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

LUNG CANCER — PART II SCREENING, DIAGNOSIS, AND CLASSIFICATION

SPECIAL REVIEW

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LUNG CANCER — PART II SCREENING, DIAGNOSIS, AND CLASSIFICATION

After years of neglect while the nation was preoccupied with other common cancers such as those of the breast and prostate, the spotlight has turned to lung cancer with efforts on many fronts to combat the high incidence and mortality associated with this devastating disease. In addition to seeking better treatment techniques, investigators are re-examining the possibility of screening and early diagnosis as a means of improving the survival of patients with lung cancer. Screening is being revived as a reasonable means of early detection and, thus, curative intervention.

LUNG CANCER SCREENING

Screening for lung cancer may face the same problems currently encountered in prostate and breast cancer screening programs, i.e. a large percent of false positives and overdiagnosis. It is possible that lung cancer (especially adenocarcinoma) behaves similarly to breast and prostate cancer, i.e., normal lung harbors multiple subclinical cancers, many of which will never become clinically relevant in one's lifetime. This may imply that the immune system keeps this malignancy in check, and/or successful continuous inhibition of angiogenesis prevents the growth of small tumors. However, screening for lung cancer should not be discouraged because it is not yet possible to discriminate preclinical but life-threatening cancer from indolent disease. Just as is the case with other common cancers for which early intervention has been shown to save lives, detection and treatment of early (preclinical) lung cancer may eventually save lives because delay in diagnosis results almost uniformly in death.

Screening of asymptomatic populations at high risk for lung cancer is not currently recommended based on results of clinical trials carried out in the 1960s and 1970s. Four prospective randomized clinical trials, involving over 37,000 male cigarette smokers, were conducted in the 1970s, to assess the effect of screening for early lung cancer by chest radiography and sputum cytology. Although all four studies indicated that screening with either or both of these methods increased rates of detection of early-stage disease, and of resectability, they did not show any reduction in mortality. Consequently, and despite the many limitations that may have contributed to these disappointing results, the conclusion was that existing methods of screening, and associated early detection, do not affect lung cancer mortality (Strauss GM, etal, Chest, Jun 1995;107(6 Suppl):270S-279S).

Among the randomized trials, conducted in the USA, that did not report a reduction in lung cancer mortality when the more intensively screened study group was compared to the control group, were:

- the Mayo Lung Project, initiated in 1971, that enrolled 9,211 males ≥45 years-of-age, who were heavy smokers. According to the protocol, subjects free of lung cancer on initial screening were randomized either to sputum cytology and chest x-ray screening, every four months, for 6 years, or to a group that was merely advised one time at baseline to seek screening annually. The study was designed to detect a 50% reduction in lung cancer mortality. Although, lung cancer cases diagnosed in the screened arm were at an earlier stage than those in the control arm, there was no impact on mortality as originally stipulated, and the study design had insufficient power to demonstrate a <50% reduction of 10% to 15% which is medically very significant (Fontana RS, in Hansen HH, ed.: Lung Cancer: Basic and Clinical Aspects. Boston, MA: Martinus Nijhoff Publishers, 1986, pp 91-111). Also, about 50% of men in the control group were screened by an annual chest x-ray, further lessening the relevance of the comparison, leading many to believe that contamination may have been sufficient to obscure any beneficial effect. Despite criticism regarding the interpretation of the data generated in this project, additional analysis taking into account confounding factors such as age at entry, history of cigarette smoking, exposure to non-tobacco lung carcinogens, or previous pulmonary illnesses, did not show any effect in the relationship between screening and lung cancer mortality, and did not alter the original findings (Marcus PM and Prorok PC, J Med Screen 1999;6(1):47-9).
- the Johns Hopkins University (Baltimore, MD) clinical trial, that randomized individuals to a sputum cytology test every four months or a control group; both groups were offered annual chest x-ray (Levin ML, etal, Recent Results in Cancer Research 1982;82:138-146, and Stitik FP and Tockman MS, Radiologic Clinics of North America, 1978;16(3): 347-366).
- the Memorial-Sloan Kettering Cancer Center (New York, NY) clinical trial, that also randomized male smokers to either an intervention or a control group; enrollees in both groups were offered annual chest x-ray but the intervention group was also screened by sputum cytology every four months (Melamed MR, etal, Cancer 1981;47(suppl 5): 1182-1187, and Melamed MR, etal, Chest 1984;86(1): 44-53).

Despite the results of these trials, screening for lung cancer to detect early disease in high risk populations is a rational and logical approach. For instance, if cigarette smoking is indeed an etiologic factor in the development of lung cancer, then it is logical to assume that screening tobacco smokers using an effective approach will result in early detection and, therefore, a higher probability of a cure. Screening for lung cancer may be even more justifiable than screening for breast or prostate cancer because, in the USA and most countries of the developed world, there is a definite pool of high-risk individuals in whom

nearly 90% of lung cancer cases in males and 78% in females occur. Although several other carcinogens including asbestos and radon, are associated with lung cancer, they have been implicated only in a small proportion of cases (Roth JA, etal, Thoracic Oncology, 2nd ed., Philadelphia, Pa: WB Saunders Co, 1995).

Although smokers represent a large population pool (Exhibit 1), they may be further classified by other risk factors such as age and intensity and duration of smoking (Exhibit 2). However, because the mechanism of carcinogenesis attributable to tobacco smoking has not been elucidated, such risk stratification may not be relevant, i.e., individuals at risk for lung cancer need only be exposed to tobacco smoke at much lower rates and still develop lung cancer later in life. Even ambient tobacco smoke may induce lung cancer in susceptible populations.

Nevertheless, despite all the hysteria about smoking, little has been done in the past to provide smokers with a means of early lung cancer detection. This is probably happening because lung cancer is a rare event among long-term smokers (about 7%-11% develop cancer in their lifetime), and there is little financial incentive to identify lung cancer early, and no lobby with any political clout is pursuing this matter. Also, lung cancer is still considered incurable, although new management techniques have significantly extended survival of early-stage lung cancer. However, preconceived notions about lung cancer are contradictory. On the one hand, lung cancer is widely considered an aggressive and impossible to treat malignancy with metastases virtually present at inception making early detection ineffective in its treatment and yet, in appropriately treated Stage I disease, the 5-year survival rate is as high as 70%. On the other hand, results of randomized clinical trials are interpreted to indicate that lung cancer is an indolent disease and that screening only serves to detect lesions that are clinically unimportant (overdiagnosis) and is, therefore, unnecessary. Such contradictions mandate some rethinking of the fundamental assumptions regarding the role of screening in the management of lung cancer (Strauss GM, Chest, Oct 1997;112(4 Suppl):216S-228S).

Another stumbling block in screening populations at risk is the cost-effectiveness test that, at this juncture, does not appear favorable to mass programs even when implementing some type of stratification. Assuming the best case scenario, i.e., mass screening will identify populations at an earlier stage of lung cancer and intervention in those cases will extend survival, the cost of performing a battery of tests at frequent intervals over a long period of time may be prohibitive. For instance, over 11 million Americans aged ≥55 years smoke over 1 pack of cigarettes daily. Any screening program using tools available today, such as chest x-ray, low-dose helical computed tomography (CT), and/or sputum cytology, would impose a very high financial burden. Novel approaches, however, such as stratification using relevant molecular markers, or other indications of risk, may change this situation by identifying more relevant smaller populations at risk. Also, availability of simpler tests, such as breath, sputum and/or blood assays, may reduce costs significantly and make mass screening feasible. Improvements in cytology, such as detection of subtle changes associated with malignancy, determined by digital morphometry, detection of genetic and/or molecular abnormalities (p53 or k-ras expression), and new radiographic techniques such as low-dose helical CT, may eventually show that a combination of modalities is a cost-effective screening approach in reducing lung cancer mortality [(Tazelaar HD, International Academy of Cytology (IAC), 13th International Congress of Cytology (ICC), Mar 1998 (ICC98)]. There are intensive efforts to improve lung cancer screening with molecular techniques. Although a number of promising molecular biomarkers have been identified, to date, they appear to have a low sensitivity, and have not been validated in large controlled studies (Ahrendt SA, etal, JNCI 1999;91(4): 332-339).

It is also possible that therapeutic advances would render early detection more effective. Also, the spectrum of lung cancer type has shifted over the last two decades. Whereas the most common type used to be squamous cell cancer (usually centrally located), the most common type now is adenocarcinoma (usually peripherally located). The latter may be more amenable to early detection by chest x-ray. In contrast, sputum cytology is more sensitive in the detection of squamous cell cancer than adenocarcinoma (Thun MJ, etal, JNCI 1997;89(21): 1580-1586, and Gazdar AF and Minna JD, JNCI 1997;89(21): 1563-1565). Although perioperative mortality associated with lung cancer procedures, estimated between 5%-10%, may be higher than that of other cancers, unlike prostate cancer where surgical treatment of early disease may result in devastating complications such as impotence and incontinence, curative surgery in early lung cancer is associated with few long-term adverse effects. In addition to its potential life saving benefits, the cost of screening to identify early disease may be offset by the huge costs of managing incurable cancer which are estimated at over $40,000 per case.

In Japan, implementation of lung cancer screening is credited with an increase in the diagnosis of lung cancer, as well as with in the number of patients diagnosed with early-stage disease. A retrospective review involving 1,177 primary lung cancer patients, who underwent surgery from 1963 to 1992, resulted in the following findings:

Cohort	Period	Screening Program Status	5-year Survival (%)
Group A	1963-1977	None	33.7
Group B	1978-1986	Local	51.8
Group C	1987-1992	National	58.4

This improvement is attributable to a relative increase in the incidence rate of Stage I cases, and a better Stage I survival rate. As lung cancer screening became widespread, more peripheral small size and/or x-ray occult lung tumors were identified which led to improved surgical results (Koike T, Lung Cancer, May 1999;24(2):75-80).

Exhibit 1
Estimated Number of Smokers over 18 Years-of-Age in the USA in 1999 by Gender and Age

Gender	USA Population (#)	Smokers (#)	Total (%)	Non-smokers (#)	Total (%)
Male	96,902,000	24,516,206	25.3	72,385,794	74.7
Female	104,879,000	21,919,711	20.9	83,064,168	79.2
Total	201,781,000	46,435,917	23.0	155,449,962	77.0
Age					
18-24	25,710,000	7,173,535	27.9	18,478,800	72.0
25-34	37,876,000	9,696,256	25.6	28,179,744	74.4
35-44	44,660,000	12,594,120	28.2	32,065,880	71.8
45-54	35,717,000	8,679,231	24.3	27,073,486	75.8
55-64	23,378,000	4,769,112	20.4	18,608,888	79.6
65+	34,440,000	3,822,840	11.1	30,651,600	89.0

Source: Adapted from Centers for Disease Control and Prevention, Behavioral Risk Factor Surveillance System (BRFSS)
Note: minor discrepancies are caused by rounding

In a comparison of death rates among Japanese screened for lung cancer at physician's offices, and controls, the odds ratios of dying from lung cancer within 12 months for the first group compared to controls was 0.535 which was statistically significant. The odds ratio in the 12-24-month period before diagnosis was 0.638, also statistically significant. These results demonstrate that screening for lung cancer by family physicians is effective in reducing lung cancer mortality (Okamoto N, etal, Lung Cancer, Aug 1999;25(2):77-85).

Chest X-ray

Although randomized trials consistently demonstrate that chest x-ray screening is associated with significant advantages in stage distribution, resectability, and long-term survival, these obvious advantages did not translate into a reduction in lung cancer mortality. In addition to the survival issue, an excess number of lung cancers were detected in populations participating in two studies, suggesting that screening leads to the detection of clinically unimportant lung cancers (overdiagnosis). This observation has become the major stumbling block in mass screening using chest x-ray (Strauss GM and Dominioni L, Surg Oncol Clin N Am, Apr 1999;8(2):371-87). However, periodic screening using chest x-ray lead to clinically meaningful improvements in stage distribution, resectability, and survival in lung cancer (Strauss GM, etal, Chest, Mar 1997;111(3):754-68). Despite the general consensus that screening does not favorably impact lung cancer mortality, there is considerable evidence that chest x-ray screening is associated with earlier detection and improved survival (Strauss GM, etal, Chest, Jun 1995;107(6 Suppl):270S-279S).

Changing views on the potential benefit of chest x-ray in lung cancer screening has prompted the NCI to sponsor the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (protocol IDs: PLCO-1, NCI-P93-0050), a randomized controlled trial to enroll 148,000 men and women aged between 55 and 74 years. The study will screen 37,000 men for prostate, lung, and colorectal cancer, and 37,000 women for lung, colorectal, and ovarian cancer. The lung component uses annual posteroanterior (PA) view chest x-ray as the screening modality. Equal numbers of men and women (74,000) are followed with routine medical care as controls (Gohagan JK, etal, Cancer 1995;75(suppl 7):1869-1873). Enrollment and randomization of participants in this trial began on November 16, 1993 at 10 screening centers nationwide, and the trial is scheduled to be completed in 16 years. As of March 1999, enrollment status was as follows:

Population	Enrollment (#)	Total (%)
Total	121,027	81.8
Men	62,409	51.6
Women	58,618	48.4
Ages		
55-59	35,700	29.5
60-64	39,310	32.5
65-69	28,754	23.7
70-74	17,263	14.3

Low-dose Helical Computed Tomography (CT)

Although chest x-ray is a valuable screening tool in lung cancer, even the highest-quality chest x-ray methods do not detect nodules smaller than 1 cm in diameter (small solitary pulmonary nodules or SSPN). Low-dose helical CT (LDHCT) can greatly improve the likelihood of detection of small non-calcified nodules, and thus of lung cancer at an earlier and potentially more curable stage. Although false-positive CT results are common, they can be managed with minimal use of invasive diagnostic procedures.

To evaluate the role of LDHCT in detecting SSNP, the NIH has funded the Early Lung Cancer Action Project

(ELCAP) which is designed to establish baseline and annual repeat screening by LDHCT in individuals at high risk for lung cancer. Being conducted under principal investigator Claudia I. Henschke, MD, PhD, a professor of radiology and division chief of chest imaging at New York Hospital/Cornell Medical Center (New York, NY), ELCAP has enrolled 1,000 symptom-free volunteers, aged ≥60 years-of-age, who have smoked one pack of cigarettes daily for 10 years, or 2 packs daily for 5 years (10 pack-years of cigarette smoking), had no previous cancer, and were medically fit to undergo thoracic surgery.

Participants were screened with conventional chest x-ray and LDHCT, and any detected non-calcified pulmonary nodules were further investigated by a work-up which included short-term high-resolution CT follow-up for the smallest non-calcified nodules. Non-calcified nodules were detected in 233 (23%) participants by low-dose CT at baseline, compared with 68 (7%) by chest radiography. Biopsies were done on 28 of the 233 participants with non-calcified nodules, which confirmed malignant disease in 27 (2.7%) by CT and in 7 (0.7%) by chest radiography; Stage I malignant disease was detected in 23 (2.3%) and 4 (0.4%), respectively. Another 3 individuals who underwent biopsy against ELCAP recommendations, all had benign non-calcified nodules. According to an interim analysis, among 22 cancers detected using CT, 17 (77%) were not visible on chest X-ray. Among the 27 CT-detected cancers, 26 were resectable. No one underwent thoracotomy for a benign nodule (Henschke CI, etal, Lancet, 10 Jul 1999;354(9173):99-105).

One of the problems with LDHCT is that lung abnormalities identified at baseline are often attributable to non-malignant conditions arising from tuberculosis and/or other pulmonary diseases. In order to eliminate unnecessary interventions such as biopsies, for such benign conditions, additional repeat imaging procedures are recommended to establish if there are any changes in time, i.e. more or larger nodules that almost always point to malignancy.

CT has been incorporated in the Japanese mass screening program for lung cancer. In 1996 a mass screening study, conducted in Japan, assessed whether population-based mass screening with spiral CT would contribute substantially to the detection of smaller cancers, and result in lower mortality. Using a mobile unit, 5,483 individuals from the general population of Matsumoto, Japan, aged between 40 years and 74 years, who had undergone annual chest radiography (miniature fluorophotography) and cytological assessment of sputum, were screened with a low-dose x-ray spiral CT scan of the thorax; 3,967 also underwent miniature fluorophotography. Suspicious lesions and small nodules of indeterminate nature were further assessed using chest radiography and conventional CT with a Hi Speed Advantage CT scanner (GE Medical Systems; Milwaukee, WI), with additional transbronchial biopsy when possible. Thoracotomy was recommended when lung cancer was strongly suspected.

Further diagnostic work-up was performed on 223 patients with abnormal CT results. Among these, 19 patients were diagnosed with lung cancer (14 deemed to probably have a malignancy, 3 with benign but suspicious lesions, and two with indeterminate small nodules), 18 cases were surgically confirmed, and one was clinically diagnosed. The mean size of lesions was 17 mm (range=6-47 mm). In only 4/19 patients, a lung abnormality was seen both on CT and miniature fluorophotography. The lung-cancer detection rate with CT was 0.48%, almost 10 times that of standard mass assessments (0.03-0.05%) done previously in the same area. CT missed one case that was found solely by sputum cytology. It is concluded from the findings of this study that miniature fluorophotography, or conventional chest radiography, detect few small cancers. CT should be considered in lung cancer mass screening because it is more accurate and may lead to early detection and an accurate diagnosis (Sone S, etal, Lancet, 25 Apr 1998;351(9111):1242-5). Also, a group in Japan has compared ultra low-dose helical CT (6 mA) to LDHCT (50 mA) and concluded that the former may also be useful in lung cancer screening (Nitta N, etal, Radiat Med, Jan-Feb 1999;17(1):1-7).

Promising results with low-dose helical CT has prompted the National Cancer Advisory Board to suggest that the NCI undertake a large randomized clinical trial to evaluate the role of LDHCT in lung cancer screening. Because nearly 50% of USA imaging centers may perform LDHCT scanning, this approach may be rapidly incorporated into a screening program without the need of additional facilities. In October 1999, the NCI Board of Scientific Advisors approved a $4.4 million grant outlay, to be awarded over 5 years, to support a consortium of imaging centers in the development of a database of helical CT lung scans.

The jury is still out on low-dose helical CT as a screening tool in populations at risk for lung cancer. Among the comments elicited from the above report, the most critical centered on the fact that out of 223 "abnormal cases" indicated by the CT test, only 8.5% proved to be malignant. Thus, 204 (91.5%) of patients referred for work-up by chest radiography and high resolution CT (some with transbronchial biopsy), proved not to have lung cancer. Such a positive predictive value may be tolerated only if the identified lung cancer cases were clinically relevant.

