blood stem cells (PBSCs) + G-CSF (Neupogen; Amgen) (Phase I; ASCO95, Abs. 1553)
Paclitaxel + G-CSF (phase II; ASCO95, Abs. 1080)
Other Combinations
GEM + IFX (phase I; ASCO95, Abs. 1063 & 1066)
IFX + VNR + G-CSF (phase I; ASCO95, Abs. 1092)
MMC + vindesine + VP-16 (phase III; ASCO95, Abs. 1102)
CPT-11 + VP-16 + rhG-CSF (phase I; Masuda N, etal, J Clin Onc, 1994 Sep, 12(9):1833-41)
Paclitaxel + hydroxyurea (phase II; ASCO95, Abs. 1126)
Paclitaxel + losoxantrone (Phase I; ASCO95, Abs. 1545)
Five-day continuous infusion of fluorodeoxyuridine + high-dose folinic acid + oral hydroxyurea (phase I; Cancer Chemotherapy and Pharmacology, 1994, 35(2):161-4)

— continued on next page

resection results in a higher rate of local recurrence, but overall survival is the same. Patients with early stage disease who are not candidates for surgery are considered for primary radiotherapy with curative intent, with 5-year survival rates ranging from 20-60% (comparable to historical controls).

Radiotherapy/chemotherapy. The addition of "adjuvant" radiotherapy or chemotherapy has not yet been shown to improve overall survival of these patients, although it does decrease the local recurrence rate and delay the time to recurrence. Many patients will unfortunately develop regional or distant metastases, and are candidates for studies further evaluating multimodality regimens.

Stage III nsclc

Early trials in stage III nsclc showed improved survival with protocols using induction chemotherapy followed by radiotherapy as compared to radiation therapy alone. However, since this therapy is rarely able to eradicate the primary tumor, surgical resection was introduced to treat residual local disease. Furthermore, among the more favorable, or "stage IIIA" group of patients, a minority have been cured with aggressive multimodality therapy. The relative roles of surgery and chemoradiotherapy remain to be determined in stage III patients, but two important questions are currently being addressed in clinical trials. First, the role of surgery in stage III patients treated with sequential chemoradiotherapy is being studied. Patients are treated with chemoradiotherapy (with cisplatin and etoposide) and then with either surgical resection of the primary tumor, or more radiotherapy with curative intent. The results of this study are expected within the next 4 years. The second question addresses the surgical "curability" of patients with favorable stage IIIA nsclc. In stage IIIA patients who present with smaller ("T1" or "T2") primary tumors, but with involvement of ipsilateral mediastinal lymph nodes, the 5-year survival after attempted curative surgery is less than 5%. Several recent small trials have shown that the addition of preoperative "neoadjuvant" cisplatin-based chemotherapy to surgery and radiation therapy improved median survival by 3 fold, and reduced recurrences by a third. These studies are small, but suggest that multimodality therapy has a role in selected stage IIIA patients, while combined chemoradiotherapy may be beneficial for patients with stage IIIB nsclc.

In a randomized 60-patient clinical trial to examine the possible benefit of preoperative chemotherapy and surgery for the treatment of nsclc, participants were randomly assigned to receive either surgery alone or three courses of combination chemotherapy consisting of mitomycin (6 mg/m^2), ifosfamide (3 mg/m^2) and cispaltin (50 mg/m^2) administered intravenously at three-week intervals and followed by surgery. All patients received mediastinal radiation after surgery. The median period of survival was 26 months for patients treated with chemotherapy

MULTIMODALITY THERAPY
Radiation and Chemotherapy Combinations
Simultaneous radiation + paclitaxel (escalating dose) (phase II; ASCO95; Abs. 1052)
Concurrent radiation + cisplatin + VP-16 (phase I; ASCO95, Abs. 1055, 1077, 1079 & 1091)
High-dose cisplatin + amifostine + vinblastine (phase II; ASCO95, Abs. 1767 & 1084)
Concurrent hyperfractionated radiation + carboplatin (phase II; ASCO95, Abs. 1081)
Carboplatin + MMC + VP-16 (phase II; ASCO95, Abs. 1813)
Concomitant chemoradiotherapy regimen with high-dose cisplatin + IFN α-2a + fluorouracil (5-FU) + hydroxyurea + radiotherapy + G-CSF (phase I; Vokes EE, etal, Cancer Chemotherapy and Pharmacology, 1995, 35(4):304-12)
Surgery, Radiation and Chemotherapy Combinations
Concomitant induction with 5-FU + cisplatin + vinblastine + radiation + surgical resection (phase II; ASCO95, Abs. 1057)
SCLC
COMBINATION CHEMOTHERAPY
Cyclophosphamide + doxorubicin (DOX)+ vincristine or VP-16 (standard therapy)
Carboplatin + teniposide (phase III; Joss RA, etal [Swiss Group for Clinical Cancer Research (SAKK)], Annals Onc, 1995 Jan, 6(1):41-8)
Carboplatin + oral VP-16 (phase II; ASCO95, Abs. 1117)
Vincristine + IFX + carboplatin + VP-16 + G-CSF (phase III; Woll PJ, etal, J Clin Onc, 1995 Mar, 13(3):652-9)
High-dose VP-16 + IFX + carboplatin + epirubicin + peripheral blood progenitor cells (phase I/II; Brugger W, etal, Seminars in Onc, 1995 Feb, 22(1 Suppl 2):3-8)
IFX + carboplatin + VP-16 (Phase III; Ettinger DS, Seminars in Onc, 1995 Feb, 22(1 Suppl 2):23-7)
MULTIMODALITY THERAPY
Radiation and Chemotherapy Combinations
Concurrent or sequential radiation + cisplatin + VP-16
Cisplatin + vincristine + DOX + VP-16 + G-CSF (phase II, ASCO95, Abs. 1110)
Cisplatin + oral VP-16 +vincristine + fractionated chemotherapy (phase II; ASCO95, Abs. 1111)
Cyclophosphamide + vincristine + cisplatin + VP-16 + thoracic radiation (Komaki R, etal, Int'l J Radiation Oncology, Biology, Physics, 1995 Feb 15, 31(4):807-11)
Concurrent or sequential radiation + cyclophosphamide + DOX + vincristine
Concurrent or sequential radiation + cyclophosphamide + methotrexate + CCNU
Vincristine + Adriamycin + procarbazine + VP-16 + irradiation (Broder LE, etal, Am J Clin Onc, 1994 Dec, 17(6):527-37)
Cyclophosphamide + CCNU + MTX, sequentially with hexamethylmelamine + MMC + vinblastine (Broder LE, etal, Am J Clin Onc, 1994 Dec, 17(6):527-37)
IFX + DOX + vincristine + VP-16 (Elisson LO and Ekberg L, Seminars in Onc, 1995 Feb, 22(1 Suppl 2):15-7)

plus surgery, as compared with 8 months for those treated with surgery alone; the median period of disease-free survival was 20 months and 5 months, respectively and the rate of recurrence was 56% and 74%, respectively. The resected tumors were evaluated by means of K-ras oncogene analysis and flow cytometry. The prevalence of mutated K-ras oncogenes was 15% among the patients receiving preoperative chemotherapy and 42% among those treated with surgery alone. Most of the patients treated with chemotherapy plus surgery had tumors that consisted of diploid cells, whereas the patients treated with surgery alone had tumors with aneuploid cells. Although preoperative chemotherapy appears to increase the median survival of patients with nsclc it is possible that the results may have been influenced by the selection process pertaining to the prevalence of mutated K-ras oncogene (Rosell R, etal, N Engl J Med, Jan 20, 1994;330:153-8).

Stage IV nsclc

Patients with stage IV disease do not benefit from surgery. Single agent chemotherapy offers response rates of up to 30-40%, but complete or durable responses are rare. In several studies combination chemotherapy has prolonged survival, but a recent meta-analysis in 1994 estimated the survival benefit to be only 2 months, with only a 10% increase in the number of patients still alive after 1 year. Of the different chemotherapy regimens employed, several cisplatin-based combinations are equally efficacious in providing this benefit. In addition, several studies have shown that dose escalation of cisplatin increases toxicity, without improving response significantly. Paclitaxel (Taxol; Bristol-Myers Squibb) appears to have activity in cisplatin-refractory nsclc. Radiotherapy is used primarily to palliate symptoms, and can be quite effective in treating focal symptomatic lesions, such as bone and brain metastases or vascular obstruction. Neither it nor chemotherapy, however, produce sufficient survival benefit to be considered "standard therapy." Consequently, chemotherapy is usually given in the context of a clinical trial or at the request of the patient to "do everything possible."

Given the extremely poor prognosis of these patients, and lack of survival benefit with current therapy, numerous other drugs and approaches are being tried. These include brachytherapy and immunotherapy, neither of which has yet been shown to result in improved survival. Endoscopic laser therapy has been used to reduce tumors obstructing bronchial passages, and direct bronchial artery administration of cisplatin chemotherapy is under investigation. Monoclonal antibodies (MAbs) conjugated to toxins or chemotherapy are also being studied. The murine MAb KS1/4, conjugated to methotrexate, has shown some activity against nsclc tumors, but the efficacy appears limited by the development of human anti-mouse antibodies (HAMA). This problem is minimized with the mouse-human chimeric MAb L6, directed against an antigen expressed in lung, colon, and breast cancer, which is less immunogenic than mouse MAbs. Other, novel chemotherapeutic agents are actively under development for inoperable stage III and stage IV lung cancer. (See Meeting Coverage in this issue).

Vinorelbine (Navelbine; Burroughs Wellcome), a semi-synthetic vinca alkaloid, is the first drug in twenty years to be approved for the treatment of nsclc. Vinorelbine was recommended by FDA's Oncology Drugs Advisory Committee (ODAC) in December 1993, received a treatment IND in May 1994 in ambulatory chemotherapy-naive patients with unresectable nsclc, was approved in December 1994 for this indication and launched by Burroughs Wellcome in the USA in January 1995. The drug was classified as "lP" to indicate a new molecular entity meriting priority review and was approved in 16 months.

Approval was based on two pivotal clinical trials that demonstrated a survival benefit of about two months compared to other chemotherapy regimens. In a European trial of Navelbine, 612 chemotherapy-naive patients with stage III or IV nsclc were randomized to one of three regimens, single-agent vinorelbine, vinorelbine and cisplatin, or vindesine plus cisplatin; median survival was 31, 40 and 32 weeks, respectively; one-year survival rates were 30%, 35% and 27%, respectively; overall objective response rates were 14%, 28% and 19%, respectively. In a North American clinical trial, 211 stage IV chemotherapy-naive patients were randomized to vinorelbine or 5-fluorouracil (5-FU) plus leucovorin (LV). Median survival for patients receiving vinorelbine was 30 weeks compared to 22 weeks for the 5-FU/LV group. One-year survival rates were 24% for Navelbine compared to 16% for 5-FU/LV. Response rates were 12% in the vinorelbine group compared to 3% in the 5-FU/LV group. A Phase IV trial is in progress by the Southwestern Oncology Group (San Antonio, TX). This trial, which began in the fall of 1993, is enrolling 350 patients to be treated with 25 mg/m^2 Navelbine plus 100 mg cisplatin or cisplatin alone. Another study is being conducted by the National Cancer Institute of Canada in breast cancer and phase II trials for ovarian and prostate cancers are in progress.

The label specifies that Navelbine is indicated as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable advanced nsclc. It may be used alone or in combination with cisplatin for stage IV nsclc but only in combination for stage III disease. Navelbine belongs to the vinca alkaloid group of agents derived from the periwinkle plant Vinca rosea that exert their cytotoxicity by interfering with mitosis in dividing cells by interacting with tubulin. According to the label the drug is unlike other vinca alkaloids because it carries a modification on the catharanthine ring of the molecule rather than the vindoline ring and has a relative selectivity for mitotic microtubule, indi-

cating that, at lower doses, it does not cause inhibition of axonal microtubule assembly, which may lead to neurotoxicity. Navelbine causes mild-to-moderate nausea, mild-to-moderate hair loss (alopecia occurred in 12% of patients treated with Navelbine) but does not cause nerve pain. Administration of Navelbine is contraindicated in patients with pretreatment granulocyte counts of less than 1,000 cells/mm^3 because of a risk of granulocytopenia which resulted in hospitalizations in 8% of patients during clinical trials. Patients treated with Navelbine should be frequently monitored for myelosuppression both during and after therapy. Hematologic growth factors, such as granulocyte-colony stimulating factor (Neupogen; Amgen), may be used 24 hours after the start of chemotherapy to reduced the incidences of severe nausea and vomiting with single-agent Navelbine. The recommended dose for Navelbine is 30 mg/m^2 weekly given as an IV infusion over six to 10 minutes. The duration of therapy is "until progression or dose-limiting toxicity." Labeling recommends that the dose be halved if a patient's granulocyte count falls below 1,500 cells/mm^3 but is above 1,000.

Navelbine was available under a treatment IND for nsclc since May 1994 with approximately 450 patients treated under the experimental protocol free of charge and another 300 patients have been receiving Navelbine on a compassionate use basis. The average wholesale price of Navelbine is $46.88 for a 10 mg 1 ml vial and $238.38 for a 50 mg 5 ml vial. The company estimates that the average cost of one week of Navelbine treatment will be $250. In the USA, Glaxo Wellcome will provide the drug free of charge to individuals with advanced unresectable nsclc (and no prior chemotherapy), who are enrolled in the program by their physicians.

Vinorelbine has also been approved for nsclc in France, Canada, Spain, Italy, Portugal, and China. Pierre Fabre Medicament which markets Navelbine in Europe for nsclc, will manufacture Navelbine for Glaxo Wellcome under a licensing agreement signed in 1989.