However, according to one comment on the paper (Vaidya JS and Baum M, Lancet, 18 Jul 1998;352 (9123):236), the fact that CT identified an equal number of cancer cases in smokers (0.52%) and non-smokers (0.48%) is contradictory to an expected minimum 5-fold risk, and the standard 10- to 20-fold risk seen in most lung cancer risk evaluation studies. Because in most other studies 95% of lung cancers are diagnosed in smokers, the results of this study suggest that the diagnosed cancers were subclinical in nature and not clinically relevant.

Sputum Cytology

Sputum cytology is a simple noninvasive test very similar to cervical cytology that has almost rid the developed world of cervical cancer deaths by identifying precancerous and early cancerous lesions of the cervix (see FO, pp 886-894). Sputum cytology has been used since the 1930s to diagnose lung cancer. Sputum of lung cancer patients contains exfoliated cells that, when examined under the microscope, can be classified as benign or malignant. However, in the USA, sputum cytology has been attempted as a screening methodology for lung cancer but was abandoned when it failed to show any reduction in mortality. For lung cancer, in general, the specificity of sputum cytology is high (98%) but its sensitivity is low (65%), resulting in many missed cases of the disease.

However, lung cancer screening by sputum cytology, as practiced in Japan, was shown effective in detecting not only early lung cancer, but also premalignant dysplastic lesions of the bronchus in a population-based lung cancer screening conducted in Miyagi Prefecture by the Council for Lung Cancer Screening, sponsored by the national government and local municipalities (Yasuki Saito, etal, ICC98). From April 1982 through March 1992, screening involving 119,240 person-years was carried out by sputum cytology and chest x-ray. Bronchoscopy was used to localize and diagnose lung cancer. Detected dysplasias were followed up by sputum cytology and bronchial brushing and/or biopsy; bronchial brushing was useful in localizing and diagnosing the grade of neoplastic squamous atypia. Based on the results of sputum cytology, 300 (0.3%) cases with severely (borderline) atypical squamous cells, 159 (0.1%) cases with squamous cancer cells with low grade atypia, and 125 (0.1%) cases with frankly malignant cells, were recommended for further follow-up.

A total of 232 (0.195%) cases of lung cancer, and 34 cases of upper respiratory tract cancer were diagnosed. Among lung cancer cases, 188 (81%) were detected by sputum cytology alone. Interestingly, among all cancers detected 213 (91.8%) were squamous cell carcinomas. Of the 66 cases of dysplasia of the bronchus detected, 55 were followed up and, in 12 patients, the dysplasia developed into squamous cell carcinoma within a mean period of 36 months. In this case, it is interesting to note that almost all cases of lung cancer involved squamous cell carcinomas that are more readily detectable with sputum cytology.

Sputum immunocytology (immunostaining), a new technology promises much greater sensitivity. Experiments with monoclonal antibody (MAb) 703D4 have shown that overexpression of an RNA binding protein, hnRNP A2/B1, is a powerful predictor of early subclinical cancer in high-risk groups. Immunostaining is being investigated in the early detection of second primary lung cancer of any histology (squamous cell carcinoma, large cell carcinoma, adenocarcinoma, including bronchoalveolar cancer) but without a small cell anaplastic component, recurrent disease, or second primary, or synchronous lung cancer of a different histology, in patients with curatively resected Stage I (T1-2 N0) nsclc, in a clinical trial (protocol IDs: E-5593, NCI-P95-0067, JHOC-9152, SWOG-9437) sponsored by the NCI and being conducted by the Eastern Cooperative Oncology Group (ECOG). This study, which was initiated in July 1995 to enroll 1,100 patients over 3 years, has been designed to:

- evaluate whether immunostaining of induced sputum specimens improves the sensitivity and specificity of routine morphologic sputum surveillance to detect second primary lung cancer in patients with previously resected nsclc
- identify patients at risk of developing a second primary lung cancer by immunostaining specimens from patients with no morphologic atypia on routine Papanicolaou (Pap) cytology
- collect archived sputum samples and bronchial washings for further analysis of new antibodies and techniques
- evaluate whether analysis of elevations of relevant growth factors in bronchial lavage fluid from patients with positive immunostaining or morphologic atypia increases the accuracy of early detection
- evaluate whether quantitation of shed antigens in sputum increases the accuracy of early detection
- evaluate whether the extent of airway obstruction, as measured by the forced expiratory volume, can predict an increased risk of developing lung cancer

Screening includes annual sputum induction for Pap cytology and immunostaining using MAbs 624H12 and 703D4. Optional pulmonary function tests, and fiberoptic bronchoscopy with bronchial washings are also being performed.

Attempts are in place to automate quantitative cytometry to facilitate mass screening using this approach. AccuMed International (Chicago, IL), in collaboration with its wholly owned subsidiary, Oncometrics (Vancouver, Canada), is developing the AcCell-Savant, an automated high-resolution image cytometer (nuclear DNA analyzer) that processes Thionin-Feulgen stained cytology specimens for DNA analysis for both the research and clinical laboratory markets. The company is developing the AcCell-Savant to meet the need for lung cancer screening. The AcCell-Savant system consists of an automated high-resolution image cytometer and a DNA staining kit. The price of the hardware is estimated at about $100,000 per unit. Consumables such as staining kits used in conjunction with the analyzer would represent a potentially high-margin continuing revenue stream. Field tests have demonstrated that the AcCell-Savant can detect the presence of early lung cancer from sputum on a microscope slide by measuring subtle malignancy-associated (MAC) changes in the DNA of cell nuclei. Samples of sputum or bronchial washings are collected and processed on site and then sent

Exhibit 2
Estimated Number of Smokers by Average Cigarettes Smoked per Day in the USA in 1999 by Gender and Age

Gender	Population (#)	Smokers of 21-40 cigarettes (#)	Total (%)	Smokers of 41 or more cigarettes	Total (%)
Male	96,902,000	22,287,460	23.0	2,422,550	2.5
Female	104,879,000	13,319,633	12.7	1,153,669	1.1
Total	201,781,000	35,607,093	17.6	3,576,219	1.8
Age					
18-24	25,710,000	2,133,930	8.3	411,360	1.6
25-34	37,876,000	5,113,260	13.5	378,760	1.0
35-44	44,660,000	8,664,040	19.4	893,200	2.0
45-54	35,717,000	8,964,967	25.1	857,208	2.4
55-64	23,378,000	5,330,184	22.8	654,584	2.8
65+	34,440,000	5,372,640	15.6	413,280	1.2

Source: Adapted from Centers for Disease Control and Prevention, Behavioral Risk Factor Surveillance System (BRFSS)
Note: minor discrepancies are caused by rounding

out to be analyzed. Results of 150 bronchial washings using AccuMed's Cyto-Savant DNA analyzer, an earlier version of the AcCell-Savant, indicated a sensitivity of 89%, and a specificity of 76% as compared to the final diagnosis. Automated analysis of 220 sputum samples from 70 healthy nonsmokers, 50 healthy smokers, 50 coal miners with pneumoconiosis, and 50 lung cancer patients, yielded a sensitivity of 54%, and a specificity of 96% (Nakhosteen JA, etal, ICC98).

Sample preparation may be critical in cytology-based lung cancer screening. Investigators have compared the ThinPrep technique (see FO, pp 888-9), commercialized by Cytyc (Boxborough, MA), with traditional sampling and the "pick and smear" technique, on induced sputum samples from 50 consecutive patients with a clinical suspicion of lung cancer. Induced sputum samples were subjected to DiThioThreitol mucolysis, and a monolayer was prepared using the ThinPrep technique. In addition to the traditional Pap test, investigators performed a cytogenetic study of chromosome 3p21.3 abnormalities that were shown to occur in early dysplastic lesions as well as in carcinomas. Preliminary results indicate that the combination of induced sputum and ThinPrep is a better diagnostic method in terms of both sensitivity and specificity. A study on early, asymptomatic, at-risk populations is being planned (Elmberger PG, etal, ICC98).

Breath Analysis

Breath analysis as a screening modality for lung cancer is based on observations that among volatile organic compounds (VOCs) in human breath are those such as alkanes, benzene derivatives, *o*-toluidine, aniline, and altered lipid-peroxidation activity, identified in the breath of patients with lung cancer. Samples from 108 patients with out history of lung cancer but an abnormal chest radiograph who were scheduled for bronchoscopy, were collected with a portable breath collection apparatus (BCA), or "breathalyser", designed by Menssana Research (Fort Lee, NJ), and assayed by gas chromatography and mass spectroscopy. More than 150 different VOCs were identified and quantified. The difference between the amount in breath and in air (alveolar gradient) of each VOC was calculated, and forward stepwise discriminant analysis was used to identify differences in VOCs between patients with and without lung cancer. Among 60 cases of histologically confirmed lung cancer, 22 VOCs, predominantly alkanes, alkane derivatives, and benzene derivatives, were identified that best distinguished patients with lung cancer from those without, regardless of disease stage. Cross-validation correctly predicted the diagnosis in 72% of patients with lung cancer, and 67% without lung cancer. For Stage I lung cancer, the sensitivity of the 22 VOCs was 100% and the specificity 81.3%. Based on these results, a "high-probability" breath VOC pattern, although not diagnostic in itself, may identify individuals at risk for lung cancer, and complement other methods under current investigation, either as markers of early cancer or, perhaps more importantly, as markers of preneoplastic bronchial epithelial changes (Rizvi N and Hayes DF, Lancet 1999 Jun 5;353(9168):1897-8 and Phillips M, etal, Lancet 1999 Jun 5;353(9168):1930-3).

Molecular Markers

Identification of molecular markers associated with premalignant states of lung cancer, in easily obtained samples such as blood or sputum, may one day revolutionize screening for this disease. Numerous markers have been identified and will be described in upcoming issues of FUTURE ONCOLOGY.

In October 1999, the NCI began funding the Early Detection Research Network (EDRN) comprised of 18 laboratories with biomarker development expertise, to discover and develop new biological tests for the early detection of common malignancies, such as prostate, breast, lung, colorectal, and ovarian cancers, and of biomarkers for increased cancer risk (Exhibit 3). The NCI funding, earmarked for this network, is $8 million in FY2000. EDRN will translate discoveries involving a variety of molecules, proteins, genes, and other biological substances that may represent early warnings that normal cells are about to

become malignant. EDRN will convert findings from advances in cancer research, including programs such as the Cancer Genome Anatomy Project, into methods for detecting warning signals, and prepare promising markers for testing in large-scale clinical trials.

Another study (protocol ID: E-1Y97), designed to identify genes that may be associated with the development of certain types of cancer by mapping of interactive susceptibility loci in siblings who have cancer of the breast, prostate, lung, or colon, is being conducted by ECOG under NCI sponsorship. This study, that began on January 28, 1998, will originally enroll 1,000 patient-sibling pairs with breast cancer, with another 1,000 such pairs to be accrued after 18 months, bringing the total to 2,000 pairs to be enrolled in 5 years. The feasibility of accruing pairs for lung, colon, and prostate cancer is also being assessed. The trial's objectives are to gather allele-sharing statistics at approximately 100 candidate loci throughout the human genome that are most likely to influence genetic risk of cancer. These allele-sharing statistics are then to be used to test the interaction of each locus individually with cancer-associated, rare alleles of HRAS1. This approach will then be generalized for one of four cancers (breast, colon, lung, or prostate), using allele-sharing statistics to test the interaction of each locus with every other locus. The study will replicate positive results in a distinct set of sibling pairs with cancer, and assess the influence of any loci, considered contributors to risk, on clinical outcomes such as survival.

The process involves completion of a questionnaire of the family history regarding incidence of cancer by each patient-sibling pair, and blood samples from the pair and from both living parents, if available. The blood samples are genotyped using approximately 300 microsatellite markers, flanking 100 candidate genes previously implicated in genetic risk for cancer. Certain loci that are a priority because of their association with HRAS1 include BRCA1 and all known mismatch repair loci; other repair genes, such as ATM; the Bloom's syndrome locus; and the XRCC group. Other genes will also be mapped. Patients are followed annually.

PRESENTATION AND DIAGNOSIS

Most commonly, persistent cough is the symptom that sends patients with lung cancer to the doctor (Mansson J, etal, Neoplasma 1999;46(2):93-9). Other clinical symptoms include hemoptysis and unresolved pneumonia. Other early clues at presentation may involve paraneoplastic syndromes, including unexplained recent onset arthritis and arthralgias (Campanella N, etal, Med Oncol, Jul 1999;16(2):129-33) and, very rarely, limbic encephalitis (Hsu CW, etal, J Formos Med Assoc, May 1999; 98(5):368-71). In asymptomatic patients, radiographic abnormalities, uncovered during routine x-ray, are the most common reason for further diagnostic evaluations. A diagnostic work-up may start with the simpler tests, such as sputum/brush cytology, and chest x-ray, and proceed to more invasive approaches such as bronchoscopy, and bronchoscopic biopsy. Histologic evaluation of biopsy specimens provides a final profile of the type of tumor involved to guide therapy. At this point several noninvasive imaging approaches may be employed such as CT, MR imaging, and various nuclear medicine procedures, to establish the scope of disease. For suspected nodules that can not be reached by bronchoscopy, various percutaneous procedures are employed, often guided by imaging techniques such as CT or transthoracic ultrasound. Finally, open surgery is performed when no minimally invasive techniques are feasible.

Brush Cytology

The accuracy of sputum cytology may be improved by using brush samples in a complementary approach. In a retrospective study involving 415 lung cancer patients, sputum collection alone was used in 200, brushing only in 119, and both methods in 96. The overall sensitivity of the sputum technique was 0.403, of the brush method 0.500, and of the combination 0.640. Diagnostic yield depended on tumor location, histology and stage. Early and peripheral carcinomas were more likely to be diagnosed with sputum specimens whereas brush specimens produced superior results with more advanced and centrally located malignancies. Either method was best suited in the diagnosis of squamous cell carcinomas (Sing A, etal, Acta Cytol 1997 Mar-Apr;41(2):399-408).

Endoscopy/Bronchoscopy

Fiberoptic bronchoscopy is a common diagnostic procedure in lung cancer, usually performed when chest x-ray and/or sputum cytology indicate malignancy. However, conventional white-light bronchoscopy (WLB) is inadequate in the identification of preneoplasias, and lung carcinoma *in situ* (CIS). A novel approach, light imaging fluorescence endoscopy (LIFE-Lung), developed by Xillix Technologies (Vancouver, BC, Canada), exploits the fact that autofluorescence from normal mucosa differs from that from dysplastic or cancerous bronchial mucosa. This technique was approved in the USA in 1996 as an adjunct to WLB bronchoscopy, and is currently in routine use with over 130 systems having been placed worldwide.

In a prospective multicenter study conducted in North America, the relative sensitivity of the combination of WLB and LIFE bronchoscopy in diagnosing intraepithelial neoplasias in 173 at-risk patients, was 6.3 compared to WLB alone. Of the 75 (43.3%) patients with one or more histologically positive lesions on biopsy, 56 (75%) were correctly identified for biopsy by the WLB-LIFE combination versus 28 (37%) by WLB alone. The sensitivity of WLB-LIFE was 0.75 compared to 0.37 for WLB alone, but the specificity of WLB-LIFE was lower, 0.22 versus 0.58 for WLB alone, resulting in a higher number of negative biopsies. In a separate analysis performed on random biopsies of "negative" sites, 19 patients with malignancy were classified as bronchoscopically negative by WLB-LIFE compared to 47 false negatives with WLB alone.

Exhibit 3
Projects Funded by the NCI Early Detection Research Network

Grant Duration and # Amount	Research Target(s)	Investigator	Industrial Collaborators
5-year grant #CA85070 ❑ $399,741 (first year)	Focuses on **lung** cancer; employs spectral image technology, differential gene expression techniques, and regular genetic and biochemical techniques to assess normal, premalignant, and malignant lung cancer cells to identify and evaluate potential biomarkers	Wilbur Franklin, MD, University of Colorado Health Science Center (Denver, CO)	Spectral Imaging (Carlsbad, CA) and COBE BCT (Lakewood, CO)
3-year grant #CA85065 ❑ $396,255 (first year)	Focuses on breast, colon and pancreatic cancer; will perform detailed mutational analysis of specific genes using a variety of technologies and develop a new technology to detect and quantify point mutations at the cytologic level	Jose Costa, MD, Yale University (New Haven, CT)	
5-year grant #CA85082 ❑ $245,578 (first year)	Focuses on breast cancer; it will characterize protein expression profiles in normal breast tissue, ductal carcinoma *in situ*, and early invasive breast cancer to identify a protein signature associated with invasive cancer and test the feasibility of detecting such a protein easily in accessible body fluids	Marc Lippman, MD, Lombardi Cancer Center (Washington, DC)	
5-year grant #CA84973 ❑ $385,069 (first year)	Focuses on **lung** cancer; will evaluate existing and potential biomarkers in archived sputum specimens from a screening trial of smokers, and former smokers	Melvin Tockman, MD, PhD, University of South Florida (Tampa, FL)	Bayer Pharmaceuticals (Emeryville, CA)
5-year grant #CA85133 ❑ $809,862 (first year)	Focuses on ovarian cancer; will determine the accurate detection of early stage disease in asymptomatic women at increased risk and early genetic changes and aberrant mRNA expression will be evaluated as potential biomarkers; uses Atairgin's platform technology in lysophospholipids (LPA) to develop an early detection marker for ovarian cancer; Atairgin will contribute additional funding to the study and will access ovarian cancer blood samples from the study group to develop its LPA test for early detection of ovarian cancer	David Fishman, MD, Robert H. Lurie Comprehensive Cancer Center, Northwestern University (Evanston, IL)	Atairgin Technologies (Irvine, CA) and Circon (Santa Barbara, CA)
5-year grant #CA84986 ❑ $599,110 (first year)	Focuses on **nsclc**; will identify biomarkers in bronchoalveolar lavage, and serum samples, from lung cancer patients, to characterize and translate into clinical tests and will develop cDNA libraries as resource	David Sidransky, MD, Johns Hopkins University (Baltimore, MD)	Research Genetics (Huntsville, AL), Oncogene Research Products (Cambridge, MA), and Zeneca Diagnostics (UK)
5-year grant #CA85069 ❑ $384,646 (first year)	Focuses on esophageal cancer; will develop assays to detect cancer-related proteins for diagnosis, screening, prevention, and treatment, using unique molecular alterations that occur during cellular progression to cancer	Stephen Meltzer, MD, University of Maryland School of Medicine (Baltimore, MD)	
3-year grant #CA84988 ❑ $382,050 (first year)	This grant focuses on esophageal, GI tract and **lung** cancer and will measure telomerase activity in non-cellular fluids, such as plasma, in patients with a variety of cancers, and evaluate the utility of plasma telomerase measurements as aids in diagnosis and as a monitoring tool during therapy to predict relapse	Edward Highsmith, PhD, University of Maryland School of Medicine (Baltimore, MD)	Advanced Bioscience Lab (Kensington, MD)
5-year grant #CA84982 ❑ $463,272 (first year)	Focuses on colon, esophagus, liver, **lung**, and ovarian cancer; will identify tumor antigens that induce a humoral response and tumor-secreted proteins and develop assays to test the utility of markers that are found	Samir Hanash, MD, PhD, University of Michigan (Ann Arbor, MI)	
5-year grant #CA84976 ❑ $446,741 (first year)	Focuses on breast and colon cancer; will create a database of expression patterns for secreted and cell surface proteins in early stage lesions of the breast and colon	David Beach, PhD, Genetica (Cold Spring Harbor, NY)	

— *continued on next page*

5-year grant #CA85146 ❑ $216,104 (first year).	Focuses on ovarian and prostate cancer and will develop protein biomarkers for early diagnosis, risk assessment, and anti-cancer drug evaluation using laser-capture microdissection and mass spectrometry	Yingming Zhao, PhD, Mount Sinai School of Medicine (New York, NY)	
5-year grant #CA84955 ❑ $400,000 (first year)	Focuses on breast cancer; will identify expression-based markers for breast cancer to detect circulating breast cancer cells and develop antibodies for gene products that may be secreted or presented on the cell surface	Jeffery Marks, PhD, Duke University Medical Center (Durham, NC)	Abbott Pharmaceuticals (Chicago, IL)
5-year grant #CA84951 ❑ $327,931 (first year)	Focuses on liver cancer; will test for serum polypeptides as potential biomarkers across the disease continuum, using people with liver cancer and those with hepatitis	Timothy Block, PhD, Thomas Jefferson University (Philadelphia, PA)	Oxford Glycosciences (Wakefield, MA)
5-year grant #CA84968 ❑ $559,290 (first year)	Focuses on colon and **lung** cancer; will develop assays to detect cancer-related proteins in body fluids and identify gene mutations using SAGE, immunoassay, and PCR-based analysis	William Bigbee, PhD, University of Pittsburgh (Pittsburgh, PA)	
5-year grant #CA85078 ❑ $651,147 (first year)	Focuses on bladder cancer; will develop markers for early detection of occult urinary bladder cancer and its progression to invasive and aggressive disease, and create shared database on all tested markers, and their performance as diagnostic probes	Bogdan Czerniak, MD, PhD, University of Texas M. D. Anderson Cancer Center (Houston, TX)	
5-year grant #CA84971 ❑ $430,454 (first year)	Focuses on **lung** cancer; will look for molecular changes using tumor DNA extracted from plasma, and create a specimen repository; markers to be studied include onset of clonality, alleleic losses at multiple regions, microsatellite alterations, and the presence of aberrantly methylated genes	Adi Gazdar, MD, University of Texas Southwestern Medical Center (Dallas, TX)	
5-year grant #CA850671 ❑ $345,773 (first year)	Focuses on breast and prostate cancer; uses customized protein chips in proteomic analysis based on Surface Enhanced Laser Ionization/Desorption, to identify biomarkers for the detection of prostate and breast cancers at different stages of cancer progression	George Wright, Jr, PhD, Eastern Virginia Medical School (Norfolk, VA)	Ciphergen Biosystems (Palo Alto, CA) and Arcturus Engineering (Mountain View, CA)
5-year grant #CA85050 ❑ $408,070 (first year)	Focuses on developing assays to detect cancer-related proteins in body fluids and tissues, and to determine which secreted proteins correlate with cancerous or precancerous lesions	Nancy Kiviat, MD, University of Washington (Seattle, WA)	ORCA Biosciences (Seattle, WA) and Corixa (Seattle, WA)

However, in another study, the relative sensitivity of the combined WLB-LIFE procedure, as compared to WLB alone in detecting moderate to severe dysplasias and CIS, in 194 examinations involving 165 patients, was only 2.7 (Khanavkar B, etal, Pneumologie, Feb 1998; 52(2):71-6). Also, in a prospective, single-center study of current and former smokers, involving 53 patients who underwent WLB and 39 LIFE-WLB, the latter approach did not improve the detection of squamous metaplasia or dysplasia. Among 105 biopsy specimens classified as abnormal by LIFE-WLB, only 26 (24.8%) exhibited squamous metaplasia or dysplasia on histologic evaluation. Also, of 140 biopsy specimens classified as normal by LIFE-WLB, 34 (24.3%) were histologically abnormal (Kurie JM, etal, JNCI, 1 Jul 1998;90(13):991-5). These findings may imply that LIFE-WLB is less precise in populations with low risk for developing cancer (O'Neil KM and Johnson BE, JNCI, 1 Jul 1998;90 (13):953-5).

A 70-patient pilot NCI-sponsored study (protocol ID: NCI-96-C-0128) of autofluorescence imaging and WLB for the early detection of lung cancer is ongoing to:

- evaluate the efficacy of autofluorescence bronchoscopy using the LIFE system with conventional WLB for the early detection of lung cancer in selected patients with known or suspected bronchogenic carcinoma, completely resected head and neck cancer, and successfully treated early-stage lung cancer
- determine the number of areas of moderate dysplasia, severe dysplasia, and CIS, in patients treated with surgery for lung cancer compared with patients treated with combined modality therapy
- determine the ability of immunohistochemistry to predict whether lesions of moderate to severe dysplasia will progress to cancer

The protocol involves sputum cytology based on a 3-day pooled sputum sample prior to tracheobronchial WLB,

followed by autofluorescence bronchoscopy using LIFE attached to a computerized video camera. Visualized tissue is classified as either normal, abnormal, or suspicious. Abnormal or suspicious tissue is biopsied, as is tissue from 1 or 2 randomly chosen normal sites. Immunohistochemical analysis of the biopsy material is conducted without knowledge of the bronchoscopic results. Patients unable to produce a sputum sample prior to bronchoscopy are required to do so after bronchoscopy.

Biopsy

Biopsy confirms diagnosis, and allows histologic evaluation of the tumor for differential diagnosis regarding the type of lung malignancy. Several approaches to minimize the trauma associated with obtaining a tissue sample are in use, or evaluation. In the case of accessible tumors, biopsy may be performed during fiberoptic bronchoscopy, or bronchial washings may be obtained, or endobronchial needle aspiration (EBNA) may be performed, followed by cytologic assessment of the washings/aspirate. In a prospective comparison of the sensitivity of these approaches, 65 consecutive patients with endobronchial abnormalities identified during bronchoscopy, underwent fiberoptic bronchoscopy with EBNA, bronchial biopsy, and bronchial wash. Malignancy was confirmed in 57 of these patients, diagnosed in 47 (82.4%) by EBNA, 42 (73.7%) by bronchial biopsy, and 36 (63.1%) by bronchial washing. The sensitivity of a combination strategy involving bronchial biopsy and bronchial washings, was 0.82; the addition of EBNA to bronchial biopsy and bronchial washings significantly increased the sensitivity to 0.95. Subset analysis revealed that this strategy was especially useful in cases of submucosal abnormalities. Collection of EBNA, followed by biopsy and washings only if immediate interpretation of EBNA is negative or inadequate, may be the most effective bronchoscopy strategy for evaluating visible endobronchial abnormalities (Govert JA, etal, Cancer, 25 Jun 1999;87(3):129-34).

In a study to evaluate the routine use of percutaneous fine-needle aspiration (FNA) biopsy, among 117 procedures performed on 113 patients between January 1, 1991, and July 1, 1996, 86 (73.5%) masses were diagnosed as malignant while 31 (26.5%) biopsy specimens were either nondiagnostic or negative; 15 (48.4%) of these were subsequently confirmed to be cancerous. The procedure-related complication rate was high; pneumothorax occurred in 64 (54.7%) biopsies, with 35 (29.9%) requiring hospitalization and 24 (20.5%) chest tube insertion. Lesion size correlated with both the diagnostic accuracy and the incidence of pneumothorax. In view of these results, percutaneous transthoracic FNAB should not be used routinely in the assessment of patients with lung masses who are medically fit to withstand surgery and are free of widespread disease, because FNAB does little to modify the course of surgical management in these patients (Odell MJ and Reid KR, Can J Surg, Aug 1999;42(4):297-301).

Among 1,181 lung FNA biopsies performed at Barnes-Jewish Hospital's South and North Campus (St. Louis, MO) over a period of five and nine years, respectively, 108 cases (9%) were cytologically negative. In 46 (43%) cases where histologic correlation was available, 23 were benign, and 19 malignant and in 62 cases without histologic correlation, 35 were benign. Based on this data, the negative predictive value of FNA biopsy was 77% (Afify A and Davila RM, Acta Cytol, Jul-Aug 1999;43(4):601-4).

If the suspected lesion is peripheral, or otherwise inaccessible by bronchoscopy, percutaneous procedures are performed under fluoroscopic, CT, or ultrasound guidance (Subhannachart P, J Med Assoc Thai, Mar 1999;82(3):268-74). Also, video-assisted thoracoscopic surgery (VATS), is increasingly used to obtain samples for diagnosis. CT-guided needle biopsy and VATS, as a combined protocol, is also employed in the diagnosis and treatment of peripheral pulmonary nodules. Open lung biopsy is also an option when other procedures are not feasible. Generally, identifying suspicious lesions for biopsy is an inexact science and, therefore, about 50% of biopsies involve benign disease.

Noninvasive Imaging

Noninvasive modalities used in the diagnosis and evaluation of lung cancer include chest radiography, CT, MR imaging and various nuclear medicine procedures. Chest radiography is the first-line imaging procedure in lung cancer because of its low cost and low radiation dose. Digital chest radiography is rapidly becoming the imaging modality of choice for lung cancer. The addition of computer-assisted diagnosis (CAD) and fractal texture analysis (FTA), further enhance the capabilities of this modality.

***Computed tomography** (CT)* is one of the key modalities in the diagnosis and evaluation of lung cancer. CT is most effective in detecting lung nodules, but it is limited in distinguishing between benign and malignant abnormalities. Currently, the real value of CT in lung cancer is in disease staging and monitoring rather than initial diagnosis of malignancy. Repeat CT, however, may be used to determine growth of solitary pulmonary nodules to diagnose malignancy. Repeat CT was performed in 15 patients with solitary pulmonary nodules (malignant=9 and benign=6) as part of a routine clinical protocol. The final diagnosis was established with surgical resection or follow-up for more than 2 years after an indeterminate biopsy. All 15 *in vivo* nodules were correctly classified with early repeat CT. Preliminary experience suggests that a single repeat CT scan, obtained 30 days after the first scan, can detect growth in tumors as small as 5 mm (Yankelevitz DF, etal, Radiology, Aug 1999;212(2):561-6).

Nuclear medicine is evolving into one of the most promising noninvasive modalities for the diagnosis, staging, restaging and monitoring of treatment progress of lung cancer. One nuclear medicine procedure, positron emission tomography (PET) in combination with ^{18}F-fluoro-2-deoxy-D-glucose (FDG), is particularly effective in distin-

guishing malignant from benign lung lesions (see FO, pp 875-84). FDG PET imaging takes advantage of the increased accumulation of FDG in cancer cells. This modality provides physiologic and metabolic information and may characterize lesions that cannot be defined by CT, accurately stages lung cancer, and provides prognostic information. FDG PET's sensitivity is about 95% and its specificity about 85%, slightly less than its sensitivity, because some inflammatory processes, such as active granulomatous infections, avidly accumulate FDG. The modality's specificity is particularly important because its high negative predictive value prevents unnecessary biopsies (Coleman RE, J Nucl Med 1999 May;40(5):814-20).

Other nuclear medicine procedures such as scintigraphy are mostly used in establishing the scope of disease and in monitoring effects of treatment and progression. Various radiopharmaceuticals have been employed in scintigraphy and immunoscintigraphy, including gallium, MAbs, somatostatin analogs, and lipophilic cations (Chiti A, etal, Eur J Nucl Med, May 1999;26(5):533-55). These approaches will be discussed in upcoming issues of FUTURE ONCOLOGY.

HISTOLOGY AND CLASSIFICATION

Lung cancer is broadly classified as small-cell and non-small cell (Exhibit 4). Mesothelioma, a rare cancer, is often also grouped with lung cancer. Mesothelioma will be the topic of an article in an upcoming issue of FUTURE ONCOLOGY. Non-small cell lung cancer (nsclc) is the most common classification based on treatment outcome rather than morphology because it comprises of many different histologies (Exhibit 4).

Incidence and prevalence of the different types of lung cancer have been changing over the years. Such changes vary with geographical location and may be attributable to socioeconomic and environmental factors. In a study performed in Osaka, Japan, between 1974 and 1993, using data from the population-based cancer registry, lung cancer incidence was classified by histologic type. Cumulative risk for lung cancer increased 1.3-fold from the 1974-77 to 1986-89 period, and then plateaued in the 1990-93 period for both genders. When divided into histologic types, irrespective of gender, cumulative risk for incidence of squamous cell carcinoma was almost constant during the study period, but adenocarcinoma increased up to 1.4-fold; this increase seemed to have reached a plateau recently for males, but not for females. Small cell carcinoma increased steadily up to 1.6- to 1.7-fold, and large cell carcinoma increased over 2-fold in both sexes; however, the estimates fluctuated because of the small number of cases. This study provides further evidence of a relative increase of adenocarcinoma compared to squamous cell carcinoma (Sobue T, etal, Jpn J Cancer Res, Jan 1999;90(1):6-15). A similar trend in increased incidence of adenocarcinoma was observed in the USA.

Most of the common cancers such as breast, colorectal and prostate, may metastasize to the lung. Lung cancer mostly metastasizes to the bone and brain. Other common sites include the lymph nodes and the liver.

SPECIAL REVIEW

ONCOLOGY TRENDS PRODUCT MARKETS — PART II

Worldwide markets of oncology drugs in 1998 were presented in the previous issue of FUTURE ONCOLOGY (pp 1054-55). A detailed discussion of the current status of commercially available drugs belonging to four major cytotoxic families with unique mechanisms of action, i.e., taxanes, platinum-based agents, topoisomerase I inhibitors, and thymidylate synthase inhibitors and related agents, was presented in FO, pp 1025-1039, and 1046-1052. Also, the development status of numerous compounds belonging to these groups, was described. This article discusses the market status and clinical development of other commercially available anticancer agents, and various adjuncts. Much of the information presented below has been culled from the November 1999 version of the NEW MEDICINE Oncology KnowledgeBASE (nm|OK).

HORMONE MODULATING DRUGS

Hormone modulating drugs, primarily used in the treatment of breast and prostate cancer, two of the most common cancers of the developed world, represent a large worldwide market, estimated at $3,358 million in 1998.

Antiestrogens

Current approval of the antiestrogen tamoxifen as a chemopreventive in healthy women at risk for breast cancer, and the ensued controversy (see FO, pp 821-23), has refocused attention on the role of estrogen in breast cancer, and optimal approaches to modulate its action. Tamoxifen carries too high a complication rate that may eventually be deemed unacceptable for healthy women. Also, in many cases, tamoxifen, after an initially successful period, becomes ineffective. It is theorized that this happens because tamoxifen as a selective estrogen receptor (ER) modulator (SERM), is an ERα agonist in some cells and an antagonist in others. It is believed that, over time, resistance emerges because tumors switch from reacting to this SERM as an antagonist, to recognizing it as an agonist.

ER was proven to be an important target in the modulation of estrogen action in breast cancer where it has been shown to be a mitogen (see FO, pp 425-26). ER is a ligand-activated transcription factor belonging to a large family of nuclear hormone receptors. ER mediates the effects of the steroid hormone 17 β-estradiol in both males and females, and is a critical target for the modulation of estrogen. Originally believed to be a single entity, a second receptor, ERβ, discovered in 1996, has changed the way the mechanism of action of estrogen is viewed. This discovery

suggests the existence of two previously unrecognized pathways of estrogen signaling, one via the ERβ subtype in tissues exclusively expressing this subtype, and the other via the formation of heterodimers in tissues expressing both ERα and ERβ subtypes (Kuiper GG and Gustafsson JA, FEBS Lett, 23 Jun 1997;410(1):87-90). ERα and ERβ subtypes differ in the C-terminal ligand binding domain and in the N-terminal transactivation domain. Mechanisms that regulate ERα gene expression and function in breast cancer include alteration of the ER gene, loss of gene expression, alternative splicing of ER RNA, posttranslational modification of the protein, and interaction of ER with other proteins that can modify its function (Ferguson AT and Davidson NE, Crit Rev Oncog 1997;8(1):29-46). The development of ER knockout mice has spurred research in this area. New knowledge about the ER may allow researchers to design more effective inhibitors of estrogen action with fewer side effects.

The most controversial application of antiestrogens is their use as preventatives in cancer-free women considered at risk for breast cancer (see FO p 903-905). Tamoxifen has been approved for this application but raloxifene may become the beneficiary as an off-label choice because of its more favorable side effects profile. Global sales of antiestrogens acting on the ER are estimated at $729.7 million in 1998.

Tamoxifen citrate (Nolvadex; AstraZeneca) has been used for years as a treatment/chemoprevention strategy in resected breast cancer but new life was breathed in this drug's market when, on October 29, 1998, it was also approved as a means of reducing the incidence of breast cancer in healthy women at high risk for the disease. However, this approval is surrounded by controversy because of the drug's serious side effects (see FO, pp 821-22). Nevertheless, in the USA, physicians seem sold on the prevention concept while their European counterparts remain skeptical.

Tamoxifen is marketed by AstraZeneca worldwide, and by Barr Laboratories (Pomona, NY) that purchases the drug from AstraZeneca, and then markets it in the USA under a non-exclusive distribution arrangement entered in 1992 between the two companies. Barr launched its tamoxifen in the USA in November 1993. In 1998 it was disclosed that the Justice Department was investigating the relationship between Barr and AstraZeneca as anti-competitive.

Worldwide AstraZeneca sales of Nolvadex were $287 million in the first half of 1999, up 8% from comparable 1998 levels. These sales include purchases by Barr that resells generic tamoxifen in the USA, but not any mark-up by Barr on such sales. In the USA, Tamoxifen sales by Barr, increased 34% to $86.3 million, compared to $64.6 million in the third quarter ending March 31, 1999. In the fourth quarter of 1999, sales of tamoxifen were $71.8 million, up 41% from $51.1 million reported in the same 1998 period, bringing the six-month 1999 sales to $158.1 million. In fiscal 1999, ended June 30,1999, Barr reported $275.1 million in tamoxifen sales, up 16% from the $236.6 million reported in fiscal 1998. Growth in Barr's tamoxifen sales, particularly in the second half of fiscal year 1999, reflects increased demand in the USA caused by the approval of tamoxifen for the cancer prevention indication. It is estimated that Barr controls 80% of the USA tamoxifen market. Barr, as well as Mylan Laboratories (Pittsburgh, PA), and Pharmachemie (Oradell, NJ), have filed ANDAs for true generic versions of tamoxifen as AstraZeneca's patent is due to expire in the USA in 2002.