Small Cell Lung Cancer

Unlike nsclc, sclc is often widely disseminated at presentation, but is extremely sensitive to chemotherapy. Therefore, all patients (both limited and extensive disease) are treated with combined modality chemoradiotherapy. Surgery is of little value. Ultimately, to provide the maximum palliative benefit for patients with extensive small cell lung cancer, the therapeutic benefit must be balanced against the costs of treatment (physical, psychological, and financial).

Etoposide (VePesid; Bristol-Myers Squibb) is approved in the USA for the treatment of sclc (see Exhibit 8) and refractory testicular tumors. Etoposide phosphate (Etopophos), an improved form of this drug, is under development by Bristol-Myers Squibb to replace VePesid whose patent expired in 1993. Etopophos, in phase III trials, allows for innovative treatment schedules and outpatient use.

Combination chemotherapy (with either cisplatin or cyclophosphamide) is more effective than single agent chemotherapy, with a response rate of 80% and a 50% chance of eliminating all visible disease. Other combinations such as cyclophosphamide/doxorubicin/vincristine, cisplatin/etoposide, and cisplatin/etoposide/ifosfamide have also produced objective responses in 55% to 65% of patients. With combination therapy, however, the median survival is only 12-14 months. Actually, recent clinical trials with single-agent chemotherapy have resulted in lengths of survival that appear comparable to that obtained with combination therapy. Single-agent approaches may be more appropriate for elderly patients (Loehrer PJ Sr, Seminars in Oncology, 1995 Apr, 22(2 Suppl 3):40-4).

High-dose chemotherapy. Because of the high response rate, yet high mortality, efforts have been made to escalate the doses of chemotherapy. In several small, single arm studies, high response rates have been noted with dose intensified cisplatin/etoposide. However, the majority of larger, randomized studies have failed to show a survival benefit, and one meta-analysis recently published failed to show a benefit to dose escalation. Since higher doses of chemotherapy are associated with increased gastrointestinal, neurologic, and myelosuppressive toxicities (even with growth factor support), they are not routinely provided outside of a clinical trial.

Very high dose (myeloablative) consolidation therapy followed by reinfusion of autologous bone marrow (bone marrow transplant) is also being studied. Among highly selected patients with sensitive disease, two-year survival rates approach 60%. Such therapy, however, failed to show a survival benefit over standard therapy in the only randomized trial published to date, and at this point remains experimental.

Radiation therapy (concurrent irradiation of the primary tumor) is usually added to chemotherapy, as it certainly improves local control and probably prolongs survival. Radiation therapy, however, is associated with increased myelosuppressive, pulmonary, and gastrointestinal toxicity. Prophylactic cranial irradiation (PCI) to prevent or delay the development of symptomatic brain metastases, although controversial, is also often recommended. In one recent study, PCI was associated with a threefold decrease in brain metastases, and a 40% improvement in two-year survival. However, brain irradiation is associated with long-term neurologic impairment, and can be a significant problem for sclc survivors.

Surgery. Because the majority of patients either have or develop metastatic disease, in general, there is little benefit to surgery. However, there are case reports of patients in whom resection of solitary pulmonary tumors

Exhibit 8
Profile of Approved Chemotherapeutics for the Treatment of Lung Cancer

Generic Name (Brand Name/Supplier)	Approved Indication/ Delivery and Dosage	WW Markets
Etoposide (VePesid, VP-16; Bristol-Myers Squibb) [Gensia in collaboration with Upjohn gained approval to market generic etoposide in the USA in February 1994 Sparta Pharmaceuticals is developing an IV form of etoposide with funds from an SBIR grant, using its Spartaject system Bio-Technology General obtained exclusive marketing rights in most major countries to etoposide from Shenzhen Boda Natural Product Company (China), in August 1994]	In combination with other cytotoxic drugs as first line therapy in sclc/IV dose ranges from 35 mg/m^2/d for 4 days to 50 mg/m^2/d for 5 days as a 30-60 min. infusion; oral dose is twice IV dose	Patent expired 12/93 1993 $290 mil. USA $210 mil. ROW $80 mil. 1994 $210 mil. USA $135 mil. ROW $85 mil.
Vinorelbine (KW-2307, Navelbine); it is licensed by Burroughs Wellcome in North America from Pierre Fabre that markets it in Europe; it sold worldwide by various other licensees, including Kyowa Hakko in Japan	As a single agent or in combination with cisplatin for first-line treatment of ambulatory patients with unresectable advanced nsclc; may be used alone or in combination with cisplatin for stage IV nsclc but only in combination for stage III disease/dose is 30 mg/m^2 weekly given in an IV infusion over six to ten minutes/AWP is $46.88 for a 10 mg 1 ml vial and $238.38 for a 50 mg 5 ml vial; average cost of one week of treatment is $250	

has led to long term survival, and surgery is occasionally considered for highly selected patients.

Mesothelioma

There is no curative therapy for most patients with mesothelioma. Radical surgery, involving resection of the entire tumor with wide margins and regional lymph nodes, can be performed in selected patients with good prognosis. However, even with surgery the 2 year survival in this highly selected population is no better than 20%, with few long term disease-free patients. Surgery does have a role in palliation of symptoms. As most patients become symptomatic from compression of regional structures, pleural effusion, or other local effects of the tumor, surgery (pleurectomy, extrapleural pneumonectomy, pleurodesis, or other procedures) can alleviate or delay the onset of such symptoms. Whether palliative surgery leads to improved survival remains unclear; also there is a 5% operative mortality with pleurectomy and extrapleural pneumonectomy.

Conventional radiotherapy is hampered by the relative lack of radiation sensitivity of the tumor and the considerable sensitivity of the underlying lung. Temporary control of symptoms has been achieved, but no survival benefit has been evident. Radiosensitizers are also being studied for their ability to improve the therapeutic ratio of conventional radiation therapy. In addition, radioactive compounds, such as colloidal gold, have been instilled into the pleural cavity to treat pleural effusion, with some anecdotal success.

Likewise, chemotherapy alone is not able to control mesothelioma effectively. Several chemotherapeutic drugs and regimens including cyclophosphamide, doxorubicin, and cisplatin, show activity against mesothelioma but, in clinical trials, response rates are at best 25%. Dose escalation of cisplatin only marginally improves the response rate, up to 35% in one study, with significantly greater toxicity. Chemotherapy has also been delivered directly to the tumor (intrapleural), either via temporary chest tubes or via a semi-permanent subcutaneous access port. Although higher local concentrations and lower systemic levels of chemotherapy are achieved, a survival benefit has yet to be shown.

Multimodality therapy, combining aggressive surgery with chemotherapy, may provide better therapeutic efficacy. In several single arm studies, pleurectomy or extrapleural pneumonectomy followed by intrapleural and systemic cisplatin-based chemotherapy led to improved survival compared to historical controls (up to 17% at 3 years). However, the chemotherapy is poorly tolerated, with 7% of patients developing significant renal toxicity in one study. Prospective, randomized trials will be required to assess the true benefit of multimodality therapy.

Trimetrexate (Neutrexin; U.S. Bioscience), a new antifolate, is also being evaluated in the treatment of malignant mesothelioma. In a phase II study of 52 chemotherapy-naive patients, conducted by the Cancer and Leukemia Group B (CALGB), 6 patients experienced PRs but there were no CRs. Trimetrexate at the delivered dose showed minor activity in the treatment of

malignant mesothelioma but higher doses may prove more effective (Vogelzang NJ, etal, Journal of Clinical Oncology, 1994 Jul, 12(7):1436-42).

Given the dismal outcome of patients with conventional therapy, much effort has been placed in the development of immunotherapy and other approaches for mesothelioma. Reinfusion of *ex-vivo* interleukin-2 (IL-2)-activated tumor infiltrating lymphocytes is being studied, as is direct intrapleural administration of lymphokines. Intrapleural interferon-γ (IFN-γ) resulted in a 20% response rate. IFN-γ appears to lead to a decrease in levels of IL-6, and an increase in activated macrophages and cytotoxic T lymphocytes. Intrapleural IL-2 led to 10 responses in 22 patients (45%), and intrapleural IFN-α 2A was associated with a 12% response rate. The addition of doxorubicin improved the response rate to 16%. In a mouse model, a selectively targeted diphtheria toxin is able to cure mice of advanced mesothelioma, but this effect has not been repeated in humans. Finally, intrapleural chemotherapy has been combined with hyperthermia, to enhance the antitumor efficacy of standard chemotherapy.

Mesothelial cells and cell lines are highly sensitive to infection by recombinant adenoviruses and may provide one of the earliest tests of gene therapy for cancer. Infection of mesothelioma cells with recombinant virus containing the herpes simplex virus thymidine kinase (HSV-tk) gene, renders them 100- to 1000-fold more sensitive to the nucleoside analog gancyclovir than uninfected cells. Even with only 10% of the cells infected, treatment with gancyclovir leads to a strong "bystander" effect, resulting in considerable killing of both infected and uninfected cancer cells. Although promising, these observations, as well as potential immunotherapy techniques, all require further study.

Recurrent Lung Cancer

Recurrent lung cancer is usually treated palliatively with radiotherapy. Recurrent tumors usually do not respond to the original chemotherapy agents, and (if not used before) paclitaxel appears to be active in this setting. For nsclc, solitary brain metastases, in the absence of disease elsewhere, are treated with surgical resection followed by whole brain irradiation. This results in prolonged survival, with a limited potential for long-term survival. For sclc, brain metastases that are rarely solitary are also treated with radiation. New solitary pulmonary lesions are surgically excised, if possible. Although recurrent lung cancer usually leads to the eventual development of multiple pulmonary metastases (so there is no benefit to surgical resection), many solitary nodules (particularly in smokers) represent second lung cancers that are potentially curable. Resection or biopsy of a pulmonary nodule, with histologic analysis, is paramount; if the nodule is indeed a second lung cancer, the patient is restaged with mediastinoscopy and often with bone scan and head CT.

Secondary Tumors

The risk of developing second cancers among smokers and former smokers who survive lung cancer is estimated at 5% per year. Chemoprevention of these tumors is an active area of research. Vitamin A deficiency and low blood retinol levels have been associated with cellular atypia and an increased incidence of cancer, and the antioxidant vitamins A and E have anticarcinogenic effects. In addition, one study of secondary chemoprevention (preventing second cancers in patients who survive lung cancer), patients with surgically resected stage I nsclc treated with retinol palmitate (derived from vitamin A) had a 50% reduction in the number of second lung cancers. However, a large randomized primary chemoprevention trial of adult smokers (to prevent the development of lung cancer) showed that therapy with vitamin A analog beta-carotene was associated with an 18% *increased* risk of developing lung cancer (N Engl J Med 1994, Apr 14; 330:1029-35). The matter remains unresolved, and currently patients should receive chemoprevention therapy only within the context of a clinical trial.

Cancers Metastatic to the Lung

A large fraction of bloodborne metastases from many different cancers are located in the lungs. This is not surprising, as the lung receives the entire cardiac output from the right side of the heart (after it has passed from the left side of the heart and through the peripheral circulation). In addition, this blood flow passes through microscopic capillaries within the lung vasculature, which acts as a "filter," trapping large cells and cellular debris (as well as blood clots). Lung cancer is the most frequent malignancy metastatic to the lungs. Of the other common solid tumors, two thirds of patients with breast cancer, up to half of patients with liver cancer, and one third of patients with colon cancer, will eventually develop lung metastases. Many other malignancies, including bladder and kidney cancer, melanoma, sarcoma, lymphoma and leukemia, and germ cell tumors also metastasize to the lungs. Based on the 1995 estimated mortality from these malignancies, one can estimate that more than 150,000 patients currently have or will develop metastases to the lungs this year.

Prognosis and therapy for metastastic cancer depend entirely on the tissue of origin of the cancer. Certain cancers such as sarcomas that recur as isolated pulmonary metastases, can be cured with surgical resection. Slow growing metastases (such as renal cell cancer) can be resected to improve survival, sometimes resulting in regression of the primary tumor. On occasion, a patient with a germ cell tumor will have a residual mass of teratoma after chemotherapy, which can only be treated with surgery. Unfortunately, up to 40% of patients with solitary metastases are found to have bilateral metastases at the time of resection. For these patients, and most patients with disseminated disease, the mainstay of therapy remains

chemotherapy (as specified by the primary tumor). The development of lung metastases, like distant metastases elsewhere, usually suggests progressive, incurable disease, and portends a dismal patient outcome.

NEW DRUGS AND ALLIED THERAPIES IN DEVELOPMENT

Lung cancer represents a very large current and potential global market for developers of agents to treat the primary disease or to act as adjunct therapies. Candidate populations for chemotherapy for primary, relapsed and metastasized disease exceed newly diagnosed populations because of multiple regimens, treatment of secondary lung cancer and treatment of patients who relapse. Numerous agents are in development based on nearly every technology and exploiting every known or suspected mechanism involved in lung cancer (see Exhibit 9).

Chemotherapeutic Agents in Late Clinical Trials

Numerous agents with broad antineoplastic activities are being studied along or in combination in lung cancer. Representative combination and multimodality regimens are presented in Exhibit 8. One of the most active drugs in combination is cisplatin (Platinol; Bristol-Myers Squibb) and its relative, carboplatin (Paraplatin; Bristol-Myers Squibb) (for more on platinum-based drugs, see FO, V1, #1, pp 16-21). Among other drugs with significant activity against lung cancer as monotherapy or in combination with other agents are the taxanes, the antimetabolite gemcitabine, the vinca alkaloid vinorelbine, the topoisomerase I inhibitors, irinotecan and topotecan (see this issue p 111) and ifosfamide (Ifex; Bristol-Myers Squibb), among others.

Ifosfamide, a synthetic analog of cyclophosphamide has been used alone and in combination in the treatment of sclc. In a randomized Eastern Cooperative Oncology Group study, single-agent ifosfamide used to treat sclc patients with extensive disease, produced a 49% response rate compared with 56% for patients receiving standard combination chemotherapy (cyclophosphamide + doxorubicin + vincristine). When the drug was combined with carboplatin and etoposide, overall response rate was 83%, median survival time was 9 months and 14% of patients survived 2 years. The major toxicity was myelosuppression (Ettinger DS, Seminars in Oncology, 1995 Feb, 22(1 Suppl 2):23-7).

Gemcitabine hydrochoride (Gemzar; Eli Lilly), a novel nucleoside analog which mimics a natural building block of DNA, was recommended for approval in July 1995 by ODAC for the treatment of advanced or metastatic pancreatic cancer. Lilly had FDA authorization to make Gemzar available in the USA through a treatment IND since February 1995. Lilly has also received permission from regulatory authorities in Sweden to market the drug for advanced or metastatic pancreatic cancer and in South Africa, the Netherlands, Finland and Australia for nsclc. Gemzar is also being studied in breast, ovarian, bladder, prostate and head and neck cancers, as well as leukemia and lymphoma. Numerous studies of gemcitabine, alone or in combination are in progress in nsclc (see this issue, Exhibit 7 and p 110). The activity of gemcitabine as monotherapy in nsclc is similar to that of other drugs in clinical trials for this indication, such as vinorelbine, the taxanes and topoisomerase I inhibitors. In combination therapy the effects of gemcitabine appeared to be potentiated when used with cisplatin. Eli Lilly also claims that in the treatment of late-stage nsclc, gemcitabine is associated with cost savings per cycle of $892 to $1,175 compared with ifosfamide/etoposide and cisplatin/etoposide combinations which is attributable to the fact that gemcitabine can be administered on an outpatient basis thus reducing hospital costs and because of cost savings associated with a less aggressive side-effect management required with the drug.

Angiogenesis

One of the potential mechanisms of tumorigenesis in lung cancer is dysregulation of the balance of angiogenic and angiostatic factors resulting in net neovascularization within the primary tumor. Numerous studies have investigated the role of a variety of molecules in the regulation of angiogenesis. A special two part series on angiogenesis will be presented in the next two issues (V1, #5 and #6) of FUTURE ONCOLOGY.

Gene Transfer/Vaccines/Monoclonal Antibodies

Introgen Therapeutics (Austin, TX), a private company, is developing several gene therapy products in collaboration with RPR Gencell to treat cancer by retroviral or adenoviral delivery of intact wild-type p53, among others. [In late 1994, Rhône-Poulenc Rorer formed RPR Gencell, a network of alliances funded by a $100 million annual budget, to gain access to R&D carried out by various highly specialized biotechnology companies.] Introgen holds several Recombinant DNA Advisory Committee (RAC) approvals obtained through M. D. Anderson Cancer Center (Houston, TX), one of the company's founders, to treat cancer by gene therapy using retroviral and adenoviral vectors. In early 1995 a patient with nsclc was treated by injection of Introgen's p53/viral vector combination to destroy any residual cancer after tumor resection. A total of five doses of the agent were administered in consecutive days. This gene therapy protocol was approved by RAC in July 1994, despite warnings that a viral vector might cause pneumonia in patients with advanced lung cancer. In a 11-1 vote with one abstention, RAC gave Jack Roth of the University of Texas M. D. Anderson Cancer Center permission to begin testing this gene therapy for nsclc, but only in patients with locally confined disease. The vector used to transport a normal p53 gene into patients' lungs is a disabled adenovirus.

PharmaGenics (Allendale, NJ), in collaboration with Johns Hopkins University School of Medicine (Baltimore,

MD) has designed assays to screen for compounds that may correct for lost p53 function. Such compounds will then be tested in cell-based cancer assays also developed by the company. Two companies, Xenova and Boehringer Mannheim have entered into agreements to use these assays in their drug development efforts.

AntiCancer (San Diego, CA) is also investigating gene therapy as a cancer treatment modality. Malignant pleural effusions in eight of 10 patients with advanced lung cancer responded (6 CRs, 2 PRs) to IL-2 gene therapy. In a phase I trial, carried out with researchers from Harbin Medical University in China, patients were treated with tumor-infiltrating lymphocytes (TILs) engineered to express IL-2. One patient's tumor decreased to a sixth of its original size after therapy, the side-effects of which included fever. Responding patients were subsequently able to receive radiotherapy to treat their lung carcinoma. Such IL-2 gene therapy may act as a vaccine, preventing tumor growth and metastasis. Development of these therapeutic genes for cancer, termed GeneCeuticals, includes use of proprietary liposome formulations for gene delivery and the company's MetaMouse as a gene screen discovery model. A similar approach is being investigated by scientists at the University of Tokyo (Heike, Y, etal, AACR95, Abs. 591). Cancer cells from pleural effusions of patients with nsclc (adenocarcinoma) that were transduced by a β-galactosidase gene (to secrete IL-2) and Adex1CA vector with a regulatory sequence of chicken β-actin promoter and an enhancer sequence derived from cytomegalovirus, induced tumor-specific immunity.

Transgène (Courbevoie, France), part of the BioMerieux Alliance, has developed and is clinically evaluating a technique to deliver cytokine genes in lung cancer patients intratumorally using an adenovirus vector. A phase I trial is currently underway in six lung cancer patients to determine if genes delivered in this manner will be expressed in the tumors. If this trial is successful, Transgène will attempt to introduce the IL-2 gene in patients suffering from lung cancer and other malignancies. Transgène has cross-licensing agreements with RPR Gencell.

Medarex (Annandale, NJ) announced in May 1995 the initiation of an NCI-sponsored trial of the company's humanized anti-cancer bispecific antibody, MDX-210, in patients with all cancers that overexpress the HER-2 receptor, including nsclc and prostate, pancreatic, breast, and ovarian cancers. The study is expected to enroll up to 42 patients. MDX-210 is designed to induce tumor cell killing by simultaneously binding to HER-2 on the surface of certain cancer cells and to a key receptor on immune system killer cells such as monocytes and other white blood cells. In May 1995 Medarex entered into a global alliance with Ciba-Geigy to develop and market MDX-210 for a variety of tumors. Under the terms of the agreement, Medarex will be primarily responsible for taking the product up to phase II clinical trials and Ciba will be primarily responsible for phase III clinical trials, regulatory approvals and commercial launch and will obtain exclusive worldwide marketing rights for the product. Under the terms of the agreement, Ciba will purchase Medarex common stock worth $8 million, $4 million immediately at a premium to market price and the remainder upon the achievement of milestones. Ciba will also make milestone payments and provide R&D funding of up to $31 million, and will pay all costs of phase III development, clinical trials, regulatory approvals, and product launch. Upon commercialization of MDX-210, Medarex will be entitled to receive royalties, and may also be the manufacturer of the product.

Bispecific MAbs are target-trigger combinations of two antibodies that link the body's own immune system killer cells directly to disease targets. Medarex has patented the Trigger component that has a special ability to engage immune cells and trigger their killing functions. A bispecific also contains a targeting arm selected to seek out a particular disease. Because the Trigger can be linked to almost any targeting arm, bispecific products can be directed toward virtually any cancer and many other diseases.

In 1994 Medarex also entered into a collaborative agreement to form a corporate partnership with Merck KGaA (Darmstadt, Germany), to develop H-447, a bispecific antibody for the treatment of tumors overexpressing the epidermal growth factor (EGF-R), including certain head and neck, prostate, lung, bladder, cervical and ovarian cancers. H-447 targets EGF-R on cancer cells using a Merck component and activates immune cells with Trigger. Medarex has filed an IND to begin clinical trials with H-447. Merck KGaA could provide funding to Medarex of up to $29 million during the development and clinical trials stages of the collaboration. In August, 1994 Merck accelerated payments under the terms of the collaboration and invested $3.15 million by immediately purchasing 450,000 shares (6%) of Medarex common stock at $7.00 per share. Medarex will hold the exclusive rights to H-447 in the USA with Merck holding exclusive rights in Europe and the two companies will jointly hold the rights for the rest of the world.

NeoRx reported at the 1995 meeting of the American Society of Clinical Oncology (ASCO) that a single dose of its Avicidin cancer therapy produced tumor regressions during a phase I clinical trial involving patients with massive tumor burdens who had failed multiple regimens of chemotherapy. The responses did not reach the 50% tumor decrease required to be PRs but cause enough of a response to justify additional studies using a humanized version of the MAb to permit multiple Avicidin doses. Also, these observations may result in using Avicidin as a pretargeting approach to treat solid tumors. In preclinical trials Avicidin produced 100% CRs in animals with

chemotherapy-resistant human lung and colon cancers. (For more on Avicidin, please see FO, V1, #2/3, p 69).

Protein Design Labs' (Mountain View, CA) SMART ABL364 is an IgG_1 class antibody directed against the Lewis Y-6 carbohydrate antigen, a hexasaccharide selectively expressed on tumors of epithelial cell origin. Lewis Y is one of the dominant surface antigens of sclc and also has a restricted distribution to breast, colorectal, pancreatic and gastric carcinomas. The antibody was initially generated from a mouse immunized with the MCF7 human breast carcinoma cell line. The SMART ABL364 MAb is the humanized version of ABL364 developed using PDL's computer-guided genetic engineering process. ABL364 has been reported to react *in vitro* with 80% of lung cancers. *In vitro* ABL364 exhibits potent antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxity (CDC) against breast carcinoma cell lines and sclc. In animal tests, the mean circulating half-life in rhesus monkeys for the murine MAb was 1.9 days while the value for the humanized ABL364 was 16.3 days following a single intravenous dose (0.8 mg/kg) to groups of three monkeys. As of August 1995, only the murine version of ABL364 has been studied in clinical trials in breast cancer as a single dose treatment. Multiple-dose phase II trials are currently underway. Phase I clinical trials with SMART ABL364 will be undertaken once preclinical evaluation is completed. PDL has worldwide manufacturing and marketing rights subjects to certain co-promotion/co-marketing rights available to Sandoz, principally in North America and Europe.

Cytokines/Growth Factors

In addition to their use as adjuncts to prevent hematologic side effects associated with certain agents and treatment protocols, cytokines also exhibit direct antiproliferative activity in lung cancer and may also act as radiosensitizers.

Interferons (IFNs) exhibit antitumor effects and act as sensitizers potentiating cytotoxicity of radiotherapy and chemotherapy. However, conflicting data has been reported as to the antitumor effects of IFNs and it is not clear what their role will be, if any, in the treatment of lung cancer.

IFN-α may act as a growth inhibitor of various cancer cell lines including lung cancer but the molecular mechanisms involved in this antitumor activity have not been elucidated. It has been proposed that inhibition of tumor cell growth by recombinant IFN-α is related to down-regulation and/or impaired function of peptide growth factor receptors (PGF-Rs) in tumor cells exposed to IFN-α. However, it has been shown that IFN-α-induced growth inhibition of human epidermoid carcinoma cells is paralleled by up-regulation of epidermal growth factor receptor (EGF-R). *In vitro* experiments showed that a crosstalk occurs between IFN-α and EGF in tumor cells; at cytostatic concentration IFN-α potentiates the effects mediated by EGF-R (Caraglia M, etal, Int'l J Cancer, 1995 May 4, 61(3):342-7).

IFN-α may also potentiate the activity of other agents, such as cisplatin, that are critical in the treatment of lung cancer. Combination regimens incorporating IFN-α are listed in Exhibit 4. However, although individual studies show some benefit with combination therapies incorporating IFN-α, others do not (Ardizzoni A, etal, British Journal of Cancer, 1995 Jan, 71(1):115-9). Preclinical data also indicate that the combination of retinoids and interferons has synergistic antiproliferative and differentiating effects in some hematologic and solid tumor models. These observations have led to clin-ical studies of 13-cis-retinoic acid (13cRA) at 1 mg/kg/day combined with IFN-α-2a at 3 or 6 million U/day. The first two such trials in patients with advanced squamous cell skin cancer produced exciting results but additional trials of the combination have not been duplicated in the other squamous tumors tested (head and neck, lung, pretreated cervix) and trials in two nonsquamous histologies (lung and melanoma) were negative (Eisenhauer EA, etal, Leukemia, 1994, 8 Suppl 3:S38-41).

Although IFN-γ inhibited cell growth in various cell lines, including sclc, clinical trials failed to show effectiveness. Recombinant IFN-γ was inactive in sclc, even when the tumor burden was substantially reduced by prior chemotherapy (Bitran JD, American Journal of Clinical Oncology, 1995 Feb, 18(1):67-70). Although IFN-γ appeared to sensitize normal lung tissue to the effects of radiation, it was also associated with life-threatening side effects such as high incidence of severe or fatal radiation pneumonitis. Therefore, IFN-γ is not recommend as a radiosensitizer in lung cancer (Shaw EG, etal, International Journal of Radiation Oncology, Biology, Physics, 1995 Feb 15, 31(4):827-31) and clinical development of IFN-γ has been suspended for this indication. However, a phase I trial of inhaled rIFN-γ indicated it may provide a way to increase alveolar concentrations of rIFN-γ and to augment respiratory burst capacity of alveolar macrophages without any major side effects. This approach may have clinical implications for the treatment of lung cancer (Halme M, etal, International Journal of Radiation Oncology, Biology, Physics, 1995 Jan 1, 31(1):93-101).