Raloxifene (Evista; Lilly) is the only SERM on the market approved and launched in the USA, and in 35 other countries worldwide, for the prevention and treatment of postmenopausal osteoporosis and associated fractures. Worldwide sales in the first quarter of 1999 were $54.6 million, up 63% from the corresponding 1998 period, and $67 million in the second quarter, up 343% from $15 million in the comparable 1998 period, bringing sales in the first half of 1999 to $121.6 million, up 150%. Worldwide sales were $93 million in the third quarter of 1999, up 182% from the $33 million reported in the same 1998 quarter, bringing total revenues for the first nine months of 1999 to $214.6 million. The majority of Evista sales in the USA are off-label, attributed to its perceived benefit in breast cancer prevention, as well as for its approved indications in the treatment and/or prevention of osteoporosis in women.

In December 1998, in a presentation at the 21st San Antonio Breast Cancer Symposium (see FO, pp 823), investigators updated findings reagarding raloxifene's effectiveness in the prevention of breast cancer by combining the data from 12,800 women, 7,700 enrolled in the MORE study (see FO, pp 904-905), and the remainder being healthy postmenopausal women enrolled in osteoporosis prevention trials. None of the women enrolled in these trials were chosen because they had a higher breast cancer risk. In addition to benefits in preventing osteoporosis, results indicated that Evista reduces the incidence of newly diagnosed invasive breast cancer by 63% among postmenopausal women treated for more than three years.

In the MORE study, raloxifene significantly reduced the risk of newly diagnosed breast cancer in osteoporotic postmenopausal women who had no history of breast or endometrial cancer. After a median of 40 months of follow-up, 54 cases of breast cancer had been confirmed, 22 (0.42%) in women assigned to raloxifene and 32 (1.24%) in women on placebo representing a relative risk (RR) of 0.35. The risk reduction was similar for women treated with either the 60 mg (RR=0.31) or 120 mg Evista dose (RR=0.38). RR for the 40 invasive breast cancers was 0.24 and for the 24 invasive ER-positive cancers was 0.10. There was no risk reduction for invasive ER-negative cancers. The relative risk (raloxifene to placebo) of endometrial cancer was 0.76. If two of the 10 total cases diagnosed within one month of randomization are excluded, the est-

imate of relative risk is 0.51. MORE is ongoing to assess the longer-term effects of raloxifene in this cohort (Cauley J, etal, ASCO99, Abs. 328:87a).

Based on the three-year analysis of the MORE study there were additional benefits with Evista therapy. Evista did not increase the risk of endometrial cancer. Women on Evista realized significant reductions in total cholesterol (about 8%), LDL (>12%) and fibrinogen (>12%). Evista did not affect triglyceride and HDL levels. Also, women administered Evista were no more likely to experience vaginal bleeding, a common side effect of conventional hormone replacement therapy, than those on placebo. A rare but serious side effect of Evista is blood clots in the veins, which occurred in clinical trials at a rate similar to that reported for current users of estrogen or hormone replacement therapy. Other commonly reported side effects in clinical trials were hot flashes and leg cramps, although in most women, these events were not considered serious enough to discontinue therapy. Despite these favorable findings, Eli Lilly has been barred from promoting raloxifene for the breast cancer prevention indication, based on a decision by the federal court that ruled that such promotion was unlawful.

Eli Lilly is also conducting the Raloxifene Use for the Heart (RUTH) study, and the Study of Tamoxifen and Raloxifene (STAR). STAR, a landmark breast cancer prevention trial slated to enroll 22,000 women at high risk of breast cancer, is being conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), a NCI-funded clinical trials cooperative group. STAR will determine the safety and effectiveness of Evista in reducing the occurrence of breast cancer in women at high risk. A pilot clinical trial of raloxifene and exemestane was also initiated in September 1999 in patients with breast cancer to determine if the combination will prevent recurrences.

Toremifene

Toremifene (Fareston; Orion) binds to ERs on breast cancer cells, thereby blocking estrogen from further stimulating tumor growth. The chemical structure of toremifene differs from that of tamoxifen by the substitution of a chlorine atom for a hydrogen atom in the 4-position of the ethyl prosthetic group of the molecule. This chlorine atom may prevent the generation of reactive metabolites that bind DNA which are characteristic of tamoxifen metabolism. However, the clinical significance of this modification has not been elucidated.

The Finnish Breast Cancer Group is conducting the first clinical trial of toremifene in an adjuvant setting. A multicenter, randomized, phase III clinical trial is comparing toremifene (40 mg/day) to tamoxifen (20 mg/day) in postmenopausal lymph node-positive breast cancer. Treatment duration is 3 years. As of early 1999, about 1,150 of a planned 1,460 patients had been enrolled. The International Breast Cancer Study Group is also conducting two adjuvant trials evaluating 5 years of toremifene (60 mg/day) versus tamoxifen (20 mg/day). As of early 1999, more than 1,000 patients ere enrolled in these two studies. The efficacy of toremifene is being explored in all of these trials. In the Finnish trial, additional protocols are evaluating treatment side effects, including the formation of DNA adducts in the endometrium and leukocytes, certain ocular problems, thromboembolic events, and subjective side effects. The effects of toremifene on lipid levels and bone density are also being studied. An interim safety analysis, performed in the Finnish study, after 500 patients were enrolled (mean follow-up=18 months), showed no significant differences between toremifene and tamoxifen in terms of efficacy or side effects. Toremifene seems to be well tolerated and may have additional positive effects [Holli K, Oncology (Huntingt), Mar 1998;12(3 Suppl 5):23-7].

According to results from a phase II clinical trial, treatment of castrate men with toremifene does not significantly change serum testosterone levels (Kaufman D, etal, ASCO99, Abs 1322:343a). Also, although cross resistance exists between toremifene and tamoxifen, toremifene (200 mg) administered daily, was shown to be a useful salvage regimen of postmenopausal women with advanced breast cancer whose disease progressed on tamoxifen, and should be considered along with other forms of endocrine therapy in this setting (Gams RA, etal, ASCO99, Abs 504:132a).

Fareston was approved in the USA on May 29, 1997, for the treatment of metastatic breast cancer in postmenopausal women with tumors that were either ER-positive or of unknown ER status. Fareston was originally marketed in the USA by Schering-Plough, but a new deal was struck with Roberts Pharmaceutical (Eatontown, NJ) in September 1999, after the Schering-Plough marketing agreement lapsed in June 1999. Roberts agreed to an upfront payment of about 2.5 times Fareston's 1998 sales, and to make a milestone payment upon FDA approval of the drug for adjuvant therapy in breast cancer. Worldwide sales of Fareston were $2.27 million in the first quarter of 1999, with most sales generated in Japan while no USA sales were reported in this quarter. The drug was awarded orphan drug status in the USA for metastatic breast cancer in September 1991, and for desmoid tumors in August 1993.

Aromatase Inhibitors

Aromatase inhibitors suppress breast cancer by inhibiting aromatase, a key enzyme that catalyzes the synthesis of estrogen (see FO, p 426). Aromatase inhibitors are second-line treatments in cases refractory to ER modulators such as tamoxifen. However, new data on anastrozole, one such inhibitor may result in these drugs being used alone, or in combination with a SERM, as first-line interventions. Also, because steroidal and nonsteroidal aromatase inhibitors bind to different parts of the aromatase enzyme implies that the action of these agents may be synergistic in suppressing plasma estrogen. Thus, use of a steroidal and a nonsteroidal aromatase inhibitors in concert may be one way to improve breast cancer treatment. Furthermore, the fact that breast cancer patients who pro-

Exhibit 4
Epidemiology of Lung Cancer in the USA by Type in 1999

	Incidence (#)	Total (%) Based on Incidence	Total (%) Based on Type
All Types	171,600	100.0	100.0
By Sex			
Male	94,000	54.8	
Female	77,600	45.2	
By Type			
Nsclc (consists of squamous cell carcinoma, adenocarcinoma and large cell lung cancer; 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)	128,700	75.0	100.0
Squamous cell carcinoma	42,900	25.0	33.3
Proximal	34,320		80.0
Peripheral	8,580		20.0
Adenocarcinoma	60,060	35.0	46.7
Large cell carcinoma	25,740	15.0	20.0
Sclc (histologic subtypes include oat cell, hexagonal cell, lymphocytic, and spindle cell; natural histories of these subtypes are virtually identical)	34,320	20.0	100.0
Mediastinal or hilar sclc	32,604		95.0
Peripheral sclc	1,716		5.0
Mixed histology (adenosquamous is most frequent mixed type, but other combinations can occur)	8,580	5.0	100.0
Metastatic Lung Cancer			
Primary lung cancer metastasized to other sites			
Bone	39,125		
Brain	30,500		
Lung cancer metastases from other primary sites	150,000		

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

gressed on nonsteroidal aromatase inhibitors respond to steroidal ones, may indicate that these drugs have different effects, most likely on the aromatization in tumor tissue (Lonning PE, Breast Cancer Res Treat 1998;49 Suppl 1:S45-52; discussion S73-7).

Like SERMs, aromatase inhibitors may also be effective as chemopreventives. For instance, it may be possible to obtain chemopreventive effects without total suppression of aromatase and circulating estrogen levels. An alternative to systemic suppression of estrogen levels is blockage of local estrogen production, potentially achievable with drugs that target a unique transcriptional promoter of aromatase gene expression, I.4, in breast adipose tissue (Kelloff GJ, etal, Cancer Epidemiol Biomarkers Prev, Jan 1998;7(1):65-78).

There are several aromatase inhibitors on the market and in development worldwide. Older drugs such as aminoglutethimide (Cytadren; Novartis) are being replaced by third and fourth generation agents whose indications appear to be broader. Global sales of aromatase inhibitors are estimated at $314.7 million in 1998.

Anastozole (Arimidex; AstraZeneca), a potent triazole derivative third-generation non-steroidal inhibitor of aromatase, was first launched in the UK in 1995 and, subsequently, approved in the USA in January 1996 as second-line treatment of locally advanced breast cancer, refractory to tamoxifen, in postmenopausal women. As of late 1999, Arimidex was available in most European countries, North America, South Africa, Australia and New Zealand.

New data presented at the 10th European Cancer Conference in Vienna, Austria, on September 15, 1999, indicate that anastrozole is at least as effective and as well-tolerated as tamoxifen and, according to the results of one of two international studies reported, it may be even more effective than tamoxifen. A randomized, double-blind, phase III clinical trial that was conducted between May 1996 and December 1998, compared the efficacy and safety of daily anastrozole (1 mg) with daily tamoxifen (20 mg)

as first-line therapy for advanced breast cancer in postmenopausal women. An ongoing open label, randomized, multicenter phase III clinical trial, which commenced in February 1998, is comparing the efficacy and tolerability of two AstraZeneca drugs, the pure antiestrogen fulvestrant (125 mg and 250 mg) with Arimidex (1 mg) in postmenopausal women with advanced breast cancer. The study is to enroll 600 patients and is slated for completion on December 31, 1999. AstraZeneca intends to use the results of this trial to obtain approval for anastrozole as first-line treatment in postmenopausal women with advanced disease.

Exemestane (Aromasin; Pharmacia & Upjohn), an androstenedione derivative, is an orally active irreversible steroidal aromatase inactivator, rather than inhibitor, because it selectively targets and irreversibly binds to the aromatase enzyme (see FO, p 476). Once the binding occurs, estrogen can not be produced by aromatase again. With the inactivation of the aromatase enzyme, exemestane cuts off the supply of estrogen to cancerous cells preventing cell growth. This method of action differs from older aromatase inhibitors because exemestane binds irreversibly to the aromatase enzyme, permanently blocking its function. Exemestane was approved in the UK, its first market, in June 1999. Extension to other European Union (EU) member states via a mutual recognition procedure had begun as of September 1999. In December 1998, an NDA was filed in the USA and, in October 1999, Aromasin was also approved in the USA for treatment of advanced breast cancer in postmenopausal women. Product launch is anticipated in early 2000. Exemestane has been evaluated in a number of phase II clinical trials as second-line monotherapy and, alone or in combination with other drugs, as first-line treatment of refractory metastatic breast cancer in comparison to tamoxifen. The drug is also being evaluated in combination with tamoxifen or raloxifene (see above) in the adjuvant breast cancer setting.

In an ongoing double blind, randomized, phase III clinical trial, to enroll 769 patients, exemestane (25 mg daily) has provided greater benefit than 4 times daily megestrol acetate (40 mg), in terms of survival, tumor reduction and duration of disease stabilization. Median survival of patients treated with exemestane was survival significantly longer than the 28 months associated with megestrol acetate. There was also a significant difference in favor of exemestane in delaying the progression of cancer with median time to progression (TTP) of 20.3 weeks versus 16.6 weeks. Additionally, 15% of patients treated with exemestane experienced at least a 50% or greater reduction in tumor size, or a complete disappearance of all known lesions, compared to 12.4% for megestrol acetate, though this was not statistically significant. Given its potent suppression of estrogen, exemestane use was associated with low-grade nausea (18.4%) and hot flashes (13.4%). The drug was also associated with less undesirable weight gain (7.6% versus 17.1%) than megestrol acetate. Aromasin should not be administered to premenopausal women (Kaufmann M, etal, ASCO99, Abs. 412:109a).

Several trials are ongoing to evaluate subsequent addition of exemestane in the treatment of postmenopausal women with primary breast cancer who have been treated with adjuvant tamoxifen for 2-3 years. A phase III randomized double-blind clinical trial (EORTC-10967), to enroll 500, was open as of March 1998. The trial will be comparing subsequent adjuvant exemestane treatment with further tamoxifen treatment. The study's endpoints are exemestane efficacy, and overall and disease-free survival.

A phase II randomized study (EORTC-10951) of first-line hormonal therapy with exemestane versus tamoxifen, in postmenopausal women with locally recurrent or metastatic breast cancer, has been open since July 1996. A total of 100 patients will be entered if there are at least 3 responses in the first 21 patients treated with exemestane. Patients are randomized to be treated with either oral exemestane or tamoxifen, daily, until disease progression or unacceptable toxicity intervenes. Patients are initially assessed for tumor response at 8 weeks, then every 3 months for 18 months, and at least every 6 months thereafter.

In a phase II USA/European clinical trial, exemestane was evaluated in 241 patients with breast cancer who failed treatment with the nonsteroidal aromatase inhibitors, vorozole (Rivizor; Janssen), anastrozole, letrozole and aminoglutethimide.

Fadrozole (Afema; Novartis), a potent nonsteroidal aromatase inhibitor was launched in 1995 in Japan. A phase III randomized, double-blind, double-dummy, clinical trial that enrolled 96 patients, was designed to assess the efficacy and safety of fadrozole (n=46) as compared to megestrol acetate (n=50) as second-line hormonal treatment in patients with advanced breast cancer. Such parameters as the objective response rate that were 3/46 (7%) for fadrozole and 3/50 (6%) for megestrol acetate, TTP, and survival, were similar in the two arms of the trial. Toxicity was also similar and consisted mainly of edema, hypertension and minor gastrointestinal symptoms. Fadrozole appears to be as active as megestrol acetate as second-line hormonal treatment of advanced breast cancer (Bezwoda WR, etal, Oncology, Sep-Oct 1998;55(5):416-20).

When such parameters as cholesterol, triglyceride, LDL, HDL, very low density lipoprotein (VLDL), antithrombin III, protein C, protein S, and fibrinogen were serially measured in 21 postmenopausal women with advanced breast cancer treated with various doses of fadrozole (1.8 mg/day, n=3; 2.0 mg/day, n=13; 4.0 mg/day, n=5) over 3 months to 24 months (mean=15.8 months), there was no statistically significant change over time in lipid parameters or coagulation factors, over 24 months of therapy. However, an increase in fibrinogen that occurred over time, did reach statistical significance. With the exception of acute phase reactant fibrinogen, this study did not identify an increase in parameters associated with cardiovascular disease in women treated with fadrozole (Costa LA, etal, Cancer 1999 Jan 1;85(1):100-3).

Formestane (Lentaron; Novartis), a potent selective, steroidal inhibitor, was one of the first aromatase inhibitors to enter the clinic as treatment of breast cancer in postmenopausal patients who relapsed while on tamoxifen. It was approved in Europe in 1995 and has since also been launched in Canada. In a multicenter prospective clinical trial, 46 patients with ER-positive (33%), or unknown receptor status (67%) advanced breast cancer, refractory to tamoxifen or that recurred during/after adjuvant tamoxifen, were treated with intramuscular formestane (250 mg) every 14 days. In 56.5% of the patients, the tamoxifen adjuvant treatment had been interrupted more than 2 years before formestane was initiated. The median tamoxifen treatment period had been 23.1 months, and the most frequent metastatic sites were bone (70%), lymph node (24%), lung (17%) and liver (3%). At the 50-week cutoff evaluation of the formestane regimen, there were 6 PR, and disease stabilized in 3, and progressed in 37. The median progression-free interval was 148 days. There were no considerable adverse events; only 3 patients complained of hot flashes and 2 of local itching at the application site. Formestane is a second-line hormonal therapy with a similar survival rate as aminoglutethimide and progestins, but with fewer side effects, consistent with a better QoL (Cervantes G, etal, ASCO99, Abs. 497:130a). In studies involving 240 patients, formestane (250 mg), administered intramuscularly every two weeks, produced CR+PR of 26% while disease stabilized in an additional 25% of patients. In clinical trials of patients not previously exposed to tamoxifen, formestane induced CR+PR in 33% of cases.

Letrozole (Femara; Novartis), a triazole derivative nonsteroidal aromatase inhibitor, was approved in the USA on July 25, 1997, for the treatment of advanced breast cancer in postmenopausal women.

An international, multicenter, double-blind, double-dummy, randomized, multicenter, 2-arm, phase III clinical trial comparing letrozole (2.5 mg) versus tamoxifen (20 mg), as first-line therapy in postmenopausal women with advanced breast cancer was ongoing as of September 1999. The study is to enroll 5,254 patients at 30 centers. Primary endpoints include efficacy, as evaluated by the primary variable of TTP. Secondary endpoints include objective response rate, duration of response, time to treatment failure between the two treatment arms letrozole (2.5 mg) once daily and tamoxifen (20 mg) once daily. A double-blind, double-dummy, randomized, multicenter, three-arm, phase III clinical trial comparing these two drugs and also a combination of letrozole and tamoxifen as first- line therapy in postmenopausal women with advanced breast cancer is also ongoing.