IFN-β (Betaseron; Berlex) may also prove useful in the treatment of nsclc. *In vitro* studies have found that IFN-β induces terminal cellular differentiation or programmed cell death in nsclc cell lines in a phenotype-specific manner. Because IFN-β-induced effects are post-translational, in order to exert a therapeutic effect this agent will probably need to be administered in combination with other agents that regulate similar cell pathways at the pretranslational level (Loshkin A, etal, J Natl Cancer Inst, 87:206-212, 1995). However, a phase II clinical trial of 41 patients with advanced nsclc who received

high dose rIFN-β (maximum dose was 720 million IU) resulted in no objective responses prompting the investigators to conclude that rIFN-β has no measurable antitumor activity in nsclc even at maximum tolerated doses (Wheeler RH, etal, J Immunotherapy with Emphasis on Tumor Immunology, 1994 Apr, 15(3):212-6).

Interleukins are also being used in the treatment of lung cancer. In addition to gene therapy approaches discussed above, IL-2 is being used in adoptive immunotherapy in conjunction with tumor infiltrating lymphocytes (TILs). Using an *ex vivo* procedure, TILs were expanded *in vitro* from surgically obtained tissue samples, including samples from both the tumor and surrounding lung, in 24 patients (stage IIIa, 14 cases; stage IIIb, 10 cases) who underwent resection for stage III nsclc. A number of TILs, ranging from 4 to 70 billion cells, were reinfused intravenously 4 to 6 weeks after surgery; IL-2 was administered subcutaneously at escalating doses for 2 weeks and then at reduced doses for 2 to 3 months. Median survival was 14 months, and 40% of patients survived for 2 years with three remaining alive and disease-free past 2 years after surgery. Multivariate analysis showed no correlation between incomplete resection and survival suggesting that this approach may be useful in patients with locally advanced disease (Ratto GB, J Thoracic and Cardiovascular Surgery, 1995 Jun, 109(6):1212-7).

Another interleukin, IL-6, has also been implicated in lung cancer. In one series, serum IL-6 was detectable in 39% of patients with lung cancer but not in patients with benign lung diseases. Moreover, serum C-reactive protein levels and plasma fibrinogen levels were significantly higher and serum albumin concentration was significantly lower in lung cancer patients with detectable serum IL-6 levels than in those without detectable serum IL-6 levels and in those with benign lung diseases. There was no significant difference in blood platelet counts among these three groups. Also, serum IL-6 levels were not significantly different in lung cancer patients with or without clinically demonstrated distant metastasis. These results suggest that IL-6 may be a mediator of various reactions, including an inflammatory response in lung cancer patients (Yanagawa H, etal, British J Cancer, 1995 May, 71(5):1095-8). IL-6 is also being investigated as chemoprotective agent. Although IL-6 has been shown to reduce the adverse effects of chemotherapy on blood cells, it does not appear that this agent alone will be clinically useful in mobilizing blood progenitor cells in cancer patients (Pettengell R, etal, (British J Haematology, 1995 Feb, 89(2):237-42). However, the combination of Sandoz' rhIL-6 and G-CSF (Neupogen; Amgen) enhanced platelet and neutrophil recovery post-chemotherapy in a phase I/II trial in 36 patients with advanced nsclc.

Recombinant interleukin-4 (rhIL-4) under development by Schering-Plough (SCH-39400) was reported to have direct antitumor effects by stimulating activated B cell proliferation and increasing the activity of antigen-specific cytotoxic T cells, while decreasing the production of IL-1, IL-6, and IL-8. (Recently, IL-8, a member of the C-X-C chemokine family, was found to be an angiogenic factor). In a phase II study in patients with nsclc, rhIL-4 induced dose-related antitumor responses. Additional phase II trials with rhIL-4 are testing dose-responses in relapsed/refractory nsclc patients, and the effectiveness of this agent as maintenance therapy in resected patients with minimal residual disease.

Photodynamic Therapy

In photodynamic therapy (PDT), used investigationally in the treatment of lung cancer since 1980, a photosensitizing agent is administered systemically and is absorbed by malignant tissue which is then ablated by using radiation of a specific wavelength delivered by a specialized optical system such as a fiberoptic probe. (Also see FO, V1, #1, p 29 and #2/3 pp 56 and 64.).

QLT PhotoTherapeutics (was Quadra Logic Technologies; Vancouver, BC, Canada) received approval in April 1994 to market its photodynamic therapy using the dye Photofrin (porfimer sodium) to treat nsclc, in the Netherlands where it was launched in December 1994 by Cyanamid (Benelux) that has licensed the drug for markets outside North America. It is indicated for the treatment of obstructing or mucosal primary nsclc or secondary lesions metastasized to the lungs. Treatment consists of an average dose of 15 mg delivered IV. Photofrin is available in two dose forms, 75 mg and 15 mg vials priced at $2,160 and $450, respectively. Lederle (Japan) is also marketing Photofrin in Japan where it was approved for early stage nsclc in September, 1994. Phase I/II clinical trials of 209 lung cancer cases in Japan showed that for superficial early lung cancer less than 1 cm in surface diameter, complete eradication can be achieved by PDT in approximately 90% of cases. Additional phase II/III clinical trials have demonstrated an average of 90% CR rates for superficial tumors less than 1 cm in diameter (Kato, H, etal, Jpn J. Cancer Res. 84, 1209-1214, November 1993). Preoperative PDT may be also used to reduce tumor burden of larger neoplasms to potentially lessen the degree of surgery required. At the British Columbia Cancer Agency, 22 patients with 30 radiologically occult cancers (30% involved two or more bronchi and more than 50% were greater than 1 cm in surface diameter; 23% of the cases were bronchial stump recurrences) were treated with PDT. In patients with bronchial stump recurrence, although a CR was obtained with PDT initially, local recurrences occurred in 75% of cases. These results suggest that recurrent tumor in the bronchial stump should not be treated with PDT because of difficulty in delivering light endobronchially to distal tissues. PDT may have a role in the palliation of advanced, inoperable, obstructive bronchial tumors. PDT, in combination with external radiotherapy may produce better local

control than external radiotherapy alone in patients with obstructive bronchial cancers. PDT and conventional Nd:YAG laser therapy appear to be equally effective in relieving intraluminal obstruction caused by tumors. An advantage of PDT for this purpose is longer time to treatment failure; a disadvantage is photosensitization that usually occurs for up to 4 weeks after treatment (Lam S, Seminars in Oncology, 1994 Dec, 21(6 Suppl 15):15-9). QLT has entered into agreements with Coherent (Santa Clara, CA) and Laserscope (San Jose, CA) to develop delivery systems for PDT applications.

Other Novel Strategies

Numerous development programs to identify or design novel agents against lung cancer are ongoing and new findings are reported on a daily basis. Many such efforts are exploiting mechanisms that have broad applicability against solid tumors, in general, and may eventually be found to have higher activity in other cancers rather than lung cancer.

Sugen (Redwood City, CA), a public company, is developing an array of anticancer agents for a variety of malignancies by manipulating signal transduction pathways that have been postulated to play a causative role in various diseases as well as cancer. The company is developing small molecule drugs that modulate two interrelated signaling molecules, tyrosine kinases (TKs) and tyrosine phosphatases (TPs), that act as intracellular switches, turning off and on certain signaling pathways. Sugen believes that many cancers can be categorized not by their location/organ involvement but according to their specific TK and TP signaling pathway defects, so that cancers of a single organ may constitute several distinct tumor types sharing only a physical location. By the same token, tumors afflicting different organs may be caused by the same underlying molecular defect and could be treated using the same drug. The most advanced program at Sugen involves a family of small synthetic molecules which inhibit the platelet-derived growth factor receptor (PDGF RTK) signaling pathway, one of which, SU101, entered the clinic in early 1995. Phase I human clinical trials of SU101 in malignant glioma are underway at Memorial Sloan-Kettering Cancer Center. In August 1995, Sugen entered into a CRADA with the NCI for the clinical development of SU101. Additional phase I studies enrolling patients with refractory ovarian cancer and other solid tumors are planned. Sugen is also developing small-molecule inhibitors of HER2 and EGF RTKs that may be applicable to lung cancer.

SunPharm (Jacksonville, FL), a public company, is developing small molecule drugs consisting of polyamine analogs that are linear molecules containing more than one amine group (nitrogen atom). They are found in all cells and participate in various internal cellular functions, including cell growth and proliferation. The SunPharm agents are being developed for a variety of indications. In the cancer area, the company is developing diethylnorspermine (DENSPM), which entered phase I clinical trials in January 1994 at Johns Hopkins Oncology Center (Baltimore, MD), the University of Florida (Gainesville, FL) and Roswell Park Cancer Institute (Buffalo, NY) against a variety of solid tumors. DENSPM kills cancer cells by depleting them of polyamines. After gaining access into cancer cells, because of its structural similarity to the naturally-occurring polyamines, DENSPM rapidly deplete intracellular polyamine supplies by down-regulating the biosynthetic enzymes, ornithine decarboxylase and S-adenosylmethionine decarboxylase, and by potently up-regulating the polyamine catabolizing enzyme, spermidine/spermine N1-acetyltransferase, depriving cancer cells of their ability to survive, grow and proliferate. The drug is licensed to Warner-Lambert, which has manufacturing and marketing rights for all cancer applications worldwide except Japan where it is licensed to Nippon Kayaku (Tokyo, Japan). SunPharm holds an exclusive license for DENSPM from the technology transfer company of the University of Florida.

MEETING COVERAGE

ADVANCES IN THE TREATMENT OF LUNG CANCER

FROM THE 31ST ANNUAL SESSION OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY, LOS ANGELES, CALIFORNIA, MAY 20-23, 1995

NEW CHEMOTHERAPEUTICS

Taxanes

Docetaxel (Taxotere; Rhône-Poulenc Rorer), a semisynthetic taxoid, has shown considerable activity as a single agent in advanced nsclc, with reported response rates of 38% and higher. Several studies were reported which evaluated the drug's efficacy and safety when combined with cisplatin for the treatment of advanced nsclc. Administration of docetaxel and cisplatin, in combination, to patients with mainly metastatic nsclc, has resulted in a promising positive response of 30%. The treatment schedule consisted of docetaxel (75 mg/m^2) and cisplatin (100 mg/m^2) on days 1, 22, and 43, and then every six weeks, with standard premedication with dexamethasone and antihistamines and hyperhydration. Fifty-one patients with histologically proven locally advanced or metastatic nsclc and no previous chemotherapy were entered into the trial. Interim results included one complete response (CR) and 14 partial responses (PRs), the results being interim because nine patients were still receiving treatment at the time findings were reported. The median duration of response was seven months. This combination demonstrated a good safety profile and, as a result of using routine premedication, previ-

Exhibit 9
Selected Agents in Development for the Treatment of Lung Cancer

Primary Developer/ Affiliate	Generic Name/ Number/Brand Name	Drug Type/Target/ Mechanism/Delivery	Status/Location/ Indication	Comments
Abbott/Kirin Brewery	Socorromycin; vicenistatin/A-85858	Macrolactam antibiotic	Preclin/USA	
Agouron Pharmaceuticals/ Cancer Research Campaign	AG337	Thymidylate synthase inhibitor/IV, PO, IP	Phase II/UK, USA	
Ajinomoto/ Roussel-Morishita; Yamanouchi	Lentinan/LC-33; YM-09222	Natural product isolated from Lentinus edobes; polysaccharide/ immunostimulant	Clinicals/Japan	L (86)/Japan/ stomach cancer
Alfacell/NIH	Onconase/P-30	Microtubule inhibitor/ 15 kD protein isolated from Rana pipiens oocytes and early embryos; pancreatic ribonuclease/degrades RNA	Phase II (5/95)/ USA/nsclc	
Allergan-Ligand Retinoid Therapeutics (ALRT; Allergan & Ligand joint venture)	9cRA/LGD1057	Synthetic 9-cis retinoic acid/oral	Phase I/IIa/USA/ solid tumors	Phase IIb trials are planned for nsclc
AntiCancer/ Harbin Medical U (China)	Interleukin-2(IL-2) gene/AC9401/ MetaGene	Gene transfer	Phase I/China/ malignant pleural effusions	
AntiCancer	AC9301-Methionase/ ONCase	Enzyme isolated from the bacterium Pseudomonas putida/causes methionine levels to rise 100-fold to combat resistance to platinum-based drugs/IP or IV	Preclin/USA/nsclc	Conjugated to polyethylene glycol (PEG)
Argonex (Oncologix)	ReT-9/OLX-209	Immunotoxin (fusion of recombinant single chain antibody (SCA) with Pseudomonas exotoxin/ erbB-2 oncogene	Preclin/USA/lung adenocarcinoma	
Argonex (Oncologix)/ Thomae (Boehringer Ingelheim) (licensor)	Mopidamol/ OLX-102; RA-233/Rapenton	Antiplatelet agent; dipyridamole analog/ phosphodiesterase inhibitor/oral	Phase II/USA/adjuvant therapy for limited nsclc and sclc	Phase II trials completed as of early 1995
Asta Medica	D 22213 (RC-3095; D-21663; RC-3440)	Bombesin/gastrin releasing peptide (GRP) antagonists/SC	Preclin/USA/sclc, nsclc	Licensed from Tulane U (Professor AV Schally)
Beaufour-Ipsen	BIM-26226	Gastrin releasing peptide/ bombesin antagonist	Phase I/USA	May be applicable to sclc
Biomeasure (Beaufour-Ipsen)/ Tulane U (licensor)	Lancreotide/ BIM-23014/ Angiopeptin, Dermopeptin, Somatuline	Octapeptide somatostatin analog/growth hormone antagonist	Phase II/France	
Bristol-Myers Squibb	Etoposide phosphate/ Etopophos	Prodrug to VePesid	NDA (6/94)/USA nscl and other cancers	More soluble; less preparation is needed for dosing
Bristol-Myers Squibb	BMS-181174; BMY-25067	Mitomycin-C analog/ DNA antagonist	Phase I/The Netherlands, UK	
Bristol-Myers Squibb	BMS-182248-01; BR96-DOX	Chimeric (mouse-human) IgG_1 anti-$Lewis^y$ MAb conjugated to doxorubicin/ RNA synthesis inhibitor	Phase I/USA	
Bristol-Myers Squibb	Oncostatins; oncostatin-M	Interferon-like proteins	Preclin/USA	
Bristol-Myers Squibb	Elsamitrucin; elsamicin-A/ BBM-2478A; BMS-181171; BMY-28090; NSC-369327	Chartreusin-related compound, isolated from Actinomyces/ DNA topoisomerase I and II inhibitor/IV	Phase II/Europe/ nsclc	A 25 mg/m^2/week given as a 5-10 min. infusion for at least 3-6 times weekly resulted in no objective responses in nsclc (Verweij J, etal, Ann Oncol, 1994, 5(4):375-6)