A multicenter clinicobiologic clinical trial, LITMaS (Letrozole Intermediate Tissue Marker Study), designed to assess the potential and feasibility of letrozole for the prevention of breast cancer in postmenopausal women was completed in May 1999. Letrozole is also being evaluated in relapsed ovarian cancer. Chugai is also conducting clinical trials in Japan with letrozole in collaboration with Novartis.

Antiandrogens

Antiandrogens used in the treatment of advanced prostate cancer, and for other conditions such as endometriosis, represent a very large worldwide market, estimated at $2,313.6 million in 1998. In addition to the drugs on the market, several other agents are in late clinical development. One such product, Viadur, a long-term depot formulation of leuprolide developed by Alza (Palo Alto, CA) using the company's DUROS implant technology, has been filed with the FDA. A DUROS implant is an osmotically-driven, miniature pump about the size of a matchstick, constructed of titanium and designed to be inserted under the skin under local anesthesia in an outpatient setting. DUROS allows continuous, steady-state drug delivery at doses ranging from 10 to 2,000 micrograms per day, and may provide therapy from 10 days to more than 12 months. Alza filed an NDA for Viadur in May 1999. However, the company needs to divest Viadur, a direct competitor to Lupron, in order to obtain FTC permission to merge with Abbott Laboratories.

Another luteinizing hormone-releasing hormone (LH-RH) agonist, RL0903, is a synthetic LH-RH under development by Roberts Pharmaceutical. The drug is in phase III clinical trials. In February 1999, in consideration of milestone payments and royalties on future sales, Roberts obtained from Hydro Med Sciences (Cranbury, NJ) exclusive rights to develop and market in the USA, Canada, and Europe, a patented hydrogel implant delivery technology to be incorporated in the phase III development of RL0903.

Another product expected to be filed in late 2000 is abarelix (see FO, pp 836-837), a LH-RH antagonist, under development by Praecis Pharmaceuticals (Cambridge, MA). Praecis licensed the rights to abarelix from Indiana University (Indianapolis, IN). In February 1999 Roche and Praecis terminated their agreement, entered in June 1998, under which Roche had licensed marketing rights in North America, Australia, Japan, and the rest of Asia. In March 1999, Amgen (Thousand Oaks, CA) entered into a collaboration with Praecis under which both companies will develop, and Amgen will commercialize, abarelix in the USA, Canada, Australia, Asia and several other secondary markets. This collaboration will result in approximately $100 million of expense in 1999 for Amgen for clinical development, scale-up and manufacturing, and marketing. Instead of upfront payments and milestones, Praecis opted to negotiate a higher percent of profits, perhaps up to 50%, to be earned when the drug is commercialized.

Based on phase II clinical trials, abarelix, in a depot formulation, appears to be the first sustained-release (SR) LH-RH antagonist that can be administered with once-monthly dosing. A phase II clinical trial, which enrolled 209 patients, assessed the rapidity of achieving castration

(testosterone=50 ng/dL), avoidance of testosterone surge, and maintenance of castration, in patients treated with an SR depot formulation of abarelix as compared to Lupron or Zoladex. Patients were treated with abarelix-depot (100 mg) on days 1 and 15 and then at a dose of 50 mg to 100 mg, every 4 weeks, for the duration of treatment. The 33 patients who served as a prospective concurrent control group were treated with Lupron or Zoladex with or without antiandrogens. At 12 weeks, 159/209 (76%) abarelix-depot patients were castrate by one week compared to none among those treated with Lupron or Zoladex. No patient treated with abarelix-depot experienced a testosterone surge compared to 100% of controls. Comparable rates of castration were seen at the end of weeks 4, 8 and 12. Also, 10/11 (91%) patients with Stage D2 prostate cancer, treated with abarelix-depot achieved an objective response at week 12 (1 CR, 2 PR, 7 SD, 1 PD). Abarelix-depot treatment was well tolerated and rapidly induced medical castration without the initial androgen surge characteristic of Lupron and Zoladex (Garnick MB, etal. ASCO99, Abs. 1233:321a).

A phase III clinical trial was ongoing as of September 1999. After consulting with the FDA, Amgen agreed to increase the number of patients in the abarelix clinical trial program by initiating a new study. A phase III clinical trial was also planned to compare the ability of abarelix in achieving androgen ablation rapidly, avoiding androgen surge, and maintaining the effect of therapy over a period of several months as compared to Lupron, in patients with large prostate glands.

Bicalutamide (Casodex; AstaZeneca), a nonsteroidal antiandrogen, was available, as of June 1999, in more than 70 markets worldwide as treatment of Stage D2 metastatic prostate cancer, in combination with an LH-RH analog. Casodex was also launched in Japan in 1999, and saw a healthy rise of its sales in France. Worldwide sales were $166 million in the first half of 1999, up 44% from the comparable 1998 period.

In June 1999, Casodex was also approved and launched in the UK as monotherapy in locally advanced, nonmetastatic prostate cancer. This approval was based on two open, multicenter, randomized phase III clinical trials (#306 and #307) that enrolled a total of 480 patients with Stage T3/T4 nonmetastatic disease, treated randomly either with oral daily bicalutamide (150 mg) or castration achieved either with bilateral orchiectomy, or with goserelin acetate (3.6 mg). In the combined survival analysis, at median follow-up of 202 and 205 weeks in studies 306 and 307, respectively, with 31% of the cases resulting in death, bicalutamide (150 mg) monotherapy was statistically equivalent to castration; the risk of death from any cause was 7% less with bicalutamide than with castration. In study 306, bicalutamide monotherapy increased time to objective progression and treatment failure, whereas in study 307, TTP, and treatment failure favored castration. Bicalutamide therapy showed significant advantages over castration for both sexual and physical aspects and was well tolerated (Iversen P, etal, Urology, Mar 1998;51(3): 389-96).

Cyproterone acetate (Cyprostat, Androcur; Schering AG) is a mixed antiandrogen used to mitigate side effects (testosterone flare, hot flashes) of hormone ablation therapy (HAT) or orchiectomy, and in refractory disease. The drug had been approved in Europe since 1980 when, in early 1995, it was reported that it was associated with 966 cases of serious hepatotoxicity resulting in 33 deaths in the UK, mostly in elderly patients on long-term therapy. In view of there reports, it is currently recommended that cyproterone be used for only short-term therapy in patients unresponsive to other agents.

Flutamide (Eulexin; Schering-Plough), a nonsteroidal antiandrogen, exerts its action by inhibiting androgen uptake and/or nuclear binding of androgen in target tissues. Flutamide was approved for use, in combination with LH-RH agonists and radiation therapy, in the treatment of advanced prostate cancer. In June 1996 a capsule form of Eulexin was approved in the USA for the treatment of locally confined Stage B2-C carcinoma of the prostate, in combination with LH-RH agonists. In September 1999, in consultation with the FDA, Schering-Plough sent a letter to physicians warning about potential liver toxicity with Eulexin. A boxed warning was also added to the label. In some patients, hepatic injury was reversible after prompt discontinuation of therapy.

Goserelin (Zoladex; Zeneca Pharmaceuticals), a synthetic decapeptide analog of LH-RH that reduces testosterone secretion, has been approved in the USA as palliative treatment of advanced prostate and breast cancer, and for the treatment of endometriosis. A new formulation of Zoladex a 10.8-mg implant administered every 3 months, was approved by the FDA in July 1996 for the palliative treatment of advanced prostate cancer. On July 27, 1998, Zoladex was approved in the USA for the management of locally confined Stage T2b-T4 (Stage B2-C) prostate cancer, in combination with flutamide.

Currently, the drug is being evaluated as part of a treatment regimen in early, resected breast cancer. A prospective randomized phase III clinical trial that began in 1990, being conducted by the Austrian Breast Cancer Study Group to test the efficacy of the endocrine combination of tamoxifen and goserelin compared with chemotherapy, enrolled 1,045 patients with estrogen and/or progesterone receptor-positive, radically operated breast cancer, representing 28% of all suitable patients in Austria. Patients were randomly assigned to IV cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2) and 5-FU (600 mg/m^2) on days 1 and 8, for 6 cycles, or subcutaneous goserelin (3.6 mg), every 28 days, for 3 years, and oral tamoxifen (20 mg) for 5 years. Among the enrollees, 51% had a T1 lesion, 46% node-negative disease and 58% had undergone breast-conserving surgery. The median follow-up was 42 months. Within this period, 157 patients experienced a recurrence

and 56 died. Although recurrence-free survival (RFS) was longer with the combination endocrine treatment, overall survival was not statistically different. According to multivariate analysis, the prognostic factors for RFS were age, tumor stage, nodal stage and type of therapy, and those for overall survival were tumor and nodal stage. Patients who developed amenorrhea following cyclophosphamide, methotrexate and 5-FU had a significantly better RFS and overall survival. Regarding side effects, 20.9% of all patients undergoing endocrine treatment terminated therapy prematurely because of such effects and only 72% in the cyclophosphamide, methotrexate and 5-FU group were treated with the full dose. Although premature, these data indicate a significant benefit of endocrine therapy as compared to standard chemotherapy (Jakesz R, etal, ASCO99, Abs 250:67a).

A randomized phase III clinical trial was initiated in the late 1980s by four trial groups using an essentially common protocol. After primary surgery, premenopausal patients with early-stage disease were randomized to tamoxifen for 2 years, Zoladex administered in 26 monthly subcutaneous injections, tamoxifen plus Zoladex, or to no adjuvant endocrine therapy. Alternatively, patients were treated with tamoxifen or not, and were randomized just for Zoladex. The study protocol permitted use of elective adjuvant chemotherapy in selected patients according to predetermined routines at each participating center. A total of 2,631 patients were included of whom 56% were node-negative. Adjuvant chemotherapy was used in 43%. ER status was available in 1,577 patients (60%).

At a median follow-up of 4.3 years the total number of first events in the trial was 591 (44.9) of which 261 (20.0%) were among patients treated with Zoladex, and 330 (24.9%) among those who were not administered Zoladex. This benefit was statistically significant and was most pronounced among those classified as ER-positive. The benefit with Zoladex appeared to be somewhat less among those treated with concurrent adjuvant tamoxifen or adjuvant chemotherapy, but the differences compared to patients who were not treated with such concurrent approaches were not statistically significant. The total number of deaths in the trial was 305, 140 (10.7%) occurring in patients allocated to Zoladex, and 165 (12.4%) among those not treated with Zoladex. This survival difference favoring the Zoladex-allocated patients was not statistically significant. This trial showed that medical castration with Zoladex, for two years, in premenopausal, ER-positive breast cancer patients, produces a statistically significant benefit in terms of event-free survival. A benefit with Zoladex was observed irrespective of the use of concurrent adjuvant tamoxifen or adjuvant chemotherapy (Rutqvist LE, ASCO99, Abs 251:67a).

Zoladex monotherapy, however, was linked to a relatively high development of second primary tumors. Among 81 premenopausal women treated with Zoladex monotherapy for two years after resection, 7/81 (8.6%) developed-primary tumors (contralateral breast=1, CML=2, Hodgkin's lymphoma=1, kidney=1, sclc=1, and ovarian=1). Any link between treatment and second primary tumors remains obscure (deMatteis A, etal, ECCO10, Abs. 819:S209).

Leuprolide acetate (Lupron; TAP Holdings), an LH-RH analog, is indicated for the palliative treatment of advanced prostate cancer, among other non-cancer applications. Lupron is available as 1-, 3- and 4-depot formulations. It is marketed in the USA by TAP (Deerfield, IL), the Takeda-Abbott joint venture, and by Abbott abroad except Japan where it is marketed by Takeda.

Nilutamide (Nilandron; Aventis) blocks the effects of testosterone at the androgen receptor level, and also interacts with the androgen receptor preventing a normal androgenic response. The drug was approved on September 19, 1996, for use in combination with surgical castration for the treatment of Stage D2 metastatic prostate cancer.

OTHER CHEMOTHERAPEUTICS

Alitretinoin

Alitretinoin (Panretin; Ligand Pharmaceuticals) is a 9-cis retinoic acid (9cRA), a derivative of vitamin A, a non-peptide regulatory hormone which influences cell growth, differentiation, apoptosis and embryonic development. It is a panagonist that binds all six known retinoid receptors with high affinity, and a natural hormone ligand for the retinoid acid receptor (RAR) and retinoid X receptor (RXR) subfamilies. Panretin, in a gel formulation, was approved and launched in the USA in February 1999 as a topical treatment of cutaneous lesions of AIDS-related Kaposi's sarcoma (KS). Panretin Gel was awarded orphan drug status for the treatment of cutaneous KS lesions in March 1998.

Approval in the USA was based on two multicenter, randomized, double-blind, vehicle-controlled phase III clinical trials involving 402 patients in the USA and abroad. One trial was conducted internationally at 30 sites in Europe, Australia and the USA, and the other was conducted at 35 sites in North America. Ligand had filed an NDA in May 1998 for this indication which was accepted for priority review by the FDA. In November 1998, ODAC voted to recommend approval for Panretin Gel for this indication. However, ODAC did not recommend Panretin as first-line treatment leaving it up to the physician to decide how a patient should be treated. Patients apply Panretin Gel themselves twice daily.

According to final results of the 134-patient international, phase III clinical trial which was initiated in the third quarter of 1996 and reported in March 1998, among 62 evaluable patients treated with Panretin gel, 23 (37.1%) experienced CR or PR, compared to 5 (6.9%) of 72 patients on placebo. The protocol involved twice-daily application of topical Panretin gel for 12 weeks. Median TTP was 29 days. Upon re-evaluation of this trial's results, ODAC lowered the response rate to 19% with Panretin compared to 4% with placebo.

In February 1999, Ligand submitted an MAA to the EMEA via the centralized procedure, for Panretin for the topical treatment of cutaneous lesions of patients with AIDS-related KS, also based on these two clinical trials. In October 1998, Ligand filed a NDS with the Health Protection Branch (HPB) of Canada and in June 1999, HPB granted a Notice of Compliance for Panretin gel for the above indication.

Anthracyclines

Several newer drugs as well as novel formulations have been commercialized that promise to reduce the side effects of current anthracycline-based regimens.

Daunorubicin HCl, in a new ready-to-use solution (5 mg/ml, 4 ml) which can be used immediately as an IV infusion to prevent reconstitution errors, marketed by Bedford Laboratories (Bedford, Ohio), was approved on January 30, 1998. Daunorubicin is indicated for use in combination with other approved anticancer drugs for remission induction in adult acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) and for remission induction in acute lymphocytic leukemia (ALL) of children and adults.

Epirubicin [Ellence (USA), Farmorubicin (outside the USA); Pharmacia & Upjohn], a second generation anthracycline antibiotic, was approved in the USA in September 1999, and launched in October 1999, as a component of adjuvant therapy in patients with evidence of axillary nodal tumor involvement (Stage II/III), following resection of primary breast cancer. However, ODAC declined to recommend the drug for a broader indication in metastatic breast cancer which was also rejected by the FDA. Ellence was also granted orphan drug status on Sepember 14, 1999, for the approved breast cancer indication.

A randomized phase III clinical trial was conducted from January 1990 to May 1998 involving 1,195 patients. The study analyzed whether the therapeutic gain with anthracycline combinations in advanced breast cancer could be translated to the adjuvant setting in 3 subgroups of patients:

- Group A: premenopausal women with node-negative, Grade 2-3 tumors
- Group B: premenopausal women with node-positive, receptor-negative or unknown receptor status tumors
- Group C: postmenopausal women with node-positive, receptor negative tumors

Following primary local treatment, patients were randomized to either a CMF regimen consisting of cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and 5-FU (600mg/m^2), or to a CEF regimen consisting of cyclophosphamide, epirubicin (60 mg/m^2), and 5-FU, or to CMF plus oral pamidronate (150 mg) twice daily for 4 years, or to CEF plus the same pamidronate schedule. Both regimens were administered IV on day 1, every 3 weeks, for 9 cycles. As of October 1998, at a median follow-up of 61 months, the 6-year survival with CMF and CEF was 83% versus 93% in group A (n=343), 60% versus 66% in group B (n=531) and 48% versus 50% in group C (n=321). In the combined premenopausal groups (groups A+B) survival was 69% versus 76%. Hematologic toxicities were evenly distributed in the two groups. Alopecia and amenorrhoea occurred more frequently in the CEF group (87% versus 7%, and 80% versus 60%, respectively) and 95% of the scheduled CMF dose was administered compared with 96% of scheduled CEF. According to these results, adjuvant CEF is superior to CMF in terms of survival in premenopausal patients with intermediate and high risk breast cancer, but does not make a difference in postmenopausal patients with high-risk breast cancer (Henning T, etal. ASCO99, Abs. 254:68a).

The drug has been available overseas for many years for a variety of other indications including ovarian cancer, malignant melanoma and NHL. A number of clinical trials are ongoing using epirubicin in place of doxorubicin in combination regimens for the treatment of a variety of tumors.

Liposomal daunorubicin citrate (DaunoXome; Gilead Sciences), was approved in the USA on April 8, 1996 for first-line treatment of advanced AIDS-related KS. As of early 1999 the drug was marketed in 22 countries worldwide. The drug is also being evaluated in refractory acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), low- and intermediate-grade refractory non-Hodgkin's lymphoma (NHL), metastatic breast cancer, mesothelioma, advanced multiple myeloma, etc.

Liposomal doxorubicin is being developed to improve the pharmacokinetic and safety profile of free doxorubicin and enhance its efficacy. Liposomal formulations may allow administration of higher doses and overcome resistance mediated by MDR1. Preclinical studies have shown a clear superiority of liposomal over free doxorubicin against various xenografts in nude mice. Currently two products, Doxil, that has been approved by the FDA and launched in many markets, and Evacet, that is still trying to gain approval, are addressing a variety of cancer indications.

Doxil (USA)/Caelyx (abroad), a formulation of doxorubicin encapsulated in long-circulating Stealth liposomes (see FO, pp 554 and 557), originally developed by Sequus Pharmaceuticals that was subsequently acquired by Alza, was approved on December 29, 1998 for the treatment of AIDS-related KS in patients whose disease had progressed on prior combination chemotherapy, or in patients who are intolerant to such therapy. Subsequently, on June 28, 1999, Doxil also gained supplemental approval for the treatment of metastatic ovarian cancer refractory to both paclitaxel- and platinum-based chemotherapy regimens.

For the ovarian cancer indication, Doxil was recommended for approval by ODAC based on three phase II clinical trials, and an interim analysis of a phase III randomized clinical trial. The overall response rate with Doxil in refractory ovarian cancer was 13.8%. There was only one CR among 27 PR but in eight PR cases there was a 100% reduction in tumor size although CT scans contained ambiguous shadows that were suggestive of remaining

tumor. TTP among responders was 15.9 weeks, somewhat better than non-responders. The most common side effects reported with Doxil therapy include neutropenia, anemia, nausea, hand-foot syndrome (Palmar-plantar erythrodysesthesia or PPE), stomatitis, vomiting, diarrhea, constipation, appetite loss, tiredness, weakness, rash and mild hair loss. Some patients experienced infusion-related and skin reactions and PPE was moderate to severe in 17% of patients. Also, some patients suffered severe cardiac side effects. Phase III clinical trials are in progress.

Doxil is being evaluated in phase II clinical trials in advanced sclc and, in combination with paclitaxel, in metastatic breast cancer. Phase II clinical trials have been completed in advanced soft tissue sarcoma where the drug was investigated as first line therapy; in mesothelioma; in the neoadjuvant setting in squamous cell carcinoma of the head and neck; as second-line monotherapy in advanced breast cancer; and in combination with paclitaxel (Taxol; Bristol-Myers Squibb) in the treatment of epithelial ovarian carcinoma, and metastatic breast cancer. Doxil was also compared with topotecan (Hycamtin; SmithKline Beecham) and paclitaxel in platinum-refractory ovarian cancer.

Evacet, being developed by The Liposome Company (TLC; Princeton, NJ), failed, to gain ODAC recommendation as first-line treatment of metastatic breast cancer in combination with cyclophosphamide. TLC filed an NDA in December 1998 based on a pivotal randomized, controlled clinical trial involving 297 patients with metastatic breast cancer who were treated with cyclophosphamide (600 mg/m^2) and Evacet (60 mg/m^2) (n=142), or doxorubicin (n=154), every 3 weeks. Patients in each arm had been treated with prior adjuvant doxorubicin. The response rates for both arms were 43%; PFS was 5.2 months versus 5.5 months, and duration of survival was 21.2 months versus 16.4 months for Evacet and doxorubicin, respectively. Grade 3/4 toxicities were CHF (0%), diarrhea (2%), and stomatitis/mucositis (4%), and CHF (4%), diarrhea (7%), and stomatitis/mucositis (16%) in the Evacet and doxorubicin groups, respectively, and Grade 4 neutropenia was observed in 62% and 75% of patients, respectively. CHF occurred in 6 patients on the doxorubicin arm and in no patients on the Evacet arm, and there was significantly less Grade 4 neutropenia on the Evacet arm. There was one case of palmar-plantar erythrodysesthesia on the doxorubicin arm but none on the Evacet arm. Less diarrhea and mucositis/stomatitis were also observed in the Evacet group. Combination therapy with Evacet is as effective as doxorubicin in metastatic breast cancer, but it is significantly less cardiotoxic and myelosuppressive (Batist G, etal, ASCO99, Abs. 486:127a).

TLC's Evacet NDA was accepted by the FDA in February 1999, but, in September 1999, ODAC voted 9-2 against recommending Evacet for approval. Members of ODAC objected to the fact that response rather than survival rates were used as the endpoint, and submitted that the drug's true efficacy could not be assessed because it was evaluated in combination with cyclophosphamide. However, the response endpoint had been approved by the FDA prior to the NDA submission because it appeared that Evacet exhibited a lower cardiotoxicity than free doxorubicin which was demonstrated in the clinical evaluation.

In October 1998, based on data from three phase III clinical trials, presented at the European Society of Medical Oncology (ESMO), response rates, PFS, and median overall survival rates were equivalent for Evacet and doxorubicin, and for Evacet and epirubicin, while Evacet proved to be significantly less cardiotoxic than doxorubicin. At that time, three phase III trials had been conducted, a single-agent clinical trial (n=224) in which Evacet was compared directly to doxorubicin, the pivotal combination trial (n=297) described above, and a European combination trial (n=160) in which Evacet was compared to epirubicin when each was administered in combination with cyclophosphamide. The reduction in cardiotoxicity was statistically significantly in favor of Evacet in the two phase III studies involving doxorubicin; 26% of the patients enrolled in the single-agent study treated with doxorubicin experienced a cardiac event versus 12% treated with Evacet, and 26% of the patients enrolled in the combination study treated with doxorubicin plus cyclophosphamide experienced a cardiac event versus 9% treated with Evacet plus cyclophosphamide. In the single-agent study, 8 patients treated with doxorubicin developed CHF, compared with one patient treated with Evacet, while in the combination study, 5 patients treated with doxorubicin plus cyclophosphamide developed CHF compared to no patients in the Evacet plus cyclophosphamide group. Also, there was significantly less severe nausea and vomiting in the single-agent clinical trial with Evacet, compared to doxorubicin, and a trend for less severe ulceration of the lining of the gullet.

In a randomized European controlled trial, conducted to demonstrate the efficacy of Evacet, 80 patients with breast cancer were administered Evacet (75 mg/m^2) and 80 epirubicin (75 mg/m^2), in both cases as a one-hour IV infusion, in combination with cyclophosphamide (600 mg/m^2). Treatment was repeated every 3 weeks for 4 cycles, and continued for 8 cycles in responders. The primary endpoint was the proportion of patients attaining a tumor response (CR and PR) of at least 6 weeks duration. Patients who had been treated with previous anthracycline therapy were excluded. Response to treatment was as follows:

Parameters	Evacet	Epirubicin
Response rate (%)	46.0	39.0
Progression-free survival (months)	7.6	6.0
Stable disease (%)	31.0	33.0
Survival (median in months)	>18.5	16.0
Grade 3-4 neutropenia (%)	47.0	36.0
Any all grades nausea/vomiting (%)	82.0	81.0
Any mucositis (%)	33.0	9.0

These results indicate that both Evacet and epirubicin are efficacious and well tolerated when combined with cyclophosphamide, in palliative therapy of metastatic breast cancer, with TTP being significantly longer in patients treated with Evacet (Erdkamp F, etal, ASCO99, Abs. 459:121a). This study was closed before reaching the original enrollment goal of 288.

However, the single-agent clinical trial (n=224) in which Evacet was compared directly to doxorubicin, produced some disturbing results regarding survival. Although patients on doxorubicin were 3.5 times more likely to develop cardiac events, median survival was higher in this group, 20 months versus 14 months. Unfortunately TLC stopped the trial early and could not explain both a low response rate (26% versus the expected 60%) and the lower survival rate. Also, the FDA did not accept results of the European study comparing Evacet plus cyclophosphamide to epirubicin plus cyclophosphamide because the two anthracyclines are not equivalent comparators. Epirubicin is not approved in the USA in the treatment of metastatic breast cancer.

In October 1999 TLC withdrew its NDA but announced plans to resubmit it by the end of 1999 after consulting with the FDA to address the issues raised by ODAC. Also, in July 1999, an NDS was filed for marketing clearance in Canada and an MAA with the EMEA for marketing clearance in the EU for this indication. In addition, Evacet in combination with Herceptin, is being evaluated in a phase II clinical trial as first-line treatment of metastatic or locally advanced breast cancer.

Mitoxantrone (Novantrone; Immunex), a drug similar in action to doxorubicin, was approved for an additional indication on November 13, 1996, for use in combination with corticosteroids as initial chemotherapy for the treatment of patients with pain related to advanced, hormone-refractory prostate cancer. Novantrone was previously indicated for use in combination with other approved drugs in the initial therapy of adult acute nonlymphocytic leukemia (ANLL). Worldwide sales were $10.8 million in the first quarter of 1999, down 19% from 1998 levels. Second quarter 1999 sales were $11.1 million, compared to $13.1 million in the comparable 1998 quarter, and third quarter sales were $11.2 million, down from $13 million reported in the comparable 1998 period. In the first nine months of 1999, total sales were $33.1 million.

Valrubicin (AD32, Valstar; Anthra Pharmaceuticals), a lipophilic anthracycline, was approved on September 25, 1998 for intravesical therapy in BCG-refractory carcinoma *in situ* (CIS) of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality. The drug is also under clinical investigation in the treatment of papillary tumors of the bladder, and intraperitoneal treatment of ovarian cancer.

In the USA, valrubicin is being marketed by Medeva (Rochester, NY) that launched the drug in February 1999 (see FO, pp 570-71). The drug is marketed by Nycomed Pharma (Oslo, Norway) in Europe, except Spain and Portugal, where it is marketed by Almirall Prodesfarma (Barcelona, Spain). In June 1999, Paladin (Montreal, Canada) acquired the exclusive Canadian license for Valstar in return for a $1.0 million equity investment in Anthra Pharmaceuticals. In addition, Paladin will make milestone payments totaling $2.25 million based upon the achievement of certain sales targets. Valstar was awarded orphan drug status in the USA in May 1994 for treatment of CIS of the urinary bladder.

Busulfan

Busulfan (Busulfex; Orphan Medical), as an injectable formulation, was approved in the USA on February 4, 1999 for use in combination with cyclophosphamide as a conditioning regiment prior to allogeneic hematopoietic progenitor cell transplantation for CML. The drug was approved in Canada in August 1999. In October 1999, Orphan Medical (Minnetonka, MN) signed a definitive agreement with Pierre Fabré Medicament (Castres, France) that granted the latter exclusive rights to market and distribute Busulfex in 21 European countries, as well as Argentina, and South Africa. Pierre Fabré will begin the registration process of Busulfex in its territories based on Orphan Medical's existing filings. After obtaining the required European regulatory approvals, Pierre Fabré's oncology division will market Busulfex using 75 marketing and sales personnel.

Carmustine Wafer

Carmustine (BCNU) wafer (Gliadel; Guilford Pharmaceuticals), an implantable system that delivers time-released BCNU into the cavity created by surgical removal of glioblastoma multiforme (GBM), was approved on September 23, 1996, for use in conjunction with surgery to prolong survival in resectable recurrent GBM. It was launched in the USA in 1997, and approved in France in December 1998, and subsequently in Luxembourg and Ireland, and in Germany in August 1999. It has been approved but not yet launched in Brazil, Argentina and Canada. A higher dose version, 20% BCNU versus the 3.85% currently approved, is also being evaluated (see FO, pp 710-12).

Gliadel is also in phase III clinical trials as first-line treatment of GBM with a one-year survival rate as the primary endpoint, and PFS, safety and QoL as secondary criteria. As of October 1999, these trials enrolled all 200 targeted patients from 42 sites in 14 countries (USA, Europe, Australia and New-Zealand). The rationale for this indication is based on an earlier randomized, placebo-controlled phase III clinical trial that was conducted in Sweden in 1992. In that trial the 1-year survival of 32 patients treated with carmustine wafer was 63% compared to 19% of controls. Side effects included healing problems, brain edema and local infections, consistent with those encountered in the trials of recurrent GBM. In the current phase III clinical

trial, maximal tumor debulking and histologic confirmation is followed by placement of up to 8 implants of Gliadel or placebo, depending on the size of the resection. Patients are also treated with a standard course of limited field radiation therapy (55 Gy to 60 Gy), starting 14 to 30 days after surgery. As of November 30, 1998, 7/127 (5.5%) patients had died. Serious adverse events included convulsions and headaches (Westphal M, etal, ASCO99, Abs. 594:155a).

Gliadel is marketed worldwide, excluding the Scandinavian countries and Japan, by Aventis. As of January 1999, Aventis and Guilford amended their agreement to share the costs of the multinational phase III clinical trials described above, subject to an aggregate cap of $3 million for Guilford. The companies will split equally certain international regulatory milestones for approvals of Gliadel in Australia, France, Germany, Italy, Spain and the UK. In August 1999, Guilford received a $2.5 million milestone payment from Aventis for regulatory developments relating to Gliadel in Germany.

Etoposide Phosphate

Etoposide phosphate (Etopophos; Bristol-Myers Squibb) was approved on May 17, 1996 for the management of small cell lung cancer (sclc), and as first-line treatment of testicular tumors, and for refractory testicular tumors, in combination with other approved chemotherapeutic agents. The drug is in numerous clinical trials in combination with various chemotherapeutics for many cancer indications.

Flutarabine

Flutarabine (Fludara; Berlex), an antimetabolite, has been approved in an oral and IV formulation in the USA and Europe. In April 1989, Berlex Laboratories (Montville, NJ) obtained orphan drug status for Fludara in the treatment of CLL and NHL. Flutarabine was recommended for approval in Japan in July 1999.

Gemcitabine

Gemcitabine (Gemzar; Eli Lilly), a synthetic pyrimidine nucleoside, was originally approved in the USA on May 16, 1996, as first-line treatment for locally advanced (nonresectable Stage II or III), or metastatic (Stage IV) pancreatic cancer, and for second-line treatment of pancreatic cancer previously treated with 5-FU. Subsequently, gemcitabine was also approved in the USA on August 26, 1998, in combination with cisplatin for first-line treatment of inoperable, locally advanced (Stage IIIa or IIIb), or metastatic (Stage IV) nsclc. As of early 1999, the drug was approved in 65 countries worldwide.

Actually, gemcitabine has proven a very versatile agent, currently being investigated in numerous combination protocols for a variety of cancer indications, and has been approved overseas for the treatment of ovarian cancer. Eli Lilly has also filed an sNDA for Gemzar in the treatment of bladder cancer, in combination with cisplatin. Response rates in phase II clinical trials of gemcitabine, in combination with cisplatin, in metastatic bladder cancer, have been possibly equivalent to the standard MVAC regimen consisting of methotrexate, vinblastine, doxorubicin and cisplatin. A phase III clinical trial with this combination has been completed. Gemcitabine may also be considered as reasonable monotherapy in patients with TCC with mild renal failure or significant underlying medical conditions. Complete responses have been achieved with gemcitabine monotherapy, even in patients >70 years-of-age (Vogelzang NJ and Stadler WM, Urology 1999 Feb;53(2): 243-50). Gemzar is also being investigated in ovarian and breast cancer.

The broad utility of gemcitabine is illustrated in the growth of its worldwide market. Worldwide sales were $114.4 million in the first quarter of 1999, more than twice the 1998 level, $87 million in the second quarter of 1999, up 1%, and $119 million in the third quarter, up 72%, resulting in 9-month sales of $320 million, up 51% from the comparable 1998 period.

Liposomal Cytarabine

Cytarabine liposomal injection [DepoCyt (USA), Savedar; DepoTech], a sustained-release formulation of cytarabine (see FO, pp 717-8) obtained accelerated approval on April 1, 1999 for intrathecal treatment of lymphomatous meningitis, based on demonstration of an increased CR rate compared to unencapsulated cytarabine. However, no controlled trials were conducted that demonstrate a clinical benefit resulting from this treatment, such as improvement in disease-related symptoms, or increased TTP, or increased survival. DepoCyt is marketed in USA by Chiron (Emeryville, CA). SkyPharma (London, UK) that acquired DepoTech (San Diego, CA) in 1998, will receive 50% of Chiron's profits from USA sales instead of royalties.

According to results from the first randomized controlled trial ever performed for any drug in patients with lymphomatous meningitis, it was demonstrated that DepoCyt's CSF pharmacokinetic profile results in a higher response rate and improved QoL. In this phase III clinical trial, performed by the DepoCyt Consortium between March 1994 and 1998, 14 lymphoma patients with a positive CSF cytology were randomized to DepoCyt (50 mg), administered every 2 weeks, or free ara-C (50 mg), administered twice weekly for one month; patients on the DepoCyt arm were treated with 1/4 as many injections as those on the ara-C arm. Responders were treated with 3 months of consolidation and 4 months of maintenance therapy. Oral dexamethasone (4 mg) was administered, twice daily on days 1-5 of each cycle (a cycle was defined on the basis of the DepoCyt dosing interval).

Although the trial was randomized, providing a concurrently treated cohort, it was not powered to detect statistically significant differences. Response rate, defined as conversion from a positive to negative CSF cytology at all sites known to be positive, was 41% for DepoCyt and 6% for ara-C. Patients on the DepoCyt arm stayed on the study for

a total of 74 cycles (median 5.5/patient) compared to 44.5 cycles (2.5/patient) for those on the ara-C arm. All patients on DepoCyt, but only 7/13 (54%) on ara-C, completed the planned one month induction. Time to neurologic progression trended in favor of DepoCyt (median 78.5 days versus 42 days), as did survival (median 99.5 days versus 63 days), but neither reached statistical significance. At the end of induction, the Karnofsky score improved in patients on DepoCyt but worsened in those on ara-C. The major adverse events on both arms were headache and arachnoiditis. When drug-related, these were largely low-grade, transient, reversible, and easily managed. Grade 3 headache occurred on 5% of DepoCyt cycles and 0% of ara-C cycles; Grade 3 or 4 arachnoiditis occurred on 8% of DepoCyt cycles, and 7% of ara-C cycles. The fact that DepoCyt can be administered once every 2 weeks was of substantial benefit. Also, the higher response rate may indicate better activity against the meningeal component of the disease (Howell SB, etal, ASCO99, Abs. 34:10a).

In May 1998, the FDA sent a non-approvable letter to DepoTech regarding its NDA for DepoCyt as a treatment for neoplastic meningitis arising from solid tumors. In January 1998, a MAA for Savedar, the European trade name for DepoCyt, was submitted to the EMEA for approval in the EU but, on October 16, 1998, DepoTech withdrew this MAA based on an assessment that additional clinical data would be required to supplement the filing. SkyPharma is conducting phase IV clinical trials for this indication that obtained orphan drug status in the USA in June 1993. The drug is also being investigated in phase III clinical trials in neoplastic meningitis arising from leukemia.

Methoxsalen

Methoxsalen (Uvadex; Therakos) was approved on February 25, 1999 for use with the Uvar photopheresis system in the palliative treatment of skin manifestations of cutaneous T-cell lymphoma (CTCL) unresponsive to other forms of treatment. It is available in a sterile solution of 20 mg/ml.

Porfimer Sodium

Porfimer sodium (Photofrin; QLT Phototherapeutics), a semisynthetic porphyrin compound acting as a photosensitizer, was originally approved in the USA in December 1995 for the palliation of refractory adenocarcinoma of the distal esophagus. The drug was approved on December 22, 1998 for the additional indication for reduction of obstruction and palliation of symptoms of completely or partially obstructing endobronchial nsclc and, on January 9, 1998, for treatment of microinvasive endobronchial nsclc not treatable by surgery and radiotherapy. Photofrin has also been approved for these and other indications in overseas markets and is being evaluated for various indications in clinical trials (see FO pp 709, 648, 918). However, despite approval of new indications and expansion of facilities offering Photofrin-based PDT from 85 in 1997 to 121 in 1998, revenues have been disappointing.