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Bristol-Myers Squibb	Paclitaxel/Taxol	Originally isolated from the Pacific yew tree (Taxus brevifolia), now semi-synthetically-produced/ inhibits mitosis by enhancing polymerization of tubulin and stabilization of microtubules	Phase III/USA/nsclc	See this issue, p 110
Bristol-Myers Squibb Pharmaceutical Research Institute	aFGF-PE40 and aFGF-PE40 KDEL and bFGF-PE40 and bFGF-PE4E KDEL	Acidic and basic FGF-Pseudomonas exotoxin fusion proteins/tumor cells bearing FGF-receptors/ angiogenesis inhibitor	Preclin/USA	
British Biotech	Batimastat/BB-94	Matrix metalloproteinase inhibitor (MMPI)/IP, IV	Phase III/UK, USA/ malignant pleural effusions	
British Biotech	BB-2516	MMPI with similar antitumor activity to batimastat/oral	Phase I/UK, USA/ malignant pleural effusions	
Burroughs Wellcome (Glaxo Wellcome)	BW2258U89	GRP receptor antagonist		
CarboMed/Vanderbilt U School of Medicine	CM101	Polysaccharide endotoxin/ angiogenesis inhibitor	Phase II/US/ lung cancer	ASCO, May 1995, Abs. 1591, 1592
Celltech/American Cyanamid (American Home Products)	Calicheamicin/ CDP-671	Cytotoxic conjugate/ rhMAb linked to calicheamicin/ anti-polymorphic epithelium mucin (PEM) conjugate	Phase I/II/USA	Also evaluated in ovarian and breast cancer
Cell Therapeutics	CT-2584			See FO, V1, #5
Centocor/Ajinomoto; Glaxo Wellcome	1083-17-1A; 17-1A; C017-1A/ Panorex	Murine IgG2a MAb	May also be effective in lung cancer	Approved (1/95)/ Germany; prereg/USA/ colorectal cancer
Chiron/Berlex (Schering AG)	Interferon-β 1b/ Betaseron	Cytokine/interferon agonist/SC, CF	Phase I/II/USA/ unresectable stage III nsclc	Radiosensitizer
Cytel	Theradigm	Antigen-specific immunostimulant	Preclin/USA/ lung cancer	See FO, V1, #2/3, pp 52 & 58
DuPont Merck	DMP-840	Bis-naphthalimide/interferes with DNA-metabolic processes (inhibits incorporation of thymidine and uridine into DNA and RNA); produces DNA single-strand breaks in a dose-dependent manner	Phase II/Canada, USA	
DuPont Merck	Losoxantrone/ CI-941; DuP-941; NSC-357885; PD-113785	Anthracycline/ DNA intercalator/IV	Phase I/USA/nsclc	Phase II/USA/ breast cancer
Eisai	E-7010	Sulfonamide agent/ dihydroteroate synthase inhibitor/PO, IV	Phase I/Lewis lung carcinoma	
Eli Lilly	Gemcitabine/ LY-188011/Gemzar	Nucleoside analog; difluoronucleoside agent/ DNA synthesis inhibitor	Approved/South Africa (94), the Netherlands, Finland and Australia; phase II/USA/nsclc	See this issue, page
Eli Lilly	LY-295501	Sulfonylurea	Phase I/USA	
Enzon/Sanofi; Research Corporation Technologies	Superoxide dismutase/Peg-SOD; Dismutec	Superoxide dismutase stimulant	Preclin/USA, Europe	
Fujisawa	Rubratin	Natural product isolated from cell wall skeleton of Nocardia rubra/macrophage stimulant	Prereg/Japan	Asta Medica (licensor) suspended development in 1993
Genelabs Technologies	GL331	Epipodophyllotoxin/ topoisomerase II inhibitor/IV	Phase I/USA/nsclc	MTD has been established at 375 mg/m^2 (ASCO95, Abs. 1571)
ImClone Systems/Memorial Sloan Kettering Cancer Center (licensor)/Merck KGaA (licensee, Europe)	BEC2	Immunostimulant; murine anti-idiotypic MAb/mimics ganglioside D3 (gD3)	Phase Ib/IIa (94)/ USA/sclc	

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ImClone Systems/ U California (licensor)	C225	Anti-EGFr MAb	Phase I completed 3/95/USA/solid tumors (may be useful in squamous lung cancer)	Also obtained license (6/94) form Rhône-Poulenc Rorer for use of anti-EGFr MAbs in combination with marketed chemotherapeutics
ImmunoGen	huN901-DC1	Humanized N901 MAb conjugated to DC1, an anticancer	Preclin/USA/sclc (tumor debulking)	
ImmunoGen/ Dana-Faber Cancer Institute (licensor); U Zurich	N901-bR/ Oncolysin S	Immunoconjugate/blocked ricin immunotoxin	Phase II (92)/USA, Switzerland/sclc (minimal residual disease after chemo)	The company is not pursuing additional trials but will collaborate with NCI (3/95)
Introgen Therapeutics/ RPR Gencell		Gene therapy/p53 repair	Phase I (2/95)/USA/nsclc	
Khepri/Genentech (licensor)	Recombinant neutral endopeptidase (rNEP)	Anti-inflammatory agent	Preclin/USA/nsclc, sclc	NEP is a membrane-bound protease that inhibits tumor growth in sclc *in vitro* (AACR95, Abs. 1582 & 2538)
Kirin Brewery	KRN-5500; SPK-241	Spicamycin derivative/ DNA and protein synthesis inhibitor	Preclin/Japan/nsclc, sclc	
Kyowa Hakko	KT-6149; E-90/007; KW-2149	Quinocarmycin; 7-aminodisulfide mitomycin C derivative/single strand DNA damage	Phase I/Japan/nsclc	
Kyowa Hakko	KW-2189	Duocarmycin derivative; structurally similar to CC-1065/DNA cleavage	Phase I/Japan	
Ligand Pharmaceuticals	LGD1069	Chemical retinoid, oral	Phase I/IIa/USA/ solid tumors	Phase IIb trials are planned for nsclc
NCI/NIH; Kyowa Hakko; New Chemical Entities; U Amsterdam Department of Chemistry	EO9; EO1; EO4; EO68; EO70; EO72; NSC-382456	Indoloquinones; mitomycin-C analogs/ DNA antagonists; inhibit mitosis through activation of DT-diaphorase	Phase II/USA, Europe, Japan/nsclc	
Sequus (was Liposome Technology)	S-Vincristine	Liposomal formulation using Stealth technology	Preclin/USA/sclc	
Medarex/Merck KGaA (was E. Merck)	H-447	Bispecific MAb/humanized MAb fragment that binds to EGF receptor linked to H-447 humanized Trigger MAb	Phase II/USA/sclc	
Medarex/Ciba-Geigy	MDS-210 Bispecific	Bispecific humanized MAb/ simultaneously binds to HER-2 on the surface of cancer cells and to immune system killer cells	May have utility in lung cancer	Phase I/II/USA/breast & ovarian cancer
Medco Research	Adenosine triphosphate	Adenosine 5'-(tetrahydrogen triphosphate)/adenosine agonist	Phase I/USA/advanced nsclc	
MGI Pharma (licensee)/U Rochester	PF-dUMP analog	Phosporamidate fluorode oxyuridine monophosphate (PF-dUMP)/thymidylate synthase inhibitor/IV	Preclin/USA	
MGI Pharma	Acylfulvenes	Semisynthetic compound; natural product derived from Omphalotus illudens mushroom	Preclin (3/95)/USA	
NCI (NIH)	Deoxyspergualin	Immunosuppressant, chemoprotective, cytotoxic	Phase I/II/USA	

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NCI (NIH)		Phenanthroline derivatives/ transformed cell inhibitors	Research/USA	Serial # 08/198,953; available for licensing (1/95)
NCI (NIH)	Interleukin-2 (IL-2)		Phase II/USA	Short term adverse reactions include low-grade and mid-grade fever, mild nausea and muscle pain
National Koranyi Institute for TBC and Pulmonology (Budapest, Hungary)	Short-chain SP antagonist, pHOPA-DTrp-Phe-DTrp-Leu-Leu-NH2 (NY3238 and analogs NY3521 and NY3460)	Substance-P (SP) analogs/ bombesin antagonists; inhibit growth of sclc cells		NY3460 was effective in inhibiting growth of NCI-H69 sclc xenografts in nude mice (Orosz A, etal, Int'l J Cancer, 1995 Jan 3, 60(1):82-7)
NeoRx	Avicidin	MAb (murine) streptavidin conjugate, galactose-albumin-biotin clearing agent and ^{90}Y-DOTA-biotin/binds to markers on tumor cell surface and kills tumor cells	Phase I/USA/sclc, nsclc	
NeXstar (was Vestar)/ Research Corporation Technologies (licensor); U Arizona (developer)	Azonafide compounds	Anthracene analog/ topoisomerase inhibitor	Preclin/USA	
NeXstar (was Vestar)	DaunoXome	Liposomal formulation of daunorubicin	Phase II/Europe, Canada and USA/sclc	
Novopharm Biotech (was Hygeia)	SK-1/Monopharm-C	MAb; Sialoglycoprotein Ag	Phase I/Canada/lung adenocarcinoma	Collaboration with Servier terminated in 1993
Novopharm Biotech (was Hygeia)	NG-1/ Monopharm-G	Immunosuppressant	Preclin/Canada	
Oxigene	Sensamide and Neu-Sensamide	High-dose formulation of the antiemetic metoclopramide; antiemetic and radiosensitizer	Phase II/III Europe (6/95)/ inoperable squamous cell lung cancer	
Parke-Davis (Warner-Lambert)	CI-980; PD-131141-54	Synthetic mitotic inhibitor	Phase I/USA/ solid tumors	
Parke-Davis (Warner-Lambert)/ DuPont Merck (licensee worldwide)	Teloxantrone hydrochloride, moxantrazole/ CI-937, DuP-937, NSC-355644, PD-113309	Anthrapyrazole derivative/ potent topoisomerase II inhibitor closely related to mitoxantrone	Phase II/USA, Canada/nsclc, sclc	
Pharmacia (Farmitalia Carlo Erba)	Iododoxorubicin/ CFCE-21954; FCE-21956	Lipophilic doxorubicin analog/RNA synthesis inhibitor	Phase II/Europe	
PharmaMar	Ecteinascidins/ ET-743; ET-722; ET-736; ET-745; ET7	Natural (marine) product derived from the Caribbean tunicate Ecteinascidia turbinata/may form covalent adducts to DNA	Preclin/Spain/nsclc	See AACR95, Abs. 2322
PharmaMar	Dehydrodidemnin B	Natural product	Preclin/Spain/nsclc	
Protein Design Labs	ABL364	Murine IgG_1 MAb against Lewis Y-6 carbohydrate antigen	Phase II/USA/sclc	
Protein Design Labs/ Sandoz (co-marketing rights in NA and Europe)	Smart ABL364	IgG_1 MAb (humanized) against Lewis Y-6 carbohydrate antigen	Preclin/USA/sclc	
QLT PhotoTherapeutics (was Quadra Logic Technologies)/Lederle Japan (American Cyanamid/Takeda)	Porfimer sodium; dihaematoporphyrin ether/CL-184116/ Photofrin	Photodynamic therapy/ radical formation agonist	L(12/94)/the Netherlands; launched (orphan drug)/ Japan/ early stage nsclc; supplemental submission/ USA	