Temozolomide

Temozolomide [Temodar (USA), Temodal; Schering-Plough], an imidazotetrazine analog (see FO, p 736), was granted accelerated approval on August 11, 1999 by the FDA for treatment of refractory adult anaplastic astrocytoma (AA) in patients at first relapse whose disease progressed on a nitrosourea- and procarbazine-containing drug regimen. The drug is available in capsules (5 mg, 20 mg, 100 mg, 250 mg). At the same time marketing authorization for the drug in AA was granted in the EU.

A worldwide multicenter phase II clinical trial of temozolomide was conducted in 162 patients with recurrent AA who had been treated with previous radiation therapy. Nitrosourea-based chemotherapy had been previously administered to 60% of patients in the study. Patients were treated with temozolomide capsules for 5 consecutive days in each 28-day treatment cycle. The primary study endpoint was PFS at 6 months; secondary endpoints included objective tumor response and overall survival. PFS at 6 months and 12 months was 46% and 24%, respectively. Median PFS was 5.4 months, and median overall survival was 13.6 months. The overall tumor response rate was 35% (8% CR and 27% PR) and disease stabilized in 27%. CR was defined as complete resolution of tumor, and PR as a decrease in tumor area of more than 50%, for two consecutive months, as measured by gadolinium-enhanced MR imaging as well as clinical improvement (Prados M, etal, ASCO99, Abs. 533:139a).

In January 1999, Temodal was also approved in all 15 EU member states for the treatment of GBM that progressed or recurred after standard therapy. In the USA, Schering-Plough filed an NDA for temozolomide for the treatment of recurrent malignant glioma in August 1998 but, in January 1999, ODAC voted against approval of Temodal for this indication, and for advanced metastatic malignant melanoma. The company has also filed for first-line treatment of advanced metastatic melanoma in the EU.

In a multicenter phase II clinical trial, 225 patients with recurrent GBM were randomized to be treated with either temozolomide capsules for 5 consecutive days, in each 28-day treatment cycle, or oral procarbazine for 28 consecutive days, in each 56-day treatment cycles. The primary endpoint of the study was PFS at 6 months, with secondary endpoints including objective tumor response and overall survival. PFS at 6 months was higher in the temozolomide group as compared to the procarbazine group (21% versus 8%). Both median PFS (2.89 versus 1.88 months) and 6-month overall survival (60% versus 44%) were higher in the temozolomide group. There were no CR but the PR and SD (defined as growth in the tumor area of less than 25% with no evidence of new tumors for 2 consecutive months) rates were higher in the temozolomide group (45.6% versus 32.7%) (Osoba D, etal, ASCO99, Abs. 541:141a).

A randomized phase III clinical trial, comparing temozolomide to dacarbazine (DTIC-Dome; Bayer) in the treatment of advanced metastatic malignant melanoma,

Exhibit 5
Antiestrogen Drugs in Development

Developer ❑ Affiliate(s)	Generic Name ❑ Number ❑ Brand Name	Description ❑ Administration Route	Status➢ Location ❑ Indication(s)
American Home Products ❑ Ligand Pharmaceuticals	ERA-923	Selective estrogen receptor (ER) modulator (SERM) ❑ PO	Phase I (o9/99)➢USA ❑ breast cancer
AstraZeneca	Fulvestrant ❑ ZD 9238; ICI 182,780 ❑ Faslodex	7-alpha substituted estradiol; pure anti-estrogen, chemically unrelated to tamoxifen with no agonist activities ❑ PO	Phase III (o5/99)➢USA, Europe ❑ tamoxifen-resistant or refractory, advanced breast cancer
Cytoclonal Pharmaceutics ❑ U California, Los Angeles		Antiestrogen	Research (11/99)➢USA ❑ breast cancer
DuPont Pharmaceuticals ❑ Duke U		Novel antiestrogen compounds that may be active in treating breast cancer, including tamoxifen-resistant breast cancer	Research (o10/99)➢USA
Eli Lilly	Arzoxifene ❑ SERM III, LY 353381 ❑ Celvista or Centera (?)	Analog of raloxifene; third generation SERM ❑ PO	Phase II (o2/99)➢USA ❑ breast, endometrial and ovarian cancer
Karo Bio ❑ U York (UK), Merck		Tissue selective therapy based on ERb structure	Research (o10/99)➢UK, USA ❑ breast cancer
Kymed GB ❑ Bradford U, Duramed Pharmaceuticals, Ultrafine Chemicals	Z-tamoxifen	Pure Z-tamoxifen isomer expected to have a more favorable side effects profile than the currently used tamoxifen version which contains traces of the more harmful E-tamoxifin isomer	Preclin (o6/99)➢UK ❑ breast cancer prevention
Nanodesign		A new chemical class of antiestrogens	Research (o7/99)➢Canada ❑ breast cancer
Novalon Pharmaceutical ❑ Duke U		Novel peptide antagonists of human ERa	Research (o7/99)➢USA ❑ breast cancer
Novogen	NV-06	Naturally-occurring phenolic compounds for anticancer development ❑ PO	Preclin (o10/99)➢Australia ❑ prostate cancer
Novo Nordisk	Levormeloxifene	Chromans SERM ❑ PO	Phase III (discontinued 9/98)➢USA ❑ prevention of breast cancer
Parke-Davis (Warner-Lambert) ❑ Ligand Pharmaceuticals		Discovery, characterization, design and development of SERM ❑ PO	Research (o9/99)➢USA ❑ breast cancer
Pfizer ❑ Ligand Pharmaceuticals, Klinge Pharmaceuticals	Droloxifene	SERM ❑ PO	Phase III (discontinued 1/98)➢USA ❑ advanced, metastatic ER+ breast cancer; phase II (o10/99)➢USA ❑ prevention of breast cancer
Pfizer ❑ Ligand Pharmaceuticals	Lasofoxifene ❑ CP336,156	Naphthaline SERM ❑ PO	Phase II (o10/99)➢USA ❑ prevention of breast cancer
Prolifix		Small-molecule drugs that regulate ER activity via cyclin D1	Research (o11/99)➢UK ❑ breast cancer
Schering-Plough ❑ Endorecherche	EM-800 (SCH 57050)	Third generation SERM acting as pure non-steroidal antiestrogen; prodrug of EM-652 (SCH 57068) ❑ PO	Phase II (o9/99)➢USA ❑ hormone-dependent breast cancer; phase III (o9/99)➢Europe ❑ relapsed breast cancer
Schering-Plough ❑ Endorecherche	EM-652 (SCH 57068)	Third generation SERM acting pure non-steroidal antiestrogen ❑ PO	Research (o9/99)➢USA ❑ solid tumors
Signal Pharmaceuticals		SERM	Research (o9/99)➢USA ❑ solid tumors
SmithKline Beecham	Idoxifene ❑ Alontril, Affidel	SERM	Phase II (discontinued 7/99) USA ❑ advanced breast cancer
Taiho Pharmaceutical	Miproxifene phosphate ❑ TAT-59	A new triphenylethylene derivative; antiestrogen ❑ PO	Phase III (o10/99)➢Japan ❑ advanced, recurrent, breast cancer

*Source: NEW MEDICINE Oncology KnowledgeBASE (nm|**OK**), October 1999*

enrolled 305 previously untreated patients who were treated with either temozolomide capsules, for 5 consecutive days, in each 28-day treatment cycle, or dacarbazine IV injection, for 5 consecutive days, in each 21-day treatment cycle. Among patients correctly diagnosed, previously untreated, and having no CNS metastasis, overall survival was longer in the temozolomide group (7.9 months versus 5.7 months). There was an improvement in PFS in the temozolomide group (1.9 months versus 1.5 months). The overall objective tumor response rate was 13.5% for the temozolomide group compared to 12.1% in the dacarbazine group. QoL was better preserved with temozolomide with physical functioning deteriorating in only 18% of patients on temozolomide treatment after 3 months, compared to 42% of patients on dacarbazine (Middleton MR, etal, ASCO99, Abs. 2069:536a). However, ODAC concluded that the results did not demonstrate any benefit with temozolomide in this setting, and rejected a reanalysis of the data.

In April 1998, Schering-Plough signed an agreement with Sparta Pharmaceuticals (Horsham, PA), now a wholly owned subsidiary of SuperGen (San Ramon, CA), which grants Schering-Plough the right to use the Spartaject technology as a drug delivery scheme for temozolomide. Sparta will receive upfront licensing fees, milestone payments and royalties on sales.

BIOLOGICALS

Aldesleukin

Aldesleukin (Proleukin; Chiron), recombinant interleukin 2 (rIL-2), was approved on January 9, 1998 for the additional indication for treatment of adults with metastatic melanoma. The drug was approved for the treatment of metastatic renal cell carcinoma (RCC) in May 1992.

In July 1999, Chiron filed with the FDA a supplement to its existing BLA for Proleukin to comply with an ongoing post-marketing commitment. Follow-up data, involving 255 patients with metastatic RCC, treated with Proleukin in seven phase II clinical trials, showed a meaningful benefit for the 37 patients who responded to the drug. As of the date of this analysis, disease had not progressed in nearly 50% of the responding patients. In a subset of 17 complete responders, 65% had remained cancer-free for as long as 10 years after Proleukin therapy. Similarly, based on results from 8 clinical trials studying 270 patients treated with Proleukin for metastatic melanoma, of the 17 patients who achieved CR with Proleukin therapy, 59% were living cancer-free at the time of this update, up to 10 years after treatment. Disease did not progress in any patients who remained in remission beyond 30 months.

Denileukin Diftitox

Denileukin diftitox (Ontak; Ligand Pharmaceuticals), a recombinant fusion protein in which the enzymatic and translocating domains of diphtheria toxin have been fused to the sequences for IL-2 ($DAB_{389}IL2$), gained accelerated approval on February 5, 1999 for the treatment of persistent or recurrent CTCL.

Ontak is also being evaluated as first-line therapy in early CTCL, and in NHL. In May 1999, ECOG initiated a phase II clinical study of Ontak in patients with NHL. The primary purpose of the multicenter study is to determine the objective response rate to Ontak, administered to patients with certain types of low- and intermediate-grade NHL previously treated with at least one systemic anticancer therapy. Ontak will be administered intravenously at a dose of 18 μ/kg , per day, for five consecutive days, to be repeated every three weeks. The duration of treatment will depend on each patient's response. The trial will include up to 74 patients, depending on the observed response rates. Ligand is also planning a multicenter trial for Ontak in patients with low-grade NHL who have been previously treated with at least one chemotherapy regimen and at least one monoclonal antibody therapy. This trial will evaluate objective response rates at a dose of 9 μ/kg per day, for five consecutive days, and compare four cycles of therapy versus eight cycles of therapy.

It appears that response of NHL to Ontak may be predicted solely by the presence of the p55 component of the high-affinity IL-2r. In order to achieve optimal cytotoxic activity *in vitro*, Ontak requires expression of the high affinity form of the IL-2r (p55, p75, p64), although cytotoxicity has also been demonstrated in intermediate affinity receptor isoforms (p75, p64). Investigators have prospectively analyzed 202 lymphoma samples for IL-2r expression by immunohistochemistry using anti-p55 (CD25) and p75 (mik-B1) antibodies. Among 202 samples screened, 54% expressed at least one component of the IL-2r with p55 expression detected in 50%, and p75 in 20%. Coexpression of p55 and p75 was detected in 19%, including 19/94 (20%) patients with CTCL, 10/35 (27%) with Hodgkin's disease (HD), and 5/36 (14%) with intermediate-grade NHL. Expression of p55 only was seen in 11/35 (31%) HD, 33/94 (35%) CTCL, and 25/73 (34%) NHL patients (low grade=14 and intermediate grade=10). No HD or NHL cases, and only 6 with CTCL, expressed p75 only. Clinical trials enrolled 73/109 patients with immunohistochemical detection of at least one IL-2r component, of whom 16 (22%) experienced clinical response. Among these cases, p55 was detected in 15; 10/15 expressed only p55 while 5/15 expressed both p55 and p75. Only one responder with CTCL expressed p75 only. Of 23 treated patients with coexpression of p55 and p75, and 52 with p55 only expression, 5 (22%) and 10 (19%) responded, respectively (Foss FM, etal, ASCO99, Abs. 48:14a).

Sales of Ontak were $0.5 million in the first quarter and $1.7 million in the second quarter, and $2.9 million in the third quarter of 1999, for a nine-month 1999 revenue of $5.1 million. In the USA, Ligand is marketing Ontak using 28 reps but plans to increase this number significantly in the near term.

In March, 1999, Ligand signed marketing and distribution agreements with Ferrer Internacional (Barcelona, Spain) to exclusively market and distribute Ontak in Spain,

Portugal, Greece, and Central and South America, as part of a multiproduct agreement. Ferrer will have exclusive rights to the products for a ten-year period, subject to extension upon mutual agreement. Ferrer was to reimburse Ligand $2.5 million for certain registration services incurred by Ligand involving these products.

Interferon α

Interferon α has been approved in most world markets for certain cancer indications such as RCC, hairy cell leukemia, CML, malignant melanoma, and NHL, and is being investigated in the adjuvant and metastatic setting, commonly in combination with chemotherapy and/or radiotherapy, for a variety of cancer indications, among them head and neck cancer (see FO, pp 655 and 643), prostate cancer, glioma, RCC, metastatic malignant melanoma, gastric and pancreatic cancer, and advanced colorectal cancer, among others.

Interferon α-2a (Roferon A; Roche) has been approved for the treatment of hairy cell leukemia, CML, and KS. However, on September 17, 1999, ODAC unanimously rejected Roferon A for the additional indication of treatment of node-negative (Stage II) malignant melanoma citing lack of meaningful endpoint data from a pivotal phase III clinical trial.

Interferon α-2b (Intron A; Schering-Plough) was approved on November 6, 1997, for use in conjunction with chemotherapy in patients with follicular NHL (see FO, p 809). The drug was also approved in the USA, in 1995, as an adjuvant treatment of malignant melanoma in patients at high risk for systemic recurrence after surgery. Intron A has also been approved in the USA for AIDS-related KS and hairy cell leukemia, and an sNDA was filed in April 1998 for CML. A pegylated form of Intron A is in phase III clinical trials in malignant melanoma and CML. This formulation is being developed in collaboration with Enzon (Piscataway, NJ). In November 1999, Schering-Plough submitted an MMA to the EMEA seeking clearance to market PEG-Intron in the EU for treatment of hepatitis C. The formulation, provided in powder form, is reconstituted in solution to be injected once weekly.

In 1999, worldwide sales of Intron A/Rebetron, a combination of Intron and ribavirin licensed from ICN Pharmaceuticals (Costa Mesa, CA), were $275 million in the first quarter, up 66% from 1998 levels, $276 million in the second quarter, and $274 million in the third quarter, bringing total nine-month sales to $825.00 million, up 36% from comparable 1998 levels. In the USA, combined sales of Intron A/Rebetron increased 50% to $165 million in the first nine months of 1999.

Rituximab

Rituximab (Rituxan; Idec Pharmaceuticals), a genetically engineered, chimeric pan-B antibody that binds CD20 antigen-expressing B cells, activates complement proteins and recruits macrophages and natural killer cells, was approved on November 26, 1997, for the treatment of relapsed or refractory low-grade or follicular, B-cell NHL.

Actually, because of its relatively benign side effects profile, a statistically significant association between higher serum levels of the drug and response and dose-limiting toxicity has not been reached in reported studies, a clinical trial was conducted to address whether higher cumulative doses and more prolonged courses of Rituximab would further increase clinical efficacy in relapsed low-grade or follicular (LG/F) NHL. In a phase II clinical trial, 37 patients (IWF-A=19%, IWF-B=49%, IWF-C=22%, IWF-D=8%) with relapsed NHL were treated with IV rituximab (375 mg/m^2) weekly for 8 weeks. There were 5/37 (14%) CR, 16/37 (43%) PR, for an ORR of 57%. This ORR compares to 48% achieved with a 4-week dosing regimen. TTP was 13.4 months with the 4-week regimen compared to 19.4+ months with the 8-week schedule. Adverse events were consistent with those previously described with rituximab and occurred primarily with the first infusion and usually resolved in less than one to two hours. However, the observed benefit with the longer duration regimen did not reach statistical significance (Piro L, etal, ASCO99, Abs. 49:14a).

Rituxan is marketed in the USA by Genentech, in Japan where it is still in clinical trials, by Zenyaku Kogyo (Tokyo, Japan), and by Roche elsewhere. USA sales were $52 million in the first quarter of 1999, up 38%, second-quarter 1999 sales were $68.3 million, up 113%, third-quarter sales were $70.2 million, up 94.5%, from comparable 1998 periods, and nine-month-sales were $190.5 million. Off-shore sales were $13.5 million in the first nine months of 1999. Cost of treatment at the manufacturer's level, in the USA, is estimated at $9,000 per regimen. Rituxan's growth is being driven in part by increased prescribing for the approved indication, and because patients who relapse after first responding to Rituxan are being retreated. A cost comparison between Rituxan and fludarabine in the treatment of LG/F NHL, performed by Idec, concluded that annual overall costs of the two drugs, whose efficacy is comparable, were nearly identical (Burchmore, MJ and Dowden S, ASCO99, Abs. 91:25a).

Idec is also developing ibritumomab tiuxetan (IDEC-Y2B8, Zevalin), a radioimmunoconjugate, for the treatment of B-cell lymphoma. Zevalin consists of a murine IgG_1 κ MAb targeting CD20 antigen on mature normal and malignant B cells, covalently linked to MXDTPA which securely chelates yttrium-90. Zevalin, in combination with Rituxan, is in phase III clinical trials in refractory NHL. In a completed phase I/II clinical trial, this combination was used in the treatment of (LG/F) NHL. IDEC-Y2B8 clinical trial dosing is standardized, based primarily on body weight and platelet count. Response rate in low-grade NHL was 82% (28/34) across all dose levels (0.2, 0.3, or 0.4 mCi/kg). Also, radiation levels to major organs and to bone marrow remained well below established safety limits. Adverse events were primarily hematologic and dose-depen-

dent. There was no renal, hepatic, pulmonary or cardiac dysfunction, and human anti-mouse or anti-chimeric antibody reactions were not a therapy-limiting factor (Wiseman G, etal, ASH98, Abs. 1721:417a).

In a phase I/II trial, 50 patients with low-grade, or intermediate-grade NHL, or mantle-cell NHL, were treated with a single dose of IDEC-Y2B8 (0.2, 0.3 or 0.4 mCi/kg); one patient was not treated. Overall response rate (ORR) was 67% (26% CR + 41% PR) with 82% ORR (27% CR + 46% PR) occurring in the low-grade group. Median TTP for responders was 12.9+ months, and duration of response was 11.7 months (Wiseman GA, etal. ASCO99, Abs. 13:4a).