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Rgene Therapeutics	RGA-0853	HER-2/neu (erbB-2) oncogene repressor gene E1A encoding p185, a membrane like receptor with intrinsic tyrosine kinase activity, complexed with cationic lipid vector, DC-cholesterol	Preclin/USA	First target is ovarian cancer
Rhône-Poulenc Rorer/ NIH; Chugai (co-developer)	Docetaxel/ NSC-628503; RP-56976/ Taxotere	Semisynthetic taxoid/ promotes assembly of microtubules and stabilizes formed tubules	Approved (8/95)/Canada; phase II/III/France, USA/nsclc; reg/Mexico, South Africa/nsclc	
RW Johnson Pharmaceutical Research Institute (Johnson & Johnson)	Loxoribine/ RWJ-21757	Immunostimulant; vaccine adjuvant/stimulates B lymphocytes; activates natural killer cells/IV, SQ, PO	Phase II/USA	No major toxicity was observed in advanced cancer patients at dosages of 5 mg/kg
Roberts Pharmaceutical (licensee); H-N Pharma (Hafslund-Nycomed) [licensee-Europe (except UK and Ireland), Middle East and Africa]; DuPont Merck (licensee-USA), Taiho (licensee-Japan)/ SRI (developer)	Etanidazole/ DuP-453, SR-2508/ Radinyl	Radio/chemosensitizer	Phase II/USA	
Sanofi Winthrop/SRI	Tirapazamine SR-4233; SR-4317; SR-4330; SR-4482; Win-59075	Radiosensitizer/selectively toxic to hypoxic cells/IV	Phase I/USA/nsclc	
Sandoz	Recombinant (E. coli) human interleukin-3 (rhIL-3)	Cytokine	Phase II/USA	
Sandoz	Octreotide/ SMS 201-995/ Sandostatin	Octapeptide somatostatin analog/growth hormone antagonist	Phase II/USA/ extensive sclc	Results did not warrant development for this indication (North Central Cancer Treatment Group; ASCO95, Abs. 1051)
Sandoz	SDZ 62-434, 53	5-aryl-2,3-dihydroimidazo [2,1-a]isoquinolines/ platelet activating factor (PAF) receptor antagonists/	Phase I/USA	In animal studies it was more effective on a milligram per kilogram basis than edelfosine
Sanofi Winthrop / Center for Therapy and Research in Cancer	Crisnatol/770U82; BW-770; BW-770U82; BW-A770U	Camptothecin analog/ DNA antagonist	Phase II/UK/lung adenocarcinoma	
Schering-Plough (DNAX Research Institute)	Recombinant human interleukin-4 (rhIL-4)/SCH-39400	Growth factor/stimulates activated B cell proliferation, increases activity of antigen-specific cytotoxic T cells, decreases production of IL-1, IL-6 and IL-8	Phase II/USA, Europe/nsclc	Induced dose-related antitumor responses
Scotia Pharmaceuticals/ St. Bartholomew's Hospital (London)	EF-13	Lithium gammalinolenate/ prostaglandin synthase inhibitor	Phase I/Europe	In early 1995 Scotia submitted its first marketing applications for EF-13 for pancreatic cancer in the UK, Denmark, and Ireland
Scotia Pharmaceuticals	mTHPC/EF-9	Synthetic chlorins, synthetic porphyrins mesotetrahydroxyphenylchlorin/photosensitizer	Preclin/UK	Photodynamic therapy
Seragen/Eli Lilly (option)	EGF fusion toxin/ $DAB_{389}EGF$	Epidermal growth factor conjugate/targets EGF receptor on tumor cells	Phase II/USA	
Servier	S-9788			See FO, V1, #5
Servier	Fotemustine/ S-10036/ Muphoran	Nitrosourea	Phase II/France, UK/ advanced nonresectable nsclc	Launched/France(89), New Zealand(91), Australia(93)/malignant melanoma

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Servier	S 16020-2	Pyridocarbazole derivative	Preclin/France/Lewis lung carcinoma	AACR95, Abs. 2303
SmithKline Beecham	Topotecan; hycatamine/ NSC-609699; SK&F-104864/ Hycamptin	DNA topoisomerase II inhibitor/IV, PO	Phase III/USA/injectable; phase I/USA/oral	
Southern Research Institute/NIH; CRC Technology (licensee, UK)	Clomesone/ NSC-338947; SRI-6155	Alkylating agent/ DNA antagonist	Phase I/USA, UK/Lewis lung carcinoma	
Sparta Pharmaceuticals	Doxorubicin/ Spartaject	RNA synthesis inhibitor	Preclin/USA	
Sparta Pharmaceuticals	Amsalog	Topoisomerase II inhibitor	Phase I/UK	
Sparta Pharmaceuticals/ NCI	IPdR (prodrug of IUdR)	Radiosensitizer	Phase I/II/USA	
SRI/ Ciba-Geigy (licensee); Memorial-Sloan-Kettering Cancer Center	Edatrexate/ 10-EDAM; CGP-30694	10-ethyl-deaza-aminopterin; methotrexate analog / dihydrofolate reductase inhibitor	Phase II/Europe/nsclc	Given at 80 mg/m2, it was inactive in sclc (Wiesenfeld M, etal, Cancer, 1994 Feb 15, 73(4):1189-93); may potentiate the cyto-toxicity of carboplatin
SS Pharmaceutical/ Bristol-Myers Squibb	Azinomycin-A, B	DNA antagonist	Preclin/USA/ Lewis lung carcinoma	
Sugen	EGF RTK antagonist	Small molecule inhibitors of EGF receptor	Preclin/USA	
Sumitomo	Amrubicin/ S-5887, SM-5887		Phase II/Japan/nsclc	ASCO95, Abs. 1105
Sunkyong Industries	SKI 2053R	Alkylating agent/ platinum-based drug	Phase II/Korea/ lung cancer	
SunPharm/Warner-Lambert (exclusive ww licensee, except Japan); Nippon Kayaku (licensee, Japan)	Diethylnorspermine (DENSPM)	Polyamine analog/ natural polyamine inhibitors	Phase I/USA	
Taiho	TOP-53	Podophyllotoxin derivative/ DNA topoisomerase ATP hydrolyzing inhibitor	Phase I/Japan/ Lewis lung carcinoma	
Taisho	NCU-190; NC-190; NCU-190Na	Benzophenazine derivative; antineoplastic/DNA inhibitor/IV	Phase II/Japan	
Targeted Genetics/ U California, Los Angeles (UCLA)	Interleukin-7 (IL-7)	Gene transfer/ retroviral vector transforms nsclc with IL-7	Research/USA/nsclc	Transformation retarded tumor cell proliferation *in vitro*
Teijin	TT-62; TEI-6170		Discontinued (was in phase II)/Japan	
Therion Biologics/ NCI (NIH)	Cancer vaccine/ TBC-CEA	Live recombinant vaccinia virus	Phase I/II/USA	See FO, V1, #2/3, p 54
Therion Biologics/ NCI (NIH)	GP100; MART-1/ RASVAC; MUVAC: PROSTVAC; TBC-RAS	Live recombinant pox virus vector used to express a tumor-specific Ag based on ras oncogene to elicit cellular response	Preclin/USA	
Thorax Hospital (Heidelberg, Germany)	Edelfosine/ ET-18-OCH3; ET-18-OME; NSC-324	Ether lipid analog/ phospholipase C inhibitor/PO	Phase II/Germany/ nsclc	At 300 mg/day, no organ toxicity was observed; adverse effects were nausea, constipation, diarrhea and anorexia
Transgéne		Delivery of cytokine genes using an adenovirus vector/ intratumoral	Phase I/France/ lung cancer	If successful, the technique will be used to transfer the IL-2 gene
Upjohn/NIH	Carzelesin/ NSC-D-619020; U-80244	Rachelmycin analog/ DNA antagonist	Phase I/USA	

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Upjohn/Yakult Honsha (Japanese co-development and co-marketing rights)	Adozelesin; adezolin/ U-73975/Adosar	Alkylating agent/ Rachelmycin derivatives/ IV	Phase I/Japan; phase II/USA/ solid tumors	See ASCO95, Abs. # 1414
Upjohn/NIH; Taiho; NCI (NIH)	Menogaril; menogarol; methylnogarol/ 7-OMEN; NSC-269148; U-52047; TUT-7/Tomosar	Anthracycline analog/ nogalamycin derivative/ DNA antagonist/IV, PO	Phase III/USA/nsclc/ phase II/Europe, Japan/nsclc	
Uniroyal Chemical	Merbarone/ NSC-336628	A typical inhibitor of topoisomerase II	Phase II/USA/nsclc	
U. S. Bioscience/Roger Bellon (Rhône-Poulenc Rorer); Swedish Orphan; Teva;Faulding; Kanebo; Schering-Plough; Wassermann-SEEF; Wyeth-Ayerst	Altretamine; hexamethylmelamine/ KB-913; NSC-13875/ Exastat; Hexalen; Hexastat	DNA antagonist	Phase II/Japan	NDA 12/90)/USA/ (ovarian cancer (orphan drug to 1997)
U. S. Bioscience/ Southern Research Institute (licensor)/ Schering-Plough (licensee)	Amifostine/ NSC-29696; WR-2721/Ethiofos; Ethyol; Gammaphos	Radiochemoprotective/ oxygen scavenger/ injectable	Phase II/USA/ nsclc	NDA (9/91), amended 1/95), USA/(recommended for approval (6/95) in cisplatin-treated ovarian cancer; approved (94)/ Europe; launched in Germany and the UK
U.S. Bioscience/Parke-Davis (Warner-Lambert; licensor)/Schering-Plough (Latin America/ Asia; licensee)	Trimetrexate/CI-898; JB-11; NSC-249008; NSC-328564; NSC-352122/NeuTrexin	Lipid soluble analog of MTX/dihydrofolate reductase inhibitor IV (oral and topical formulations in research)	Phase II/USA/ mesothelioma	Approved 12/93 USA and 9/94 Europe; launched 1/94 USA as alternative therapy for Pneumocystis carinii; orphan drug; USA patent expires 10/2000
Xenova (ww license)/ Cancer Research Campaign (CRC) Technology; U Auckland	XR-5000	Acridine carboxamide/ DNA topoisomerase I and II inhibitor	Phase I/UK/ lung cancer	
Yakult Honsha/ Daiichi Pharmaceutical; Prodesfarma (Spain); Rhône-Poulenc Rorer (Europe); Upjohn (USA)	Irinotecan/ CPT-11; DQ-2805; SN-38/ Campto and Topotecin (Japan)	Semisynthetic analog of camptothecin/ topoisomerase I inhibitor	Phase II/USA/sclc, nsclc; reg (1/95)/Japan/ primary lung cancer	Also see FO V1 #1 and FO V1, #2/3
Zeneca/CRC Technology	ZD-2767/ADEPT	Immunoconjugates/prodrug generates the corresponding active drug upon interaction with a bacterial nitroreductase conjugated to MAbs that recognize tumor-selective antigens	Preclin/UK/solid tumors, lung cancers	Compared to actinomycin D, drug to prodrug dose ratio for similar cytotoxicity was > 100; prodrug was 20-100x less toxic to mice (Mauger AB, etal, J of Medicinal Chemistry, 1994 Oct 14, 37(21):3452-8)
Zeneca/BTG	ZD-1694; ICI-D-1694/ Tomudex	Thymidylate synthase inhibitor	Phase II/USA, UK	

Source: New Medicine

ously reported drug-induced side effects were considerably lessened (Le Chevalier T, etal, Proceedings of 31st ASCO, 1995, Vol 14; Pg 350:1059).

In a related presentation, the combination of docetaxel and cisplatin proved to be highly effective and relatively well tolerated in the treatment of advanced nsclc. In the phase I portion of the study, the drugs were given at various dosages to determine the appropriate doses to be used in phase II studies. Doses used included docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 (6 patients); docetaxel 75 mg/m^2 plus cisplatin 100 mg/m^2 (10 patients); and docetaxel 85 mg/m^2 plus cisplatin 100 mg/m^2 (6 patients), every three weeks with steroids and antiemetics for acute and delayed emesis. Twenty five patients were enrolled in the study but it was too early to evaluate three patients at the time results were reported. A major response occurred in 46% (10/22) of the patients, with duration of survival not reached as yet. Dose levels of docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 or docetaxel 75 mg/m^2 plus cisplatin 100 mg/m^2 were deemed appropriate for phase II trials. Granulocytopenia was the only dose-limiting activity, because the corticosteroid regimen

used for preventing emesis also prevented fluid retention problems (Cole JT, etal, Proceedings of 31st ASCO, 1995, Vol 14; Pg 357:1087).

Rhône-Poulenc Rorer filed an NDA for Taxotere for the treatment of breast cancer and nsclc in July 1994 but, in December 1994, ODAC did not approve either indication. A scheduled appearance in front of this committee was subsequently canceled in May 1995 to give the company more time to analyze its existing data. In July 1995 Taxotere was approved in Canada for nsclc and breast cancer for patients in whom initial therapy failed. The drug is also approved for nsclc in Mexico and South Africa.

Paclitaxel (Taxol; Bristol-Myers Squibb) administered at doses of 200-250 mg/m^2, resulted in response rates of over 20% in advanced nsclc. The combination of paclitaxel and carboplatin exhibits an additive cytotoxicity, with overall response rates of 25% and improved or stable quality of life in patients with advanced (Stage III-IV) nsclc. In a phase II clinical trial, 51 patients with histologically proven nsclc and measurable disease, were treated with paclitaxel 135 mg/m^2 IV infusion over 24 hours and carboplatin 300 mg/m^2 (16 patients); paclitaxel 135 mg/m^2 and carboplatin (AUC=6 calculated by Calvert formula) (12 patients), or paclitaxel 175 mg/m^2 and carboplatin (AUC=6) (23 patients), with cycles repeated every 28 days. Overall, there was a response rate of 25%, with 13 PRs in 51 patients. There also were two minor responses and 16 patients had stable disease. Median survival was 38 weeks. In addition, overall quality of life evaluations showed improvement or stabilization of quality of life in 10 of 19 individuals. With regard to the drug combination's toxicity profile, grade 3 or 4 infection occurred in the 175/AUC group in eight of 14 persons, including two toxic deaths secondary to neutropenic sepsis and one death secondary to *Klebsiella pneumoniae* sepsis. Since less myelosuppression was seen with shorter duration of paclitaxel infusions, the regimen has been modified to a one hour outpatient paclitaxel infusion followed by the carboplatin infusion. (Paul D, etal, Proceedings of 31st ASCO, 1995, Vol 14; Pg 361:1103).

Parenthetically, the first semisynthetic version of Taxol was introduced in the USA in mid-1995 after receiving FDA approval in December, 1994. This version uses the needles and twigs of the European yew (Taxus baccata) rather than the bark of the Pacific yew tree (Taxus brevifolia). Efforts also continue to produce paclitaxel using cell culture technology. In May, 1995 Bristol-Myers Squibb entered into an exclusive licensing agreement with Phyton Catalytic (Ithaca, NY) that is developing a cell culture method to produce paclitaxel.

Antimetabolites

Gemcitabine (Gemzar; Eli Lilly) has shown considerable cytotoxic activity as a single agent against advanced nsclc, along with a relatively mild side effect profile. In combination with cisplatin, gemcitabine induced a high response rate both in stage IIIB and IV nsclc, with modest side effects. In a phase II clinical trial, 46 eligible patients with advanced, unresectable stage IIIB or disseminated stage IV nsclc were given gemcitabine 1.0 g/m^2 administered weekly on days 1, 8, and 15, followed by a week's rest, and cisplatin 100 mg/m^2 on day 2 of each 28 day cycle. All 46 patients were evaluable for response and toxicity. The overall response rate was 58% (27/46), with one CR and 26 PRs. Two patients with PR are currently free of disease after surgery and radiotherapy. Median survival time and median duration of response have not yet been reached. The main toxicity was thrombocytopenia, with 51% of individuals having grade III-IV toxicity, but this was usually short-lived and there were no serious bleeding episodes (Crino L, etal, Proceedings of 31st ASCO, 1995, Vol 14; Pg 352:1066).

In a related presentation, gemcitabine and cisplatin again proved to be effective and well tolerated in the treatment of advanced nsclc. Using a previously established treatment regimen of cisplatin 100 mg/m^2 on day one and gemcitabine 1,000 mg on day one, eight, and 15, every 28 days, 30 patients with unresectable advanced or metastatic nsclc were enrolled into a phase II clinical trial. The overall response rate in 29 evaluable patients was 34.5% (10/29), with two CRs (6.9%) and eight PRs (27.6%). Time to disease progression was 5.7 months. Toxicity was principally hematologic, occasionally requiring missed doses of gemcitabine on day eight or 15, but, generally, the combination was well tolerated (Sandler AB, etal, Proceedings of 31st ASCO, 1995, Vol 14; Pg 357:1089).

Vinca Alkaloids

Vinorelbine (Navelbine; Burroughs Wellcome) is effective and relatively well tolerated as first-line, single-agent treatment in patients with previously untreated advanced nsclc. The drug was administered at a dose of 30 mg/m^2 weekly to 30 persons. There were eight PRs for an overall response rate of 26.7% and four patients had stable disease (13.3%). Median duration of survival was 10.5 months. Main toxicities were leukopenia, constipation and diarrhea, with a third of the patients having grade III-IV leukopenia (Depierre A, etal, Proceedings of 31st ASCO 1995. Vol 14; Pg 348:1050).

Vinorelbine plus ifosfamide offers very high activity against advanced nsclc, using a novel vinorelbine schedule with granulocyte-colony stimulating factor (G-CSF) (Neupogen; Amgen) support. Initially, ifosfamide 2.0 gm/m^2/day times three with vinorelbine 15 mg/m^2 were given over three consecutive days in a 21 day cycle. Because two of three patients experienced neutropenic fever, the remaining 39 persons in the study received ifosfamide 1.6 gm/m^2/day times three and given vinorelbine daily times three, escalated in cohorts of three to six patients from 15 to 35 mg/m^2. Also, G-CSF was given at 5 mcg/kg/day for seven days, starting on day five. Three

of four patients treated with vinorelbine at 35 mg/m² developed neutropenic fever, pointing to a maximum tolerated dose for vinorelbine of 30 mg/m²/day times three. Of 36 patients evaluable for tumor response, 17 had a PR (47%) and 13 (36%) had stable disease for at least two cycles. Median survival was 58 weeks, with a median follow-up of 44 weeks for patients still alive. The dose-limiting toxicity was myelosuppression, but using a vinorelbine dose of 30 mg/m²/day times three with G-CSF support overcame much of this problem (Hoffman P, etal, Proceedings of 31st ASCO, 1995, Vol 14; Pg 358:1092).

Topoisomerase I Inhibitors

Irinotecan (CPT-11) is a camptothecin derivative with selective topoisomerase I inhibitory properties. Topoisomerase I is an enzyme essential for cell division and inhibition of this enzyme results in the death of cancer cells. (Also, see FO, V1, #2/3, p 56) The combination of irinotecan and etoposide appears to be moderately active against previously untreated metastatic nsclc. To evaluate the efficacy and safety of this combination, 63 patients with metastatic nsclc were entered into a multicenter phase II clinical trial to receive irinotecan 60 mg/m² as a 90-minute infusion, followed by a 60-minute infusion of etoposide 60 mg/m² daily, for three consecutive days, every three weeks. As support, G-CSF 50 mg/m² was administered on days four to seventeen. Overall response rate was 23.6%, with 13 PRs in 55 evaluable patients. Median survival time was 9.5 months, after the median follow-up of 6.5 months. Major drug-induced toxicities were diarrhea grade 3 and 4 (18%) and dyspnea grade 4 (7.0%). A phase I clinical trial of sequential administration of irinotecan (days 1-3) and etoposide (days 4-6), or vice versa, is ongoing. (Goto K, etal, Proceedings of 31st ASCO, 1995, Vol 14; Pg 362:1108). In July 1995 irinotecan was approved in France for the treatment of colorectal cancer in patients, originally treated with 5-FU, in whom disease has advanced. It is sold in Japan, its first market, as Topotecin (see Exhibit 9, p 109).

Topotecan (SmithKline Beecham) is a water soluble semisynthetic analog of the topoisomerase I inhibitor camptothecin which was shown to be active as monotherapy in previously untreated patients with sclc. To evaluate topotecan's usefulness in the treatment of metastatic sclc, 30 patients with sclc (including patients with stable or asymptomatic brain metastases) refractory to etoposide (no response or recurrence within three months of drug discontinuation), were given topotecan 1.25 mg/m²/day IV as a 30-minute infusion for five consecutive days. Of 25 evaluable persons, three achieved PRs (12%), with durations of seven, eight and eight weeks, respectively. Severe toxicities were limited to myelosuppression, lasting less than seven days in most cases. No toxic deaths or toxicity-related withdrawals occurred (Perez-Soler R, etal, Proceedings of 31st ASCO, 1995, Vol 14; Pg 355:1078).

CHEMOTHERAPEUTIC SUPPORT AND ENHANCEMENT

Amifostine

Amifostine (Ethyol; U.S. Bioscience) is a new injectable selective cytoprotective agent that protects normal tissue from the toxicity of chemotherapy and radiation therapy without reducing the antitumor effects of these modalities. In June 1995, ODAC recommended that amifostine be approved as pretreatment with cisplatin (100 mg/m²) for six-cycle or longer courses of therapy in ovarian cancer to reduce the cumulative renal toxicity associated with cisplatin. In metastatic nsclc, a phase II clinical trial of amifostine, cisplatin and vinblastine demonstrated that amifostine potentiates the activity of cisplatin and vinblastine, resulting in a highly effective treatment regimen. Twenty-five patients with previously untreated metastatic nsclc received amifostine 740 mg/m² or 910 mg/m² (the 740 mg/m² dose was preferable because it produced significantly less hypotension) prior to cisplatin 120 mg/m² (higher than the dose used in the ODAC recommendation), every 28 days and vinblastine 5 mg/m² weekly, with vigorous antiemetic and fluid support. Overall, 15 of 21 (71%) evaluable patients had an objective partial response to the triple drug combination. Survival at six and 12 months, as calculated by Kaplan-Mein technique, was 85% and 65%, respectively; median survival was not reached at the time of the presentation of the report. Acute toxicities were reversible and, while hypotension was common, all except three persons were able to continue on amifostine. Furthermore, in 13 patients who completed four cycles of the combination, only one individual had a greater than 40% reduction in creatinine clearance, pointing to the possibility that amifostine may be protective against renal toxicity generally seen with high cumulative cisplatin doses (Schiller JH, etal, Proceedings of 31st ASCO, 1995, Vol 14; Pg 356:1084).

G-CSF and PBSC Support

High dose paclitaxel plus escalating doses of carboplatin has been shown to be a very active combination for the treatment of a variety of solid tumors, including metastatic nsclc, and can be administered to outpatients with a low likelihood of hospitalization when the chemotherapeutic regimen is supported by peripheral blood stem cells (PBSCs), primed by G-CSF (Neupogen; Amgen). To reach this conclusion, 27 previously untreated untreated patients with metastatic nsclc (7 patients), adenocarcinoma of primary unknown origin (5 patients), breast cancer (3 patients), ovarian cancer (2 patients), colon cancer (2 patients), and eight with other cancers were treated as inpatients with paclitaxel 250 mg/m² as a 24-hour infusion, followed by escalating doses of carboplatin as a one-hour infusion, according to the Calvert formula (AUC ranges from 8 to 20), every 21 days. The first cycle of therapy was supported by PBSCS collected after seven days of G-CSF (5 or 10 mg/kg/day subcutaneously) priming. The PBSCS collected after

cycle one of chemotherapy were divided evenly and reinfused after cycles two, three, and four. Patients were discharged after chemotherapy and given ciprofloxacin (Cipro; Miles) 250 mg twice daily and G-CSF 5 mg/kg/day subcutaneously until neutrophil recovery occurred.

Twenty one of 23 patients who were eligible for more than one cycle of therapy, including eight of ten at the three highest dose levels, completed all four courses of therapy every 21 days. Major responses were seen in 14 of 24 (58%) evaluable patients, including six of the seven individuals with nsclc. Up to the carboplatin AUC of 18, cumulative myelosuppression was not observed between cycles one and four. Neutrophil nadirs occurred at a median of day eight, with a median duration of one day at less than 500/ml and platelet nadirs occurred at day 11 with a median of no days under 20,000/ml for all four cycles (Shea T, etal, Proceedings of 31st ASCO, 1995, Vol 14; Pg 478:1555).

SDZ PSC-833

SDZ PSC-833, a unique, non-immunosuppressive, non-nephrotoxic analog of cyclosporine A, in development by Sandoz, acts as a modulator of multidrug resistance, increasing tumor cell retention of chemotherapeutic agents with an overall result of a selective enhancement of the beneficial effects of anticancer drugs. In a phase I clinical trial designed to determine safe dosages of PSC-833 alone and in combination with etoposide, 26 persons with a variety of incurable cancers [lung (4), ovarian (4), sarcoma (3), GI (3), and others (5)] were treated with etoposide 150 mg/m^2 IV daily times three, followed three weeks later with oral PSC-833 over a wide range of doses, every six to eight hours for four to five days. Ten days later, PSC-833, up to the maximum tolerated dose (MTD) of 5 mg/kg every six hours, was administered together with etoposide 60-75 mg/m2 every day times three. When combined with PSC-833, a 50% to 60% reduction of etoposide achieved comparable myelotoxicity to full dose alone. Reversal of resistance to etoposide was observed in two patients. Although this study was not designed to evaluate the effectiveness of this regimen, clinical observations were promising, with several patients experiencing significant reduction in the size or rate of spread of their cancers (Hausdorff J, etal, Proceedings of 31st ASCO, 1995, Vol 14; Pg 181:407).

MECHANISMS IN MALIGNANCY

DRUG RESISTANCE IN CANCER-PART II

- Multidrug resistance (MDR) may be the single most critical reason for failures associated with chemotherapeutic approaches for the treatment of primary and relapsed cancer
- Worldwide, the efficacy of over 1,200,000 million chemotherapeutic regimens is compromized by some type of resistance to the drugs involved
- This is the second part in a series of articles on MDR; the first part appeared in FUTURE ONCOLOGY, V1, #2/3 and the third will appear in V1, #5

APPROACHES TO OVERCOMING DRUG RESISTANCE

Approaches to overcome failure of chemotherapeutic agents in the treatment of cancer include efforts to both prevent and circumvent the emergence of drug resistance (see Exhibit 10). Overall, clinical trials of MDR reversal agents have yielded objective response rates in chemotherapy-resistance cancers ranging between 5% and 40% (NH Patel and ML Rothenberg, Invest New Drugs, [1994] 12:1). However, while various mechanisms of cancer cell resistance to anticancer drugs have been elucidated, many important issues remain unresolved. For instance, there is a need for standardized and reliable methods to identify and quantitate MDR in tumor cells; the relative clinical importance of resistance processes must be better clarified in controlled, prospective examinations of patient tumor specimens and correlations with therapeutic responses to chemotherapy; and better MDR reversal agents that are less prone to result in normal tissue toxicity are needed. Nevertheless, many of the pathways of antineoplastic drug inactivation or transport are targets for pharmacologic manipulations that may reverse or circumvent the resistance of tumors to some drugs, suggesting potentially useful approaches to overcoming clinical drug resistance. These approaches include the rational choice of conventional agents or design of novel drugs that are less likely to share resistance mechanisms. Yet, despite these efforts, many tumors will remain refractory to conventional chemotherapeutic drugs; their successful treatment may require novel modalities such as combined use of MDR reversal agents and biologic response modifiers, liposomal drug encapsulation, inhibition of protein kinase C, the addition of surfactants to MDR-related drugs, or the use of MDR-directed MAbs or immunotoxins.

Oncotech (Irvine, CA), a molecular oncology laboratory, has developed a test, extreme drug resistance (EDR) assay, to measure the degree of resistance of tumors to individual chemotherapeutic agents. The assay measures inhibition of DNA synthesis in patients' tumor cells in the presence of the drug by calculating their rate of proliferation using a thymidine incorporation methodology. Based on 560 clinical correlations between measured and actual outcomes, EDR can identify drug resistance with a 99.2% specificity. Three levels of drug resistance identified include extreme, intermediate and low.