In August 1999, Idec entered into a Clinical Trials Agreement with the Division of Cancer Treatment and Diagnosis (DCTD) of the NCI, to study of the safety and efficacy of Zevalin as treatment for conditions outside those currently under investigation by Idec, including intermediate and high-grade NHL, as well as cases with extensive bone marrow involvement not eligible for pivotal studies being conducted by Idec. Other areas could include combination regimens with chemotherapy, and retreatment of relapsed disease.

In June, 1999, Idec entered into a licensing agreement granting Schering AG exclusive marketing and distribution rights to Zevalin outside the USA, valued at approximately $47.5 million. Idec has retained USA rights to Zevalin. Under the terms of the agreement, Schering paid Idec $13 million as an upfront licensing fee and committed funding of an additional $15 million for the development of Zevalin. Furthermore, Schering will make milestone payments, of up to $19.5 million, based on the achievement of certain development goals and pay Idec royalties on product sales outside the USA.

A close competitor to Zevalin is tositumomab (Bexxar; Coulter Pharmaceutical), consisting of anti-CD20 (anti-B1) murine MAb labeled with iodine-131. In November 1998, SmithKline Beecham and Coulter (South San Francisco, CA) signed an agreement to jointly commercialize Bexxar. The agreement has a potential value to Coulter of up to $132 million, plus shared profits and royalties. Under terms of the agreement, SKB made an upfront payment of $41.5 million to Coulter, including the purchase of $7.25 million in equity, and the provision of a $15 million credit line. Coulter may potentially receive an additional $76 million based upon completion of certain milestones. Future development expenses for Bexxar are being shared by both companies, with Coulter retaining responsibility for funding certain predetermined development costs. In addition, the companies will jointly explore the potential of Bexxar for other indications. Coulter and SKB will jointly market Bexxar in the USA following regulatory approval, sharing profits equally. Outside the USA, excluding Japan, Coulter has granted SKB exclusive marketing and distribution rights in return for product royalties. SKB also has access to second generation anti-CD20 compounds under development by Coulter.

In June 1999, Coulter submitted a BLA to the FDA for Bexxar which was designated a fast-track product, for treatment of relapsed or refractory low-grade and transformed low-grade B-cell NHL. Also in June 1999, Nancy Valente, MD, presented long-term follow-up data from all of the clinical trials with Bexxar at the International Conference on Malignant Lymphoma. At that time, Bexxar had been administered to 432 NHL patients at approximately 40 centers throughout the USA and UK. Most of these patients were heavily pretreated with a median of 3 prior chemotherapy regimens. At the time of the analysis, 249 of the 432 patients (58%) were free of disease progression. Subsequent therapies were administered following Bexxar treatment and, generally, neither the low blood counts nor HAMA-positive readings associated with Bexxar precluded patients from being treated with other therapies including rituximab.

Of the 432 patients treated with Bexxar, 183 progressed following Bexxar treatment; 156 of the 183 patients who progressed were administered subsequent therapies, including pretreatment with Bexxar, single-agent or combination chemotherapy, radiation therapy, rituximab, bone marrow or stem cell transplantation, biological therapy, and/or steroid therapy. The majority of patients (101 patients or 65%) went on to chemotherapy following Bexxar. The chemotherapy regimens included various combination and salvage therapies; 20 patients (13%) were retreated with Bexxar, 15 (10%) underwent stem cell or bone marrow transplantation, 41 (25%), 6 of whom were known to be HAMA positive, were treated with Rituximab, and 25 were not treated with subsequent therapy primarily because of slowly progressive disease not requiring therapy. Only one patient was not treated with subsequent therapy because of low blood counts.

Short-term side effects associated with Bexxar included a decrease in blood counts which were generally reversible and self-limiting. Only 5% of patients experienced platelet counts less than 10,000 cells/mm^3, but a minority of patients required growth factor support. Additional short term side effects included a mild to moderate flu-like syndrome observed in approximately one-third of patients. Longer-term side effects were infrequent and included increases in thyroid stimulating hormone (TSH) in a small percent of patients. Myelodysplastic syndrome also was noted in a small percent of cases consistent with previous exposure to chemotherapeutic agents, i.e. alkylating agents or etoposide. HAMA was detected in 9 (6%) previously treated patients. A higher HAMA rate was observed in previously untreated patients with 35 (54%) testing positive for HAMA.

In August 1999, the FDA requested reformatting of certain sections and additional analyses of existing data in the BLA. No additional trials were requested nor did the FDA require new information from ongoing trials or on manufacturing. As of November 1999, Coulter had not resubmitted its BLA, waiting for FDA clarification as to the required modifications.

Trastuzumab

Trastuzumab (Herceptin; Genentech), a humanized MAb (4D5) targeting a protein receptor, Her-2/neu, on tumor cells, was approved on September 25, 1998 for use as monotherapy in breast cancer refractory to standard chemotherapy or, in combination with paclitaxel, as a first-line treatment for metastatic disease (see FO, pp 903-906, 872, 813-814). Since then, Herceptin sales grew rapidly in the USA. They were $39 million in the first quarter of 1999, $86.1 million in the first half of the year and $47.9 million in the third quarter of 1999, bringing the total nine months sales to $134 million. Despite its rapid acceptance in the USA, outside the USA Herceptin is only available in Switzerland since 1998 and, in August 1999, was also approved in Canada. Roche filed for EU approval in February 1999 and has also filed for approval in many other countries worldwide.

Although Herceptin has been shown to improve survival by 25% when added to the chemotherapy regimen in metastatic breast cancer, its true opportunity lies in the treatment of early breast cancer. In this setting, its safety profile will come under close scrutiny. Herceptin causes a number of side effects such as pain, fever, chills, nausea and vomiting, headache, and weakness, but these are mild and usually subside after the first infusion. Also, Herceptin does not cause hair loss, nausea or hematologic side effects. However, in combination therapy, Herceptin appears to significantly increase the risk of life-threatening congestive heart failure (CHF), particularly when used in combination with an anthracycline-based regimen. In an analysis of the drug's safety profile (Exhibit 6), J. Baselga of Hospital Vall d'Hebron (Barcelona, Spain) reviewed the records of 338 patients who participated in the monotherapy trial, and 469 in the combination trials, involving either an anthracycline or paclitaxel, in terms of rates of cardiac dysfunction. In these settings, cardiac toxicity was less severe with the Herceptin and paclitaxel regimen (ECCO10, Abs. 1299:S324).

Two large trials are slated to begin in early 2000 to evaluate Herceptin in a combination regimen in the adjuvant setting in resected breast cancer where its safety profile is expected to be critical in deciding if it will play a role in this indication. In one of the trials, to be conducted by the NSABP (protocol B-32), Herceptin, in combination with paclitaxel, will be administered sequentially rather than concurrently with an anthracycline-based regimen. Randomization involves two arms:

- 4 cycles of doxorubicin or epirubicin plus cyclophosphamide, followed by 4 cycles of paclitaxel (175 g/m^2), plus Herceptin (4 mg/kg loading dose and 2 mg/kg maintenance dose), weekly, for 1 year
- 4 cycles of doxorubicin or epirubicin plus cyclophosphamide, followed by 4 cycles of paclitaxel

The trial, to be conducted in two stages, will enroll 2,700 women. Stage I, to enroll 1,000 women, will assess cardiac safety and determine the toxicities of adding weekly Herceptin to adjuvant Taxol, following doxorubicin or epirubicin plus cyclophosphamide for 1 year. If the incidence of cardiac toxicity in this arm falls within the boundaries set by the protocol, the study will proceed to the second stage. Patient accrual will be increased to another 1,700 patients in Stage II in order to evaluate the efficacy of adding Herceptin to chemotherapy in prolonging disease-free survival (DFS) and overall survival. As of mid-November 1999, this trial had been approved by the NCI and awaited FDA approval. The other trial is still in the designing stage. In May 1999, Bristol-Myers Squibb and Genentech also entered into an agreement to continue clinical research and enhance the safe use of the combination of Herceptin and Taxol in the treatment of metastatic breast cancer.

ADJUNCT THERAPIES

Amifostine

Amifostine (Ethyol; U.S. Bioscience), was approved on June 24, 1999, for the additional indication to reduce the incidence of moderate-to-severe xerostomia in patients undergoing postoperative radiation treatment for head and neck cancer, when the radiation port includes a substantial portion of the parotid glands. Ethyol was approved for this indication in the EU in April 1999. Ethyol was originally approved on December 1995, as a selective cytoprotective agent to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer. On March 15, 1996, an sNDA was approved by the FDA, on an accelerated basis, for the reduction of cumulative renal toxicity associated with repeated administration of cisplatin for the treatment of nsclc. In the USA, Ethyol was awarded orphan drug status for the xerostomia indication in May 1998 and, in May 1990, as a chemoprotective agent in cisplatin-treated metastatic melanoma, cyclophosphamide-treated advanced ovarian cancer and cisplatin-treated advanced ovarian cancer. Currently, Ethyol has been approved in over 34 countries worldwide.

Ethyol is also being investigated as a bone marrow stimulant in myelodysplastic syndromes (MDS) to increase bone marrow production of red blood cells, neutrophils, and platelets. Also, several phase III clinical trials are ongoing in the approved indications to satisfy follow-up regulations associated with accelerated approvals.

Ethyol is marketed by Alza Pharmaceuticals in the USA, and by Schering-Plough overseas. USA sales, reported by Alza, were $17.7 million in the third quarter of 1999, and $34.8 million in the first 9 months of 1999, up 48% from the comparable 1998 period.

Colony-Stimulating Factors

There are several colony stimulating factors (CSF) on the world market for managing cancer treatment-related complications. Also, a recombinant Streptomyces-derived GM-CSF is being evaluated by Cangene (Mississauga, Ontario, Canada) in a phase III multicenter clinical trial in

Exhibit 6
Adverse Cardiac Events with Herceptin

Adverse Cardiac Events	Herceptin + Anthracycline (%)	Anthracycline Alone (%)	Herceptin + Taxol (%)	Taxol Alone (%)	Herceptin Alone (%)
Grade 3/4 (initial)	16.0	3.0	2.0	1.0	3.0
Grade 3/4 (post-treatment)	6.0	0.7	0	0	1.5
Deaths	0.7	0.7	0	0	0.9
Total (all grades)	27.0	7.0	12.0	1.0	4.0

the USA for the mobilization of peripheral blood stem cells in patients with breast cancer.

Filgrastim (Neupogen; Amgen), a recombinant form of granulocyte colony-stimulating factor (rG-CSF), was approved on April 2, 1998 for the additional indication for reducing the recovery time of neutrophils, and the duration of fever, following chemotherapy treatment in patients with AML. Neupogen is currently marketed for use in decreasing the incidence of infection in patients undergoing myelosuppressive chemotherapy, for reducing the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation, for reducing symptoms in patients with severe chronic neutropenia, and for use in mobilization of peripheral blood progenitor cells (PBPC) for stem cell transplantation. Clinical trials investigating Neupogen as an adjunct to dose-intensified chemotherapy in patients with various tumor types, were ongoing as of early 1999.

Amgen is also developing SD/01, a sustained duration (pegylated) version of Neupogen to provide for less frequent dosing, possibly once-per-cycle of chemotherapy and, thus, render treatment more convenient and improve patient compliance. SD/01 completed phase II clinical trials for this indication and is about to enter phase III clinical trials. Also, in July 1998, the Biological Response Modifier's Advisory Committee (BRMAC) to the FDA voted 10 to 1 to recommend approval of ancestim (Stemgen; Amgen) for stimulation of PBPC in autologous stem cell transplants in patients with breast cancer, in combination with Neupogen.

Amgen markets Neupogen directly in the USA, Canada and Australia and comarkets the drug with Hoffmann-La Roche in the EU. Amgen and Roche entered into a long-term agreement, until 2010, to collaborate on the commercialization and further clinical development of Neupogen in the EU, sharing in related costs and profits from sales. Amgen has most of the responsibilities for marketing, promotion, distribution and other key functions relating to product sales, and it distributes the product in most EU countries from its European Logistics Center. Amgen and Roche are also collaborating on the development of a second generation G-CSF product for the EU. The two companies have also entered into an agreement to commercialize Neupogen in non-EU countries. Under this agreement, Roche markets Neupogen in these countries and pays a royalty to Amgen on sales. Kirin-Amgen and Roche have also entered into an agreement to commercialize Neupogen in certain territories not covered by the above Amgen/Roche agreement. Under this agreement, Roche markets Neupogen in these countries and pays a royalty to Kirin-Amgen on sales.

Neupogen's worldwide sales were $287 million in the first quarter of 1999, up 10%, $304 million in the second quarter of 1999, up 12%, and $313 million in the third quarter, up 9% from 1998 levels. Sales for the first 9 months of 1999 were $904 million.

Lenograstim [Granocyte (Europe) and Neutrogin (Japan)], another rG-CSF, is marketed in 24 European countries by a Chugai and Aventis joint venture. Chugai also markets Neutrogin in China, South Korea, Thailand, and Taiwan, and a licensee, Amrad (Richmond, Victoria, Australia), markets the product in Australia. European sales by Aventis were about $23 million in the second quarter of 1999, up 21.5% from the comparable 1998 period and $44 million in the first half of 1999, up 19.2%.

Sargramostim (Leukine; Immunex), a recombinant granulocyte macrophage colony-stimulating factor (rGM-CSF), has been approved for several indications, namely to facilitate allogeneic and autologous bone marrow transplantation (BMT) used for treatment of acute leukemia, lymphoma, and Hodgkin's disease, and in rescuing patients with failed BMT grafts, to accelerate neutrophil recovery and reduce mortality in AML, and to mobilize PBPC and in post-transplantation support. A controlled phase III clinical trial in resectable (Stage III or IV) melanoma at high risk for relapse, is also being conducted by a cooperative oncology group. Also, GM-CSF is being investigated in oral mucositis to establish whether it is effective in reducing the severity and duration of this condition associated with certain types of chemotherapy and with irradiation. To date the drug has shown similar outcomes whether administered orally or parenterally. Also, various phase II clinical trials are ongoing using GM-CSF as a cancer vaccine adjuvant.

An aerosol formulation of GM-CSF was evaluated at Mayo Clinic (Rochester, NY) in a phase I clinical trial in cancer metastasized to the lung. GM-CSF was administered

at 3 dose levels (60 mg, 120 mg, 240 mg), twice daily for 7 days. If there was no toxicity, after a 7-day rest, patients were treated and monitored at the next dose level. Six patients were treated at all three dose levels. There was no incidence of pulmonary toxicity, bone pain, fevers, or malaise. Disease progressed in 2 patients with measurable lung metastases from RCC and melanoma. The other 4 patients were treated with an additional 2–5 months of intermittent aerosol GM-CSF at dose level 3 (240 mg) without toxicity. Two of these patients, one with leiomyosarcoma and the other with osteosarcoma, remained free of lung metastases, disease stabilized in one patient with Ewing's sarcoma, and one patient with melanoma was responding at the time of this report. Aerosol delivery of GM-CSF appears to achieve effective immunologic activation without significant toxicity (P. Anderson P, etal, ASCO99, Abs. 1734:449a).

USA sales of Leukine were $16 million in the first quarter, $16.6 million in the second quarter, and a record $17.5 million in the third quarter of 1999, totaling $50.1 million in the first nine months of 1999.

Octreotide Acetate

Octreotide acetate (Sandostatin; Novartis) acts by inhibiting excess release of intestinal tumor cell secretions, thus eliminating the source and cause of severe diarrhea. Sandostatin LAR Depot, a new once-monthly formulation of octreotide, was approved on November 25, 1998 for all the indications subcutaneous octreotide had already been approved, namely suppression of severe diarrhea and flushing associated with malignant carcinoid syndrome, for the treatment of the profuse watery diarrhea associated with VIPoma (vasoactive intestinal peptide tumor), and for the reduction of growth hormone and IGF-1 in acromegaly. In a 6-month multicenter phase III clinical trial that enrolled 93 patients with malignant carcinoid syndrome, this long-acting repeatable (LAR) formulation of octreotide acetate, administered as a monthly depot IM injection, exhibited similar safety and efficacy to the subcutaneous formulation (Rubin J, etal, ASCO97, Abs. 993:).

Oprelvekin

Oprelvekin (Neumega; Genetics Institute) is a recombinant human interleukin-11 (rhIL-11) that stimulates all phases of development of megakaryocytes, the cells which produce platelets. The drug was approved on November 25, 1997, for the prevention of severe thrombocytopenia, and for the reduction of the need for platelet transfusion following myelosuppressive chemotherapy in patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia.

The tolerability of Neumega, administered during and after chemotherapy and autologous PBCT, is being investigated in a phase I double-masked, placebo-controlled clinical trial that is also aiming to assess and characterize Neumega's effect on the severity and duration of chemotherapy-induced oral mucositis. The trial enrolled patients with solid tumor or lymphoma who were administered escalating doses of Neumega. Generally, Neumega was well-tolerated. Adverse events that occurred more frequently in Neumega-treated patients were mild to moderate and included fever, ecchymosis, increased cough, asthenia, edema, and ileus. Abnormal liver function tests or diagnosis of veno-occlusive disease were reported in 28% of all patients of whom two, treated with 3 and 25 µg/kg of Neumega, died from venous occlusion and one, treated with 10 µg/kg of Neumega, died of multiorgan failure, at least 3 weeks after completion of treatment. The proportion of patients with infections or sepsis was 14% in those treated with 25 and 50 µg/kg of Neumega, compared with 55% in all other groups. The effects of Neumega on mucositis suggest a trend of decreasing incidence of severe mucositis with increasing dose of Neumega. The median number of days of severe mucositis also was reduced to none with a dose of 50 µg/kg of Neumega, compared to 4 days in controls. Neumega appears to be well-tolerated and may reduce the severity, incidence and duration of severe oral mucositis (Schwerkoske J, etal, ASCO99, Abs. 2256:584a).

Pamidronate Disodium

Pamidronate disodium (Aredia; Novartis), an IV bisphosphonate, was approved for the additional indication for the treatment of osteolytic bone metastases of breast cancer on July 16, 1996. Aredia was previously indicated for hypercalcemia associated with malignancy, osteolytic bone lesions of multiple myeloma, and Paget's disease. Aredia's worldwide sales were up 58% in the first quarter of 1999. Novartis Pharma KK (Tokyo; Japan) has been conducting phase II clinical trials of Aredia in Japan for treatment of skeletal osteolytic lesions resulting from multiple myeloma and breast cancer, in conjunction with standard chemotherapy.

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