Interestingly, MDR may also be exploited for its protective effect against the cytotoxicity of chemotherapeutics. Several companies are attempting to insert the mdr1 gene in bone marrow and blood precursor cells to protect them from high-dose chemotherapy intended to kill tumor cells.

In late 1994, Ingenex (Menlo Park, CA), a Titan Pharmaceuticals (Menlo Park, CA) company, initiated a pilot

clinical study at M.D. Anderson Cancer Center in which a proprietary mdr1 gene is to be inserted in the bone marrow and blood precursor cells of ten patients with advanced ovarian cancer to protect them from the toxic effects of paclitaxel therapy. The study involves *ex vivo* transfer of the mdr1 gene using a safety-modified retroviral vector. CD34 cells are isolated using Cellpro's (Bothell, WA) Ceprate SC system, are modified to express the mdr1 gene and then reinfused into patients. In the event the technique proves promising, similar pilot studies are planned in patients with advanced breast cancer and lung cancer.

Exhibit 10
Approaches to Prevent, Reverse or Circumvent Drug Resistance

Prevention
■ Appreciation of factors influencing drug resistance mechanisms, i.e., avoidance of drugs with sporadic activity against a specific tumor type but likely to select for cross-resistance to more active agents
■ Aggressive combination chemotherapy with non-cross-reacting drugs, i.e., elimination of tumor before the selection of multiple resistant tumor cell clones occurs
Reversal
■ New drug discovery through large-scale screening programs or rational drug design
■ Use of dose escalation or drugs with alternative transport mechanisms to avoid drug uptake defects
■ Use of agents capable of reversing increased efflux
■ Augmentation of drug activation or efficacy through use of cofactors
■ Inhibition of drug inactivation
■ Application of novel treatment modalities based on immunotherapy, cytokines, or differentiating agents

In August 1995, Genetic Therapy (GTI; Gaithersburg, MD), a unit of Sandoz acquired in July 1995, in collaboration with NCI, began an 18-patient phase I trial of a similar approach to protect progenitor (stem) cells of patients with metastatic breast cancer using gene transfer techniques. Treatment involves the transfer of the mdr1 gene into stem cells to render them resistant to certain types of chemotherapy. According to this protocol, peripheral blood stem cells and bone marrow stem cells are harvested from patients who achieve PRs and do not show bone marrow involvement after four to five cycles of chemotherapy. About 70% of the cells thus obtained are cryopreserved while CD34 cells (which include stem cells) are removed from the remaining 30% of cells and transfected *ex vivo* with a retroviral vector incorporating the mdr1 gene. Subsequently, the genetically altered stem cells, together with the cryopreserved unmodified cells, are reintroduced into patients following high-dose chemotherapy (ifosfamide + carboplatin + etoposide). The aim of the procedure is to provide the patient with a new supply of bone marrow cells that will be resistant to subsequent chemotherapy treatments that may be necessary in relapsed disease. A similar project has combined the resources of Genetix Pharmaceuticals (New York, NY), RPR Gencell and Applied Immune Sciences (Santa Clara, CA). In a phase I trial, Genetix is evaluating the possibility of inserting genes in stem cells to protect them during chemotherapy using technology exclusively licensed from Columbia University (New York, NY) which holds patent rights to the AM12 retroviral cell-packaging line, to which RPR Gencell has commercial rights.

OVERCOMING P-GLYCOPROTEIN-MEDIATED RESISTANCE

Although a number of different drug resistance mechanisms have been identified, perhaps none has been must more intensively studied than classical MDR mediated by P-glycoprotein (P-gp). A number of clinical strategies have been applied to overcome P-gp-mediated MDR:

- high concentrations of cytotoxic drugs can be used to overwhelm the P-gp pump
- drugs may be used which are not recognized by P-gp (e.g., cyclophosphamide, methotrexate, platinum agents)
- a constant low concentration of drug administered by continuous intravenous infusion to maintain steady-state drug concentrations within the cell

Another option is to directly inhibit the P-gp pump activity using MDR reversal agents that inhibit the efflux of P-gp substrate drugs out of cells and result in the "resensitization" of resistant cells. Exhibit 11 lists some of the many agents that have demonstrated ability to reverse MDR in laboratory models. These agents are all believed to be substrates for P-gp, and although the mechanism(s) by which these agents reverse MDR is not fully understood, it is thought that there is a direct interaction between these agents and P-gp that interferes with anticancer drug efflux activity through competitive binding and transport (S Kajiji, etal, Biochemistry, [1994] 33:5041).

Use of MDR-reversing agents may be of some benefit against P-gp-positive refractory tumors. However, before such reversing drugs or strategies can be recommended, additional clinical trials must be performed that correlate antitumor response with the presence of P-gp, as well as the identification of reversing agents with lower toxicity, and determinations of optimal dosages and schedules. One of the problems encountered most frequently with MDR modulators has been the unacceptable toxicity of these drugs when used at levels effective in sensitizing cancer cells *in vivo*. In addition, failures in clinical trials have been traced to insufficient modulator levels, their short half-life and rapid clearance. Another potential problem facing the development of MDR reversing agents is the possibility that tampering with the function of "normal" P-gp in healthy tissues may lead to unacceptable

levels of toxicity from naturally occurring substances as well as from drugs used in chemotherapy (ASD Spiers, Hematol Oncol, [1994] 12:155). The potential effects of modulation of normal tissue P-gp on cytotoxin pharmacokinetics and pharmacodynamics might include decreased excretion and increased toxicity in biliary tissue and the proximal renal tubule, increased myelosuppression in hematopoietic stem cells, and increased nausea and vomiting due to drug effects on the brain endothelium.

Calcium Channel Blockers

The first category of chemosensitizing agents found to modulate the function of the P-gp pump was the calcium channel blockers.

Verapamil was found to partially restore antineoplastic drug sensitivity to vincristine or doxorubicin in leukemia cells even before scientist described the function of P-gp; the transport system affected was subsequently identified to be the P-gp drug efflux pump. However, due to the high incidence of cardiac side effects associated with racemic verapamil, other less toxic calcium antagonists capable of modulating MDR were sought. Both *in vitro* and *in vivo* studies have shown that while the R stereoisomer of verapamil is some ten-fold less potent as a calcium antagonist than the S-isomer, it is approximately equally effective in increasing the cellular accumulation of anticancer drugs (JA Plumb, etal, Biochem Pharmacol, [1990] 39:787). The R-isomer of verapamil has entered phase I clinical testing at NCI (Bethesda, MD) as a more selective modulator of MDR (D Riseberg, etal, Proc ASCO, [1995] 14:180, abstract 403). NCI scientists are also conducting phase I/II studies of the D verapamil enantiomer in refractory lymphomas overexpressing P-gp; the D enantiomer is equipotent to racemic verapamil in its P-gp reversing effect but has potentially less cardiotoxicity (Wilson WH, etal, Proc ASCO, [1995] 14:180, Abs. 404).

Dipyridamole, a coronary vasodilator and platelet aggregation inhibitor, was recently found to augment the activity of such anticancer agents as 5-FU, MTX, and cisplatin and to sensitize MDR cells to MDR-associated drugs. The major biochemical effects of dipyridamole are inhibition of nucleoside membrane transport and cyclic AMP phosphodiesterase. However, while the combined use of 5-FU and dipyridamole for cancer treatment has been studied before, no therapeutic advantage has been reported. One of the possible reasons for this may be insufficient dipyridamole concentrations *in vivo.* Hence, more potent agents with pharmacological properties similar to dipyridamole have been sought. BIBW022, a phenylpteridine analog of dipyridamole was identified as the most effective analog in blocking P-gp function and inhibiting nucleoside transport (H-X Chen, etal, Cancer Res, [1993] 53:1974). Researchers at Thomae (Boehringer Ingelheim) chose this agent amongst a number of dipyridamole analogs evaluated with respect to their ability both to reverse the MDR phenotype and inhibit nucleoside transport but further development of this agent has not been reported.

Exhibit 11
Examples of Agents Shown to Reverse P-gp-Mediated MDR *In Vitro*

DRUG TYPE	DRUG TYPE
Calcium Channel Blockers	**Antibiotics**
Verapamil	Cefoperazone
Nifedipine	Ceftriaxone
Diltiazem	Erythromycin
Nicardipine	
Nimodipine	**Neuroleptics**
Bepridil	Trifluoperazine
Niguldipine	Trioridazine
Prenylamine	Chlorpromazine
Tirapamil	Fluphenazine
	Flupenthixol
Cardiovascular Drugs	Clopenthixol
Dipyridamole	
Quinidine	**Plant Alkaloids**
Amiodarone	Napavin
Reserpine	Vindoline
Steroidal Agents	**Antidepressants**
Tamoxifen	Tricyclic
Toremifine	Clomipramine
Progesterone	
Megestrol acetate	**Surfactants**
	Tween-80
Immunosuppressants	Triton X-100
Cyclosporine	Cremophor-EL
	Solutol HS 15
Antimalarials	
Chloroquine	**Other Agents**
Quinine	Tumor necrosis factor
Quinicrine	Retinoids
	Anti-P-gp MAbs

Hormones

Estrogen antagonists such as tamoxifen and toremifene have also been found to be effective against the MDR phenotype. For example, tamoxifen and its major metabolite N-des-methyltamoxifen have been shown to enhance the intracellular concentration of MDR-related antineoplastic drugs at concentrations as low as four to six micromolar, and have demonstrated 3-10-fold augmentation of cytotoxicity for these drugs *in vitro* (DL Trump, etal, J Natl Cancer Inst, [1992] 84:1811). In this regard, tamoxifen has been shown to

antagonize the activation of cyclic AMP-phosphodiesterase mediated by calmodulin. It has also been reported that tamoxifen binds to a protein termed the ABS protein, which is present predominantly in the microsomal membranes in almost all tissues. ABS appears to be a growth-promoting histamine receptor, and interaction of tamoxifen with this receptor is thought to induce the antiproliferative effects. Together, these observations may explain the antiproliferative action of tamoxifen in estrogen receptor-negative MDR cell lines (US Rao, etal, Biochem Pharmacol, [1994] 48:287). Unfortunately, in the clinical setting, sufficient concentrations of free tamoxifen or toremifene may be difficult to obtain because of protein binding to alpha glycoprotein in the plasma.

Progesterone, and its synthetic derivative megestrol acetate, can also block P-gp function, and have been shown to reverse MDR in human colon and breast cancer cell lines (GF Fleming, etal, Cancer Chemother Pharmacol, [1992] 29:445).

Medroxyprogesterone acetate (MPA), also a synthetic progestin, was investigated by researchers at the IRCCS Fondazione Clinica del Lavoro (Pavia, Italy) and Universita degli Studi (Pavia, Italy), in regards to its the ability to reverse MDR in a doxorubicin-resistant human breast cancer cell line [N Gibelli, etal, ICACC, (31 January-3 February 1995; Paris, France), Abs. P393; C Zibera, etal, Proc ASCO, [1995] 14:183, Abs. 416]. It was found that subtoxic concentrations of MPA enhanced doxorubicin accumulation in resistant cells, causing dose-dependent reduction of doxorubicin ID50 values. In addition, MPA was twice as active as verapamil as a chemosensitizer of MDR resistance at equimolar doses. Since high doses of MPA can be safely administered *in vivo,* this progestin may play a potentially important role in current sequential cytotoxic treatments for breast cancer by maintaining chemosensitivity and/or by reversing doxorubicin resistance.

Immunosuppressants

Cyclosporine and its analogs that are also transported by P-gp have been shown to competitively inhibit drug efflux and to reverse MDR *in vitro* and animal models (PR Twentyman, Biochem Pharmacol, [1992] 43:109). However, *in vitro* concentrations required for effectiveness have generally been much higher than those typically achieved clinically. Concerns about the use of cyclosporine have largely focused on potential that even short-term use of immunosuppressive therapy may increase the risk of infection. It is for these reasons that attention has been directed to the development of more selective cyclosporine analogs that may have improved therapeutic indices in terms of reversing MDR.

SDZ PSC-833, one promising new agent in this regard, is an oral cyclosporine analog without immunosuppressive or renal toxic effects developed by scientists at Sandoz Pharma (Basel, Switzerland) (D Boesch, et al, Cancer Res, [1991] 51:4226). PSC-833 has been shown to be approximately 10-fold more potent than cyclosporine (D Boesch and F Loor, Anti-Cancer Drugs, [1994] 5:229), and has been used to suppress the MDR phenotype and delay the appearance of resistant cells in drug-selected human cancer cell lines (M Mallarino, et al, Proc Am Assoc Cancer Res, [1995] 36:320, abstract 1906). Phase I trials of paclitaxel and etoposide in combination with PSC-833 have been recently initiated in the USA at Stanford University School of Medicine (Stanford, CA) (HL Collins, et al, Proc ASCO, [1995] 14:181, abstract 406; J Hausdorff, etal, Proc ASCO, [1995] 14:181, abstract 407).

Next issue: *Other development programs and strategies to reverse P-gp-mediated MDR, overcoming other types of MDR, a database of agents in development and a list of clinical trials.*

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RESEARCH ASSOCIATES: **Sarah Nghiem and Fred Hall**

CIRCULATION MANAGER: **Lee Kenyon**

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NEW MEDICINE, INC. MAILING ADDRESS:

P.O. Box 909
Lake Forest, California 92630
Tel: 714. 830. 0448 ■ Fax: 714. 830. 0887
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